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COVID-19 vaccine hesitancy, safety and effectiveness

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COVID-19 vaccine hesitancy, safety and effectiveness

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Parents' reasons to vaccinate their children aged 5–11 years against COVID-19 in Italy

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Objectives: The aims of this cross-sectional study were to investigate why parents decide to vaccinate, as well as the determinants, their children aged 5–11 years against COVID-19 in Italy.

Methods: The survey was conducted from January through May 2022. All parents/guardians who came in randomly selected days to immunization centers for the administration of the first dose of the COVID-19 vaccine to their child were asked to complete a questionnaire about socio-demographic characteristics, attitudes toward COVID-19 infection and vaccination, reason(s) regarding their decision to vaccinate their child, and source(s) of information.

Results: A total of 358 questionnaires were collected. Parent's perception that COVID-19 is a severe illness for the child, assessed using a 10-point Likert scale, was 7.5. The overall mean scores of the risk perception for their child of having the COVID-19 before and after the vaccination were 8.1 and 6.3. A significantly higher parents' level of risk perception for their child of having the COVID-19 after the vaccination has been observed among those not having a university degree, those with the child having at least one chronic medical condition, and those who perceived that COVID-19 is a severe illness for the child. The mean value of respondent trust in the information provided by the pediatricians on a 10-point scale Likert type was 7.6. Female, not having a university degree, higher perception that COVID-19 is a severe disease, not having received information about the vaccination from pediatricians, and needing information had a significantly higher concern of side effects after the vaccination. The most common reasons for vaccinating their children included wanting to protect the child against COVID-19, to attend the school with less risk, to prevent the transmission to family members, and to practice sport and other activities with less risks. Participants with a university degree were more likely to have vaccinated their child for attending the school and practicing sport and other activities with less risks.

Conclusions: More publicity should be promoted among parents of children aged 5–11 years which would increase the coverage rates and thus lower the transmission of SARS-CoV-2 and reduce the occurrence of COVID-19.

KEYWORDS

children, COVID-19, Italy, parents, reasons, vaccination

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Introduction

As of the end of April 2022, in Italy the number of reported confirmed cases of COVID-19 exceeded 16.8 million with more than 16 thousand deaths caused by the SARS-CoV-2 (1). It is well-known that children had similar incidence rates of SARS-CoV-2 infection compared with adults (2) and that the vaccination among this group is essential to reduce infection and transmission to the susceptible person.

On December 1, 2021, the Italian Medicines Agency (AIFA) has authorized the administration of two 10-µg doses of the Pfizer-BioNTech BNT162b2 mRNA COVID-19 vaccine 21 days apart to children ages 5 through 11 years (3). On December 7, 2021, the Ministry of Health announced that this age group who do not have contraindications to the vaccine could receive this free complete series (4). On December 16, 2021, the national vaccination campaign started in almost all regions of the country throughout the community vaccination centers. However, despite the high frequency of the disease and the safe and real-world data on vaccine effectiveness among children aged 5 to 11 years of age in reducing symptomatic disease, hospitalizations, and deaths (5–8), as of May 17, 2022, in Italy the vaccination rates were low in this group since only 37.9% had received one dose and 34.5% had received their second dose (9).

Parents' COVID-19 vaccination hesitancy or likelihood of their children getting this vaccine has been widely debated (10–13). However, until now very few studies have focused on parents' reasons to have their child 5–11-year-olds vaccinated and the associated factors and understanding this issue is essential in planning effective measures for increasing vaccination uptake and avoiding fueling vaccine hesitancy. Therefore, the present cross-sectional study attempts to investigate why parents decide to vaccinate, as well as the determinants, their children aged 5–11 years against COVID-19 in Italy.

Materials and methods

Setting and target population

Data were collected as a part of a larger project on perceptions and behaviors toward COVID-19 vaccination among different groups of people living in Southern Italy (10, 11, 14–18). This cross-sectional survey was conducted from January through May 2022 in two randomly selected immunization centers located in the geographic area of Naples, Southern part of Italy. All parents/guardians aged ≥ 18 years of children 5–11 years of age who came in randomly selected days to the immunization centers for the administration of the first dose of the COVID-19 vaccine to their child were approached in the waiting rooms and asked about their interest in participating in the study.

The sample size was calculated by using single population proportion formula, assuming that 25% of the respondents vaccinated their child for attending the school and practicing sport and other activities with less risks, with a margin of error of 5%, a confidence interval of 95%, and an expected response rate estimated of 85%. This gives the final sample size of 321 participants.

Study procedures

The protocol and the informed consent of the study were approved by the Ethics Committee of the Teaching Hospital of the University of Campania "Luigi Vanvitelli". Before participation in the study, well-trained research team members in conducting surveys with self-administered questionnaires approached each parent/guardian and, after introducing themselves, asked if he/she would be interested in participating in this study. They were fully informed about its purpose and significance, that the participation was completely voluntary, that the questionnaire was anonymous and will not include any identifiers or personal information of the participants, that the information will be kept private and confidential, that they could stop completing the questionnaire at any stage, and the information will only be used for scientific research purposes.

The research team members collected the study questionnaires from parents/guardians once they were filled. Informed written consent was obtained from participants before the questionnaire was administered to them. No incentives or rewards were offered to participants as compensation for their time.

Survey instrument

The questionnaire was developed on the basis of previous instruments used in similar surveys carried out by some of us to evaluate parental and/or individual COVID-19 vaccination acceptability enrolling different populations (10, 11, 14–18). A total of 10 non-selected individuals were asked about the questionnaire's clarity, wording, and as well as whether any of the questions were difficult to comprehend, before disseminating the final questionnaire to the research population. Participants in the pilot study were not included in the final study sample.

The questionnaire was self-administered and took approximately 5 min to complete. The questionnaire was organized into three parts. In the first part, questions were asked about parents' socio-demographic characteristics (i.e., gender, age, employment status, educational level, marital status, number of children in home, having been infected with SARS-CoV-2) and children's characteristics (i.e., age and gender). In the second part, attitudes toward the COVID-19 infection (risk perception for their child of having the COVID-19 before and after the vaccination, perceived severity of COVID-19) and attitudes toward the COVID-19 vaccination (concern about serious adverse effects from COVID-19 vaccine for their child, trust in the information provided by the pediatricians). These questions were collected on a 10-point Likert scale, ranging from 1 representing not at all to 10 representing at all. In the third part, the parents were asked whether they had received and from whom the recommendation for COVID-19 vaccine for their child, the reason(s) regarding their decision to vaccinate their child, and also whether they had any doubts regarding the COVID-19 vaccine for their child and the reason(s) associated with. In the response with 8 options, respondents could select all that apply. Finally, the participants were asked which source(s) of information about COVID-19 vaccination for children 5–11-year-olds they had used, including mass media, Internet, pediatrician, physician (other than pediatrician), friends, social network, official government organizations, and scientific journals, and they were asked to select all responses that applied. Respondents were also asked whether they would like to obtain additional information on this topic in the future.

Statistical analysis

First, descriptive statistics including relative frequency, mean, and standard deviation were used to summarize the personal characteristics of respondents and their child. Second, bivariate associations between each variable and the continuous or dichotomous outcome have been tested using when appropriate the chi-square test or the Student's *t*-test. Variables associated in the bivariate analysis with a p-value ≤ 0.25 were entered into the multivariate linear and logistic regression models. Third, multivariate linear and logistic regression models were employed to identify the determinants of the following dependents variables: risk perception for their child of having the COVID-19 after the vaccination (continuous) (Model 1); concern that their child can report side effects after receiving the vaccination (continuous) (Model 2); and having vaccinated their child for attending the school and practicing sport and other activities with less risks (no = 0; yes = 1) (Model 3). The following independent variables have been selected because potentially related to all dependents variables: gender of the child being vaccinated (male = 0; female = 1), age of the child being vaccinated (continuous), child being vaccinated with at least one chronic condition (no = 0; yes = 1), respondent's age in years (continuous), gender (male = 0; female = 1), baccalaureate/graduate degree (no = 0; yes = 1), having other children in home (no = 0; yes = 1), having received the COVID-19 vaccine (no = 0; yes = 1), having contracted SARS-CoV-2 (no = 0; yes = 1), at least one parent/cohabitant partner who contracted SARS-CoV-2 (no = 0; yes = 1), at least one parent/cohabitant partner who received the COVID-19 vaccine (no = 0; yes = 1), believing that COVID-19 is a severe illness (continuous), having being recommended to vaccinate their child (no = 0; yes = 1), having received information on COVID-19 vaccination from pediatrician (no = 0; yes = 1), and need of additional information on COVID-19 vaccination (no = 0; yes = 1). The variable marital status (unmarried = 0; married/cohabited with a partner = 1) was included in Models 2 and 3; the variables at least one parent/guardian being a healthcare worker (no = 0; yes = 1) and having trust in the information received from the pediatrician (continuous) were added in Models 1 and 2; and the variables risk perception for their child of having COVID-19 before the vaccination (continuous), risk perception for their child of having COVID-19 after the vaccination (continuous), concern about serious adverse effects from COVID-19 vaccine for their child (continuous), and having doubts regarding the COVID-19 vaccine for their child (no = 0; yes = 1) were included in Model 3.

A stepwise method was used to retain or to exclude in the final multivariate models the variables with a threshold of $p = 0.2$ and $p = 0.4$, respectively. In the multivariate logistic regression model, odds ratio (OR) with a 95% confidence interval (CI) was computed, whereas in the linear regression models standardized regression coefficient (ß) was used. All statistical tests were two-tailed and p-values equal to or <0.05 were considered to be statistically significant. All statistical analyses were conducted in STATA software version 15.1.

Results

Of the 370 parents/guardians who were randomly selected only 12 refused to participate in the survey and 358 agreed for a response rate of 96.8%. The socio-demographic and general characteristics of the respondents are presented in Table 1. The mean age was 41.7 years, 70.1% was female, more than three-quarters were married, for 34.4% the highest level of education was a university degree, 66.2% was employed, less than one-third had one child, almost all had been vaccinated against COVID-19, and 21.6% have had at least one cohabitant who have contracted SARS-CoV-2.

The perception that COVID-19 is a severe illness for the child, assessed using a 10-point Likert scale, was generally high among the respondents with a mean value of 7.5 and about a third reported a value of 10 (30.2%). Table 2 reported the results of the multivariable linear and logistic regression analysis examined the independent association of several determinants and the different outcomes of interest. Multivariable linear regression analysis showed that a significantly higher parents' level of risk perception for their child of having the COVID-19 after the vaccination has been observed among those who did not have a university degree, those with the child having at least one chronic medical condition, and those who perceived that COVID-19 is a severe illness for the child (Model 1). Regarding

TABLE 1 Socio-demographic and general characteristics of the study population.

Characteristics	N	%
Parent		
Age, years	41.7 ± 6.5 (23-60)	
Gender		
Female	251	70.1
Male	107	29.9
Marital status		
Married/cohabited with a partner	323	90.5
Unmarried/separated/divorced/widowed	35	9.5
Educational level		
High school degree or less	223	62
Baccalaureate/graduate degree	135	38
Professional status		
Employed	237	66.2
Unemployed	121	33.8
Partner's professional status		
Employed	277	80.5
Unemployed	81	19.5
Number of children		
1	107	29.9
> 1	251	70.1
Having been infected by SARS-CoV-2		
No	284	79.3
Yes	74	20.7
Having at least one parent/cohabitant partner who had been infected by SARS-CoV-2		
No	280	78.4
Yes	77	21.6
Vaccinated against COVID-19		
No	8	2.2
Yes	350	97.8
At least an adult cohabitant vaccinated against COVID-19		
No	12	3.3
Yes	346	96.7
At least another son/daughter vaccinated against COVID-19		
No	155	43.3
Yes	203	56.7
Vaccinated child		
Age, years	8.4 ± 2	
Gender		
Female	161	45.5
Male	193	54.5
Birth order		
First	211	59.1
Second	121	33.9
≥Third	25	7
Underlying chronic medical conditions		
No	268	74.9
Yes	90	25.1
Parent's rate health status	9.3 ± 1.1 (5–10)	

*Mean ± Standard deviation (range).

the risk perception for their child of having the COVID-19, the overall mean score was, respectively 8.1 before and 6.3 after the vaccination. Overall, 43.5 and 19.8% respondents had the higher score giving a rating of 10. Only 14.7% of participants expressed the higher concern, with a response of 10 on a 10-point Likert type scale, about serious adverse effects from COVID-19 vaccine use for their child with an overall mean value of 6. In a multivariable linear regression model examining the association of multiple factors with the concern of reporting side effects after receiving the vaccination it has been observed that female gender, not having a university degree, higher perception that COVID-19 is a severe disease, not having received information about the vaccination for their children from pediatricians, and needing additional information about COVID-19 vaccination for children 5–11-year-olds were associated with a higher level of concern (Model 2 in Table 2). The mean value of respondent trust in the information provided by the pediatricians on a 10-point scale Likert type was 7.6, but only less than one-third (29.9%) expressed the higher level of trust. More than half of the parents/guardians (58.9%) reported receiving recommendation for COVID-19 vaccine for their child and the health care providers in the pediatric primary care setting were those who most frequently make the recommendation (75.4%). The most common reasons the parents reported for vaccinating their children against COVID-19 included wanting to protect the child against COVID-19 (86.9%), to attend the school with less risks (33.8%), to prevent the disease transmission to other family members (27.4%), and to practice sport and other activities with less risks (17%). Overall, only 12.6% of the parents vaccinated their child for attending the school and practicing sport and other activities with less risks. The results of a multivariable logistic regression model showed that participants with a university degree were more than two times (OR = 2.32; 95% CI 1.21–4.46) more likely to have vaccinated their child for this reason than those with a lower level of education (Model 3 in Table 2). In addition, the respondents' worry about the adverse effects of the vaccination (59.1%) and the feeling that they did not have enough information regarding the child's vaccination (38.5%) were their main doubts before the vaccination.

Most of the sample (87.2%) had learned about COVID-19 vaccination for children 5–11-year-olds. Almost half of the respondents said that their child's healthcare provider (45.5%) was the most important source of information about vaccines followed by the physicians (36.3%). Additional sources were government agencies (27.4%), mass media (18.7%), and Internet (16.5%). One-third (31.7%) reported that they want to obtain more information regarding vaccination.

Discussion

The results of the present survey provide a detailed description that contributes to an understanding of the reasons

TABLE 2 Determinants of the different outcomes of interest using linear and logistic regression analysis.

Variable	Coeff.	SE	*t*	*p*
Model 1. Parents' risk perception for their child of having the COVID-19 after the vaccination				
$F_{(8, 29)} = 8.22$, $p < 0.0001$, $R^2 = 16.7\%$, adjusted $R^2 = 14.6\%$				
Believing that COVID-19 is a severe illness	0.27	0.05	5.11	<0.001
Not having a baccalaureate/graduate degree	−0.92	0.27	−3.40	0.001
Child vaccinated with at least one chronic condition	0.73	0.31	2.34	0.02
Female	0.49	0.28	1.70	0.089
Female child vaccinated	0.41	0.26	1.56	0.12
At least one parent/cohabitant partner who contracted SARS-CoV-2	0.44	0.32	1.39	0.164
Need of additional information on COVID-19 vaccination	0.31	0.29	1.10	0.273
Neither parent/guardian being a healthcare worker	−0.49	0.50	−0.98	0.329
Model 2. Parents' concern that their child can report side effects after receiving the vaccination				
$F_{(11, 327)} = 6.68$, $p < 0.0001$, $R^2 = 18.3\%$, adjusted $R^2 = 15.6\%$				
Female	1.30	0.30	4.33	<0.001
Believing that COVID-19 is a severe illness	0.20	0.05	3.45	0.001
Not having received information on COVID-19 vaccination from pediatricians	−0.80	0.28	−2.81	0.005
Need of additional information on COVID-19 vaccination	0.65	0.30	2.18	0.03
Not having a baccalaureate/graduate degree	−0.60	0.28	−2.14	0.033
Child vaccinated with at least one chronic condition	0.65	0.33	1.94	0.053
Having been recommended to vaccinate their child	0.50	0.28	1.77	0.077
At least one parent/cohabitant partner who received the COVID-19 vaccine	1.31	0.77	1.70	0.089
Female child vaccinated	0.44	0.27	1.63	0.104
Neither parent/guardian being a healthcare worker	−0.55	0.54	−1.02	0.307
At least one parent/cohabitant partner who contracted SARS-CoV-2	0.33	0.33	1.02	0.31
	OR	**SE**	**95% CI**	***p***
Model 3. Parents having vaccinated their child for attending the school and practicing sport and other activities with less risks				
Log likelihood $= -127.56$, $\chi^2 = 13.72$ (4 df), $p = 0.0083$, adjusted $R^2 = 5.1\%$				
Having a baccalaureate/graduate degree	2.32	0.77	1.21–4.46	0.012
Having doubts regarding the COVID-19 vaccine for their child	1.81	0.63	0.91–3.60	0.089
Not having parent/cohabitant partner who contracted SARS-CoV-2	0.56	0.26	0.23–1.41	0.221
Lower risk perception for their child of having COVID-19 after the vaccination	0.93	0.06	0.82–1.06	0.285

of parents for deciding to vaccinate against COVID-19 their children aged 5–11 years, as well as the determinants. These results can provide a useful guidance to decision makers and healthcare workers on approaches to take when designing interventions in this field.

It is interesting to note that several reasons have been reported by parents in support of the decision to vaccinate their children against COVID-19. The vast majority of the respondents reported that they vaccinated their children because they were to protect the child from the disease, whereas additional reasons were aligned as feeling that vaccination was a means of attending the school with less risks and protecting the family members. These reasons are confirmed by several previous studies on parents' willingness to accept the COVID-19 vaccination for their children (10, 19, 20). Moreover, the present survey demonstrates that parents' concerns about adverse effects of the vaccination were the biggest doubt before the vaccination. This is consistent with the findings of several previous studies, local and abroad, also regarding the willingness or hesitancy of the vaccination (11–13, 21, 22). However, this finding is surprising particularly because it has been observed worldwide that the most reported adverse events of the COVID-19 vaccination in children and adolescents, particularly with the mRNA vaccines, were mild in severity and short in duration (23, 24). These results highlight the responsibility of policymakers in addressing the critical issue of educating the public on the safety of the vaccination.

It has been observed that the physicians were the highly preferred source of information among parents/guardians about the COVID-19 vaccination for their children. Compared to parents who heard about COVID-19 vaccine through physicians, concern about side effects of the vaccine has been more likely to be reported by those who said that they did not acquire information from this source. This is consistent with the findings in the literature showing the important role of these professionals in providing comprehensive and objective information on this issue and for increasing the confidence of the vaccine (10, 18, 25–29). This finding also underlined the fact that physicians play a larger role in how healthcare is provided, and they have a unique opportunity to ensure that parents understand the benefits, safety, and efficacy of the COVID-19 vaccine and the importance of getting the vaccine as an essential preventive health care. Discussions with physicians, as with other health care professionals, are also important for providing education and parents should be able to have open conversations with them and to address their concerns and questions. Such conversations about the opportunities for vaccination would enable parents to work together with these providers to consider how best to protect their children. Moreover, it should be underlined that only half of the parents/guardians had received recommendation for COVID-19 vaccine for their child and the health care providers in the pediatric primary care setting were those who most frequently make the recommendation. This finding could be used by healthcare providers to deliver appropriate messages about risks and benefits to parents and this is also confirmed by the fact that one-third of the respondents had indicated an interest in receiving additional information. Another interesting finding of the present study was the small proportion of respondents that had used Internet as a source of information. This result is comfortable due to the anti-vaccination messaging and the spread of inaccurate and misleading public health information around COVID-19 and its vaccines circulating online since the beginning of the pandemic (30–32).

Multivariate regression analysis revealed that a number of socio-demographic and general characteristics of the respondents and of the vaccinated child were associated with the different outcomes of interest. It has been identified that gender and educational level have a significant impact. Indeed, females and those with a lower educational level had a higher concern of side effects of the vaccination and this reflects the general trend in access to COVID-19 vaccine disparities that has been observed in several previous studies (33–37). The reason by which females are more concerned may be explained by the fact that in Italy they were more affected than men although male presented a higher risk of death (38). With regard to the results of the educational level, a possible explanation is that parents with a higher level are able to get more information easier than the general population that makes them advantageous over part of the other societies. Similar explanation for significant impact of the finding with parents less educated that were more likely to perceive a higher level of risk perception for their child of having the COVID-19 after the vaccination. Further, it has been observed that the health condition of the vaccinated child has also a significant impact, with parents of the child with at least a chronic medical condition had a higher level of risk perception for their child of contracting the SARS-CoV-2 after the vaccination. This may suggest that these parents still perceived for their child a higher degree of vulnerability than those without a chronic medical condition. Finally, the finding that individuals who perceive COVID-19 to be a severe disease are anxious about contracting it for their child is consistent with the literature in other countries (39–41).

The findings should be interpreted in the light of some potential methodological limitations derived from the nature of this study. Firstly, because of the nature of the cross-sectional study method that has been used the identified associations may be difficult to interpret since it is difficult to draw conclusions regarding the direct causal inferences and the direction of causality. Secondly, since the participants were selected in one city, the generalization of the results to other geographic areas of Italy should be made with caution, but they could reflect the population with similar socio-demographic characteristics. Thirdly, as in most surveys, parent-reported information is subjective and may be affected by social desirability. However, since COVID-19 can be a sensitive and important issue for the majority of respondents, it is unlikely that social desirability bias resulted, for example, in under-reporting of their own or their familiar having been infected with SARS-CoV-2. We are likely to expect that respondents' reporting of their experience should be reasonably accurate, as having the infection is a rather an important event and therefore likely to be memorable.

In conclusion, parents of children aged 5–11 years exhibited, although vaccinated, concerns about side effects and a lower use of healthcare workers as a source of information about vaccines. This finding shows the essential role played by the physicians to provide adequate information to the parents about benefits, safety, and efficacy of the COVID-19 vaccine. In this context it is also interesting that only half of the participants had received recommendation for COVID-19 vaccine for their child. Since the COVID-19 vaccination rate is low in this age group, this study underlines the need to improve publicity among parents of children aged 5–11 years in order to increase the rates and thus lower the transmission of SARS-CoV-2 and reduce the occurrence of COVID-19.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of the Teaching Hospital of the University of Campania "Luigi Vanvitelli". Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

AN, GMG, FC, and LF participated in the design of the study, contributed to the data collection, the data analysis, and interpretation. IFA the principal investigator, designed the study, was responsible for the statistical analysis and interpretation, and wrote the article. All authors have read and approved the final version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Effect of inactivated COVID-19 vaccination on intrauterine insemination cycle success: A retrospective cohort study

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Background: Vaccine hesitancy was found in couples seeking artificial reproductive technology (ART) services. As the main vaccine used in China, investigations into the influence of inactivated coronavirus disease 2019 (COVID-19) vaccines on human fertility is needed.

Methods: This retrospective cohort study included data on COVID-19 vaccination, clinical characteristics, and reproductive outcome of 1,000 intrauterine insemination (IUI) cycles in 653 couples from March 2021 to March 2022 in a single university hospital-based center for reproductive medicine. The IUI cycles were divided into two categories based on sperm source, including 725 cycles in 492 women undergoing artificial insemination with their husband's sperm (AIH) and 275 cycles in 161 women undergoing artificial insemination with donor sperm (AID). Women were then divided into two groups. The vaccine exposed group included women vaccinated prior to insemination and the unexposed group included women who were not vaccinated or vaccinated after insemination. Reproductive outcomes including ongoing pregnancy rate, clinical pregnancy rate, and miscarriage rate were assessed.

Results: Inactivated COVID-19 vaccinated women prior to intrauterine insemination in AIH cycles have comparable ongoing pregnancy rate (11.1 vs. 10.3%, $P = 0.73$), clinical pregnancy rate (12.5 vs. 11.3%, $P = 0.60$) as compared with unvaccinated counterparts. Similarly, there were no significant differences in ongoing pregnancy rate (20.9 vs. 28.1%, $P = 0.17$), clinical pregnancy rate (21.7 vs. 28.8%, $P = 0.19$) between vaccine exposed and unexposed groups in AID cycles. Multivariable logistic regression analyses showed that inactivated COVID-19 vaccination status cannot independently influence the reproductive outcomes of AIH and AID cycles. Subgroup analysis of vaccine exposed cycles showed that doses of vaccination and Interval between the last dose of vaccination and insemination have no influence on the reproductive outcomes of AIH cycles.

Conclusions: No negative effects were found on female fertility in IUI cycles following exposure to the inactivated COVID-19 vaccine. These findings indirectly reflect the safety of inactivated COVID-19 vaccine toward reproductive health and help to mitigate vaccine hesitancy among people planning to conceive.

KEYWORDS

COVID-19, inactivated vaccine, SARS-CoV-2, IUI, infertility

Introduction

The outbreak of Coronavirus disease 2019 (COVID-19) has developed into a global pandemic recognized by the World Health Organization (WHO) on the 11th of March 2020 and continues to pose a great threat to public health and safety (1). As of March 2022, over 455 million confirmed cases and almost 6 million deaths had been reported globally (2). COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) wild-type strain and its variants, a novel positive-stranded RNA virus belonging to the Coronaviridae family (3). Because of the vulnerability of SARS-CoV-2, the development of safe and effective vaccines has become the most urgent goal for the scientific community. Globally, various vaccines are being developed, including live-attenuated virus vaccines, inactivated virus vaccines, protein subunit vaccines, replication-deficient vectors, and genetic vaccines (DNA and RNA) (4). According to data from the WHO, there are at least 149 vaccine candidates in clinical phases, 40 of which have reached Phase III trials based on different vaccine platforms (5). Inactivated vaccines are the most commonly used in China because three double-dose inactivated vaccines (Sinovac and SinoPharm) have been approved for emergency use. After being adopted in a nationwide anti-COVID-19 vaccination program, over 3,100 million doses of inactivated vaccines were administered in mainland China (6).

Studies have shown that the SARS-CoV-2 virus initiates infection through the interaction of its spike proteins with the human angiotensin-converting enzyme 2(ACE2) receptors (7), which are abundant in the ovarian and testicular tissue of the human reproductive system (8, 9). This highlights the potential for detrimental effects on the future fertility of people infected with SARS-CoV-2. It is also particularly concerning for the uptake of COVID-19 vaccines, given its importance for people of child-bearing age. Based on our understanding of the immune response to inactivated vaccines and the efficacy and safety data from clinical trials (10–13), current guidelines from various world organizations do not restrict COVID-19 vaccination from people trying to conceive or undergoing ART. However, given the lack of information on the specific effects of COVID-19 vaccination on reproduction, there is no consensus on the need to postpone conception after vaccination. Guidelines from the European Society of Human Reproduction and Embryology (ESHRE) and the Chinese Expert Group recommend postponing ART for at least a few days after administration of the vaccine to allow the immune response to settle (14). Conversely, other organizations such as the American Society for Reproductive Medicine (ASRM), the Centers for Disease Control and Prevention (CDC), and the Joint Committee on Vaccination and Immunization (JCVI) do not stress this point (15). Additionally, we found that couples seeking artificial reproductive technology (ART) services in our reproductive center focused more on the effect of COVID-19 vaccination on ART and future pregnancy, which led to vaccine hesitancy and extremely low vaccination coverage.

Intrauterine insemination (IUI) also known as artificial insemination, is the first-line treatment for unexplained and male-factor infertility. With this treatment, the sperm from a partner or donor is prepared and inseminated directly into the uterus around the time of ovulation, representing the relatively natural fertilization process compared to *In vitro* fertilization embryo transfer (IVF-ET) (16). Therefore, this study aims to identify the effect of inactivated COVID-19 vaccines on reproductive outcomes in a cohort of women undergoing IUI cycles to increase confidence and

Abbreviations: ART, Artificial reproductive technology; COVID-19, Coronavirus disease 2019; IUI, Intrauterine insemination; AIH, Artificial insemination with their husband's sperm; AID, Artificial insemination with donor sperm; WHO, World Health Organization; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; ACE2, Angiotensin-converting enzyme 2; ESHRE, European Society of Human Reproduction and Embryology; ASRM, American Society for Reproductive Medicine; CDC, Centers for Disease Control and Prevention; JCVI, Joint Committee on Vaccination and Immunization; IVF-ET, *In vitro* fertilization embryo transfer; AFC, Antral follicular count; AMH, Anti-Müllerian hormone; BMI, Body mass index; COS, Controlled ovarian stimulation; FSH, Follicle-stimulating hormone; PR, progressive motility; TMSC, Total motile sperm count; HMG, Human menopausal gonadotropin; LH, Luteinizing hormone; hCG, Human chorionic gonadotropin; IQR, Interquartile range; SD, Standard deviation; RR, Risk ratio; CI, Confidence interval; GI, Generalized estimating equation.

reduce hesitancy toward these vaccines in women trying to fall pregnant.

Materials and methods

Study design and participants

A retrospective cohort study was conducted at the Center for Reproductive Medicine of the Third Affiliated Hospital of Guangzhou Medical University (Guangzhou, China). Women who had undergone IUI cycles from March 2021 to March 2022 were enrolled. Inclusion criteria included: (i) at least 12 months of infertility, (ii) regular menstruation (21–35 days), and (iii) normal uterine cavity with at least one patent fallopian tube (established by hysterosalpingography or laparoscopy). Exclusion criteria included: (i) advanced maternal age (older than 40 years), (ii) no COVID-19 vaccination data, (iii) cycle cancellation due to a low ovarian response (lack of development of lead follicle at least >14 mm), ovulation from the side of known tubal occlusion, multifollicular response and premature ovulation, and (iv) presence of other infertility factors including severe endometriosis e(ASRM grade III-IV), decreased ovarian reserve function (antral follicular count (AFC) <5–7 follicles or anti-Müllerian hormone (AMH) <0.5–1.1 ng/ml), endometrial disorders (polyps or submucosal fibroids) and hydrosalpinx. From the 1,127 infertile couples identified (1,936 cycles), 916 women (1,554 cycles) underwent artificial insemination with their husband's sperm (AIH), and 213 women (382 cycles) underwent artificial insemination with donor sperm (AID), primarily due to severe male factor infertility (17). These people were further screened by the above exclusion criteria. Finally, 725 AIH cycles and 275 AID cycles were included in the study and each was divided into two groups. The vaccine exposed group included women vaccinated prior to insemination and consisted of 335 AIH cycles and 115 AID cycles. The unexposed group included women who were not vaccinated or vaccinated after insemination and consisted of 390 AIH cycles and 160 AID cycles (Figure 1).

The baseline clinical characteristics and cycle variables were collected from a fertility department database. Vaccination status was determined by telephone follow-up. General patient information such as female age, body mass index (BMI), type of pregnancy, infertility duration, treatment cycle type, IUI indication, and cycle number was recorded. The indications for IUI were divided into male factors, unexplained or other factors, while treatment cycle types were divided into cycles with controlled ovarian stimulation (COS) and natural cycles. Cycle variables cover an index that reflects ovarian function, including basal follicle-stimulating hormone (FSH) level, AMH level, and bilateral AFC; male sperm parameters including progressive motility (PR) after processing and the total motile sperm count (TMSC) after processing; and the numbers of dominant follicles and endometrial thickness on the day of hCG administration. Vaccination status included the male partner vaccinated or not, the doses of vaccination, and the interval between the last dose vaccination and insemination in exposed cycles.

This study was approved by the local Ethics Committee of the Third Affiliated Hospital of Guangzhou Medical University.

IUI protocol

Details of the IUI protocol have been described previously (18). A transvaginal ultrasound was performed on cycle day 35 to exclude ovarian cysts larger than 30 mm. According to the maternal age and ovarian reserve testing, the women started intramuscular injections of human menopausal gonadotropin (HMG, Livzon, Zhuhai, China), ranging from 37.5 to 75 IU to control ovarian stimulation. These injections continued daily until ovulation of at least one follicle ≥17 mm in diameter.

The trigger criteria for ovulation were: (i) the leading follicle was ≥17 mm in diameter, (ii) the serum luteinizing hormone (LH) was elevated and the leading follicle was at least 14 mm in diameter, (iii) the serum P concentrations were ≥1.5 pg/l and the leading follicle was at least 14 mm in diameter. If one of these three criteria were observed, ovulation was triggered with human chorionic gonadotropin (hCG) ranging from 5,000 IU to 10,000 IU.

Insemination was performed 12–36 h after hCG injection. The sperm was collected by masturbation after 2–7 days of sexual abstinence. Sperm samples in the AID cycles were obtained from the Human Sperm bank of Guangdong Province. Sperm from each washed semen sample were counted and evaluated for motility, and 0.2–0.5 mL was introduced into the woman's uterus by syringe.

Ovulation was identified by free fluid in the Douglas pouch and visible corpus luteum and/or the disappearance of the follicle during a transvaginal ultrasound. After insemination, micronized progesterone (200 mg vaginal capsule, twice daily) was used for luteal support. The serum β-HCG level was tested for pregnancy 2 weeks later.

The primary response variable for this study was the ongoing pregnancy confirmed by intrauterine pregnancy beyond 12 weeks' gestation through transvaginal ultrasound examination, and clinical pregnancy defined as the presence of a yolk sac with heartbeat at 7 weeks gestation. Secondary outcomes included rates of biochemical pregnancy, early miscarriage, and ectopic pregnancy. Biochemical pregnancy was determined as the detection of serum level of HCG more than 10 mIU/ml 14 days after operation. Biochemical pregnancy loss was determined as elevated HCG levels but no detectable gestational sac was observed with transvaginal sonography 4 weeks following operation. Early miscarriages were those pregnancy losses with detectable intrauterine gestational sacs within gestational 12 weeks. Ectopic pregnancy was identified as embryos implant

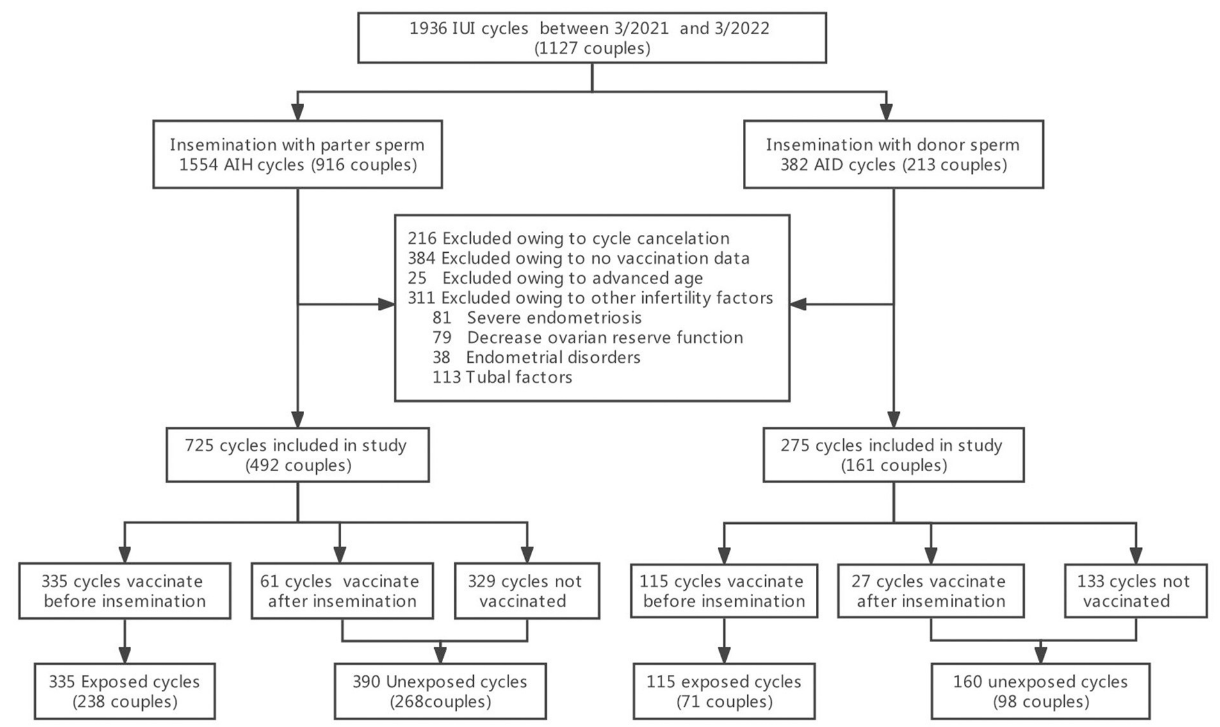

FIGURE 1
Study flowchart.

at any other sites except for intrauterine cavity. Biochemical pregnancy loss rate, spontaneous miscarriage rate, and ectopic pregnancy rate were calculated based on the number of women with biochemical pregnancy.

Statistical analysis

The mean ± standard deviation (SD), median and interquartile range (IQR 25 to 75%) were determined for continuous variables, while categorical variables were expressed as cycle numbers and percentages. A Mann-Whitney U-test was used to compare the response variables between groups for skewed data, and a *t*-test was used for normally-distributed data. A chi-square test was used to compare qualitative data between groups. Clinical pregnancy, biochemical pregnancy, and miscarriage rates were compared for vaccine-exposed or unexposed groups in AIH and AID cycles. First, the unadjusted risk ratio (RR) and 95% confidence interval (CI) were calculated for clinical pregnancies, using unexposed cycles as the reference. A log-binomial regression model for multivariate analysis was then performed, controlling for female age, BMI, infertility duration, treatment cycle type, IUI indication, sperm parameters after processing, ovarian reserve function, dominant follicles, endometrial thickness on the day of hCG administration, and the vaccination status of male partner. Next, a generalized estimating equation (GEE) was used to examine the relationship between individual factors and the outcome of ongoing pregnancy, controlling for multiple cycles within the same couple. RR and 95% CI were calculated for candidate factors. A *p*-value of <0.05 indicated statistical significance. Statistical analysis was performed in SPSS 28.0 software (IBM).

Results

From March 2021 to March 2022, data from 1,000 IUI cycles in 653 couples were included in this study, of which 725 were cycles with partner sperm (492 couples) and 275 were cycles with donor sperm (161 couples). There were 335 AIH cycles in the COVID-19 vaccine-exposed group and 390 cycles in the unexposed group. Similarly, 115 AID cycles were in the COVID-19 vaccine-exposed group, and 160 cycles were in the unexposed group. Table 1 summarizes baseline characteristics per artificial insemination cycle stratified by vaccine exposed or not. The mean female age was 31.2 ± 3.6 years in AIH cycles and 29.6 ± 3.5 years in AID cycles. There were no statistically significant differences in the female age, BMI, infertility duration, distribution of infertility types, treatment

TABLE 1 Baseline characteristics per artificial insemination cycles with husband or donor semen stratified by vaccination exposed or not.

Variables	AIH cycles			AID cycles		
	Exposed group	Unexposed group	*P*-value	Exposed group	Unexposed group	*P*-value
No. of cycles	335	390		115	160	
Female age, mean (SD), y	31.2 (3.8)	31.2 (3.6)	0.95	30.5 (2.4)	29.4 (3.8)	0.02
BMI, mean (SD), kg/m^2	21.9 (3.3)	22.0 (3.4)	0.74	22.0 (2.7)	21.2 (2.8)	0.09
Type of infertility, *n* (%)			0.87			0.09
Primary infertility	218 (65.9)	252 (65.3)		102 (88.7)	130 (81.3)	
Secondary infertility	113 (34.1)	134 (34.7)		13 (11.3)	30 (18.8)	
Infertility duration, median, median (IQR), y	3 (2–4)	3 (2–4)	0.53	4 (2–5)	4 (2–5)	0.67
Treatment cycle type, *n* (%)			0.55			0.08
Natural	169 (50.4)	188 (48.2)		73 (66.1)	89 (55.6)	
COS	166 (49.6)	202 (51.8)		39 (33.9)	71 (44.4)	
IUI indication, *n* (%)			0.06			0.63
Unexplained/other	146 (44.6)	199 (51.6)		4(3.5)	4 (2.5)	
Male factors	185 (55.4)	187 (48.4)		111 (96.5)	156 (97.5)	
Cycle number, *n* (%)			0.06			0.08
First	197 (58.8)	253 (64.9)		56 (48.7)	60 (37.5)	
Second	117 (34.9)	127 (32.6)		40 (34.8)	49 (30.6)	
Third or more	21 (6.3)	10 (2.6)		19 (16.6)	51 (31.8)	
Male partner vaccination, *n* (%)	326 (98.2)	197 (51.6)	<0.01			

TABLE 2 Vaccination status of vaccines exposed group.

Variables	AIH cycles	AID cycles	*P*-value
Doses of vaccination, % (*n*)			0.33
Single dose prior to insemination	23.3 (78/335)	27.8 (32/115)	
Double doses prior to insemination	72.5 (243/335)	70.4 (81/115)	
Three doses prior to insemination	4.2 (14/335)	1.8 (2/115)	
Interval between the last dose and insemination, %(*n*)			0.73
<3 months	27.8 (93/335)	26.1 (30/115)	
≥3 months	72.2 (242/335)	73.9 (85/115)	

cycle types, IUI indication, or cycle number between vaccine-exposed and unexposed groups in AIH cycles ($P > 0.05$). In AID cycles, women with vaccine exposure were significantly older than those unexposed (30.5 vs. 29.4, $P = 0.02$).Other baseline characteristics did not differ significantly. The vaccination coverage of women seeking for IUI treatments was 45%. The vaccine coverage rate of male partner in the female vaccine-exposed group was significantly higher than in the unexposed group in AIH cycles (98.2 vs. 51.6%, $P < 0.01$).

Table 2 shows the vaccination status of vaccines exposed group both in AIH and AID cycles. There were no statistically significant differences between AIH and AID cycles in the distribution portion of the vaccination doses as well as the interval between the last dose vaccination and insemination ($P > 0.05$). For women vaccinated before insemination, Over 70% of them have been vaccinated double doses before undergoing intrauterine insemination, and the interval between the last dose vaccination and insemination was more than 3 months.

There were no statistically significant differences between vaccine-exposed and unexposed groups in the indexes representing female ovarian function, sperm parameters after processing, dominant follicles, or endometrial thickness on the day of hCG administration in AIH cycles ($P > 0.05$). The only significant difference found in AID cycles was PR after processing, which was higher in the exposed group than in the unexposed group (84.2 vs. 78.1%, $P < 0.01$, Table 3).

Table 4 shows the frequencies and adjusted RR for reproductive outcomes of artificial insemination cycles stratified by vaccine-exposed or unexposed. In AIH cycles, there were no significant differences in reproductive outcomes between

TABLE 3 Cycle variables per artificial insemination cycles with husband or donor semen stratified by vaccination exposed or not.

Variables	AIH cycles			AID cycles		
	Exposed group	Unexposed group	*P*-value	Exposed group	Unexposed group	*P*-value
Ovarian reserve function, median (IQR)						
Basal FSH level, mIU/mL	5.65 (5.0–6.90)	5.68 (4.87–6.46)	0.61	5.03 (4.75–6.71)	5.30 (4.54–6.27)	0.71
AMH level, ng/mL	4.15 (2.79–5.88)	4.21 (2.75–6.56)	0.17	3.66 (2.61–5.53)	3.99 (2.48–6.41)	0.84
Bilateral AFC	19 (15–25)	20 (15–26)	0.83	19 (14–29)	20 (16–25)	0.25
Sperm parameters, median (IQR)						
PR after processing, %	93.8 (91.3–96.2)	94.0 (90.5–96.0)	0.38	84.2 (75.6–87.7)	78.1 (72.6–82.8)	< 0.01
TMSC after processing, 10^6	26.44 (17.19–39.97)	29.39 (16.74–44.63)	0.51	13.39 (11.07–15.99)	12.86 (11.15–15.47)	0.13
Dominant follicles, median (IQR)	1 (1)	1 (1)	0.98	1 (1)	1 (1, 2)	0.16
Endometrial thickness on the day of hCG administration, median (IQR), mm	9.4 (8.6–11)	9.8 (8.4–11)	0.93	9.0 (7.3–10.0)	9.5 (8.8–10.4)	0.11

TABLE 4 Reproductive outcome of artificial insemination with husband or donor semen stratified by vaccine exposed or not.

Variables	Exposed cycles, % (*n*)	Unexposed cycles, % (*n*)	*P*–value	Adjusted*	
				RR (95% CI)	*P*–value
AIH					
Biochemical pregnancy	13.1 (44/335)	12.8 (50/390)	0.90	1.085 (0.688–1.711)	0.73
Clinical pregnancy	12.5 (42/335)	11.3 (44/390)	0.60	1.189 (0.740–1.912)	0.47
Ongoing pregnancy	11.0 (37/335)	10.3 (40/390)	0.73	1.128 (0.684–1.860)	0.64
Biochemical pregnancy loss	4.5 (2/44)	12.0 (6/50)	0.28#		
Early miscarriage	6.8 (3/44)	8.0 (4/50)	1.00#		
Ectopic pregnancy	4.5 (2/44)	0 (0)	0.22#		
AID					
Biochemical pregnancy	22.6 (26/115)	30.6 (49/160)	0.14	0.721 (0.401–1.295)	0.27
Clinical pregnancy	20.9 (24/115)	28.8 (46/160)	0.19	0.759 (0.416–1.383)	0.37
Ongoing pregnancy	20.9 (24/115)	28.1 (45/160)	0.17	0.751 (0.408–1.380)	0.36
Biochemical pregnancy loss	7.7 (2/26)	6.1 (3/49)	1.00#		
Early miscarriage	0 (0)	2.0 (1/49)	1.00#		
Ectopic pregnancy	0 (0)	0 (0)	1.00#		

*Adjusted for female age, BMI, infertility duration, treatment cycle type, IUI indication, sperm parameters after processing, ovarian reserve function, dominant follicles, and endometrial thickness on the day of hCG administration.
#Fisher exact test was used.

groups (11.0 vs. 10.3% for ongoing pregnancy rate, $P = 0.73$; 12.5 vs. 11.3% for clinical pregnancy rate, $P = 0.60$). The rates of biochemical pregnancy (13.1 vs. 12.8%, $P = 0.90$) and biochemical pregnancy loss (4.5 vs. 12.0%, $P = 0.28$) were similar in the vaccine exposed group compared with the unexposed group. In AID cycles, the rates of reproductive outcomes were slightly lower in the exposed group, but this difference was not statistically significant (20.9 vs. 28.1% for ongoing pregnancy rate, $P = 0.17$; 21.7 vs. 28.8% for clinical pregnancy rate, $P = 0.19$; 22.6 vs. 30.6% for biochemical pregnancy rate, $P = 0.14$). Multivariable logistic regression analyses showed no independent influence of vaccine exposed on the reproductive outcomes of AIH and AID cycles (Adjusted RR 1.128 for ongoing pregnancy rate in AIH cycles, 95% CI 0.684 to 1.860; Adjusted RR 0.751 for ongoing pregnancy rate in AID cycles, 95% CI 0.408 to 1.380). The rates of biochemical pregnancy loss (7.7 vs. 6.1%, $P = 1.00$) were similar between groups. Early miscarriage occurred 3/44 (6.8%), 4/50 (8.0%), and 1/49 (2.0%)

TABLE 5 Subgroup analysis of reproductive outcomes of artificial insemination with husband within exposed cycles.

	Biochemical pregnancy	Clinical pregnancy	Ongoing pregnancy	Biochemical pregnancy loss	Miscarriage
Doses of vaccination, % (*n*)					
Single dose prior to insemination	17.9 (14/78)	16.7 (13/78)	14.1 (11/78)	7.1 (1/14)	7.1 (1/14)
Double dose or more prior to insemination	11.7 (30/257)	11.3 (29/257)	10.1 (26/257)	3.3 (1/30)	6.7 (2/30)
P-value	0.15	0.21	0.33	0.54*	1.00*
Interval between the last dose and insemination					
<3 months	18.3 (17/93)	16.1 (15/93)	14.0 (13/93)	11.7 (2/17)	0 (0)
≥3 months	11.2 (27/242)	11.2 (27/242)	9.9 (24/242)	0 (0)	11.1 (3/27)
P-value	0.08	0.22	0.29	0.14*	0.27*

*Fisher exact test was used.

in the exposed group of AIH cycles, the unexposed group of AIH cycles, and the unexposed group of AID cycles, respectively. Ectopic pregnancy occurred 2/44 (4.5%) in the exposed group of AIH cycles.

Subgroup analysis of vaccination status among vaccinated women in AIH cycles on reproductive outcomes was performed. As presented in Table 5, the reproductive outcomes were slightly poor in the group taken double dose or more inactivated COVID-19 vaccines than the group that took a single dose vaccine prior to intrauterine insemination, but this difference was not statistically significant (10.1 vs. 14.1% for ongoing pregnancy rate, $P = 0.33$; 11.3 vs. 16.7% for clinical pregnancy rate, $P = 0.21$; and 6.7 vs. 7.1% for miscarriage rate, $P = 1.00$). Similarly, the reproductive outcomes were slightly poor in the group that had undergone intrauterine insemination more than 3 months later after taking the last dose of COVID-19 vaccine than the group that within 3 months (9.9 vs. 14.0% for ongoing pregnancy rate, $P = 0.29$; 11.2 vs. 16.1% for clinical pregnancy rate, $P = 0.22$; and 11.1 vs. 0% for miscarriage rate, $P = 0.27$).

The predictors in the GEE model for ongoing pregnancy are presented in Table 6. After controlling bias from multiple cycles within the same couple, no independent influence factor was found to predict the reproductive outcome of AIH cycles, including COVID-19 vaccine exposed.

TABLE 6 Adjusted binary logistic regression model for predictors of ongoing pregnancy of artificial insemination with husband semen (725 cycles in 492 couples) using generalized estimating equations.

Factor	Adjusted RR (95% CI)	*P*-value
Female vaccine exposed	1.060 (0.591–1.901)	0.85
Male partner vaccinated	0.729 (0.370–1.435)	0.36
Female age, y	1.022 (0.957–1.092)	0.51
BMI, kg/m^2	0.968 (0.904–1.036)	0.34
Infertility duration, m	0.953 (0.824–1.103)	0.52
Treatment cycle type		
Natural	Ref.	
COS	0.684 (0.421–1.111)	0.13
IUI indication		
Unexplained/other	Ref.	
Male factors	0.870 (0.530–1.427)	0.58

Discussion

This cohort study was designed to identify potential detrimental effects of the inactivated COVID-19 vaccine on female fertility during IUI cycles and found no significant effects on clinical pregnancy rates in either AIH or AID cycles.

The public health impact of the COVID-19 pandemic is beyond everybody's imagination 2 years after the first case was reported. China's early physical epidemic prevention measures, such as strictly blocking the transmission chain of SARS-CoV-2, have achieved great success in limiting the domestic epidemic of COVID-19. Given the integration of the world economy, and the need to open the country to the outside world, the full implementation and promotion of vaccination was the only solution. However, any resulting reproductive issues must be known and considered by reproductive medical workers. To date, there have been no reports of female reproductive system damage in COVID-19 patients, but indirect evidence suggests that COVID-19 may infect female ovarian tissue and granulosa cells through ACE2 receptors, reducing ovarian function and oocyte quality (9, 19, 20). Based on existing research on the potential impact of SARS-CoV-2 infection on female fertility, national guidelines recommend that women with pregnancy planning be actively vaccinated against COVID-19. However, these recommendations have not been accepted by the population. On the one hand, our follow-up data showed that the vaccination coverage of COVID-19 is far from establishing herd immunity in couples undergoing ART (21). On the other hand, Flynn et al. (22) investigated the impact of the COVID-19 pandemic on human pregnancy-planning behaviors through an online questionnaire and found that 53% of subjects reported that COVID-19 had affected their pregnancy plans, among which 72% chose to postpone pregnancy. These abnormal behaviors may be attributed to the lack of knowledge about the potential effects of COVID-19 vaccination, which led to much apprehension and caution among patients planning to conceive.

Current vaccines have already advanced into clinical trials, and published data mainly include inactivated virus vaccines, virus-vectored vaccines, and mRNA vaccines. The latter two were gene-based vaccines that deliver genes encoding viral antigens to host cells for *in vivo* production, which target a single protein or protein fragments of SARS-CoV-2 (23). In contrast, inactivated virus vaccines are physically or chemically inactivated but preserve the integrity of the virus particle, using the whole virus as vaccine targets. The targeted immune response of an inactivated vaccine is usually humoral and cellular, with little reactogenicity, resulting in a high safety profile (4). As for mRNA vaccines, several studies have indirectly illustrated their safety in terms of fertility. A recent report using the v-safe safety monitoring system data showed that 4,800 people had a positive pregnancy test after receiving the first dose of an mRNA COVID-19 vaccine (24). A randomized, blinded Pfizer-BioNTech trial also showed a similar number of women conceived after receiving the vaccine as those who received the placebo (15). Morris et al. (25) found no difference in implantation rates among SARS-CoV-2 vaccine seropositive, infection seropositive, and seronegative women following *in vitro* fertilization frozen embryo transfer cycles. Similarly, two observational studies have assessed the influence of the mRNA SARS-CoV-2 vaccine (BNT162b2) on IVF treatments, and neither the before-after study (26) nor the cohort study (27) demonstrated any detrimental effect on the patients' performance and ovarian reserve in IVF cycles. In addition, researchers found no significant changes in sperm characteristics before or after two doses of a COVID-19 mRNA vaccine among cohorts of healthy men (28, 29). Despite these findings, investigations into the effect of inactivated COVID-19 vaccines, the main vaccine used in China, have not been done.

This study is the first to evaluate the possible effect of inactivated COVID-19 vaccines on human reproduction, using the IUI cycle as a model. This is an effective method to study the impact of one factor on implantation, on the one hand, the fertilization process of it is relatively natural compared to IVF-ET, on the other hand, the process of IUI bypass many of the variables that normally impact the ability to conceive like ovulation and sperm selection compared to natural conception process (30). When grouping the subjects, we played close attention to the relative time between vaccination and insemination and chose a more rigorous grouping method instead of just dividing people into vaccinated and unvaccinated groups. We classify people vaccinated after insemination as vaccine unexposed group because at that time the vaccine could be considered no longer affect the process of early pregnancy. Besides, the follow-up period of our study was the period when vaccination was just started in China, at that time, sperm samples stored in the sperm bank must have come from unvaccinated donors. Since the sperm samples in AID cycles were from the sperm bank, the donor can be regarded as not affected by the vaccine. Therefore, the AID cycle is a particularly effective model for studying the effect of vaccines on female fertility by excluding any interference of male vaccination on reproductive outcomes. Although our data showed a 25% reduction in ongoing pregnancy rates in the vaccine exposure group compared to the control group during the AID cycle, there was no significant difference. The small sample size in this group limited the statistical efficacy of the AID cycle and was unable to provide conclusive results with the existing data set. However, considering the unique features of the AID cycle compared with the AIH cycle, relevant clinical data are still listed for researchers' reference.

There are several limitations of this study. Firstly, the sample size was too small to allow an in-depth stratified analysis of vaccination status with a convincing conclusion, and this will be rectified in future studies. Secondly, retrospective studies are subject to bias, and although variables linked to IUI success in prior studies were included in the GEE analysis, it was impossible to identify and control for all confounding variables. Thirdly, the participants in the present study were women undergoing ART treatments and do not represent those undergoing natural conception. Finally, due to the lack of data on the timing of male vaccination, it was impossible to judge whether the husband had been vaccinated before IUI treatment, which may lead to inaccurate results even after adjusting for the vaccination status of male partner in AIH cycles. However, these defects were partly compensated by data from AID cycles because it was known that the semen from the sperm bank had no vaccine exposure.

Conclusions

This study provides a unique contribution to the effect of inactivated COVID-19 vaccine on female ability to conceive under a relatively rigorous design, including choosing IUI cycles as the fertility model, strict inclusion and exclusion criteria, and the application of GEE adjusted for confounding covariates based on an extensive data set of baseline and in-cycle characteristics. The present study shows no negative effects on female fertility in IUI cycles following exposure to the inactivated COVID-19 vaccine. These findings indirectly reflect the safety of inactivated COVID-19 vaccine toward reproductive health and add an extra step toward reducing vaccine hesitancy (31) among people planning to conceive.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of the Third Affiliated Hospital of Guangzhou Medical University. Written informed consent for participation was not required for this study in accordance with the National Legislation and the Institutional requirements.

Author contributions

ZX designed the study, carried out data analysis, and drafted the manuscript. YW and YL participated in data analysis, collected all relevant data, and assisted in study conception and design. JL and HL conceived the study, participated in its design and coordination, and helped draft the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Decrease in COVID-19 adverse outcomes in adults during the Delta and Omicron SARS-CoV-2 waves, after vaccination in Mexico

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Mexico, one of the countries severely affected by COVID-19, accumulated more than 5. 1 all-cause excess deaths/1,000 inhabitants and 2.5 COVID-19 confirmed deaths/1,000 inhabitants, in 2 years. In this scenario of high SARS-CoV-2 circulation, we analyzed the effectiveness of the country's vaccination strategy that used 7 different vaccines from around the world, and focused on vaccinating the oldest population first. We analyzed the national dataset published by Mexican health authorities, as a retrospective cohort, separating cases, hospitalizations, deaths and excess deaths by wave and age group. We explored if the vaccination strategy was effective to limit severe COVID-19 during the active outbreaks caused by Delta and Omicron variants. Vaccination of the eldest third of the population reduced COVID-19 hospitalizations, deaths and excess deaths by 46–55% in the third wave driven by Delta SARS-CoV-2. These adverse outcomes dropped 74–85% by the fourth wave driven by Omicron, when all adults had access to vaccines. Vaccine access for the pregnant resulted in 85–90% decrease in COVID-19 fatalities in pregnant individuals and 80% decrease in infants 0 years old by the Omicron wave. In contrast, in the rest of the pediatric population that did not access vaccination before the period analyzed, COVID-19 hospitalizations increased >40% during the Delta and Omicron waves. Our analysis suggests that the vaccination strategy in Mexico has been successful to limit population mortality and decrease severe COVID-19, but children in Mexico still need access to SARS-CoV-2 vaccines to limit severe COVID-19, in particular those 1–4 years old.

KEYWORDS

COVID-19 in children, COVID-19 in pregnancy, COVID-19 vaccination, Omicron sub-lineages, SARS-CoV-2 Delta VOC, excess mortality, COVID-19 epidemic in Mexico

Introduction

SARS-CoV-2 was first detected in Mexico in February 2020 (1, 2). A large national epidemic ensued, with over 325,000 deaths confirmed from COVID-19 (2) and 662,000 all-cause excess deaths (3) in 2 years. In 2020–2021, Mexico ranked in the top-5 countries in excess deaths (4, 5) and in the top-30 in COVID-19 mortality (6), with 5.1 all-cause excess deaths and 2.5 COVID-19 confirmed deaths in every 1,000 inhabitants, similar to other severely hit countries like the USA, Brazil, Peru or Russia (1, 4–6).

Mexico's response to the pandemic in 2020 focused on organizing public medical attention for severe COVID-19 (1, 7), and less on infection detection or containment; while in 2021–2022 the focus was on anti-SARS-CoV-2 vaccination (8, 9). The country has endured five well-defined incidence waves, peaking approximately every 6 months. The first two waves happened before vaccination; the third wave presented in parallel to growing vaccination and to the colonization of the Delta SARS-CoV-2 variant (B.1.617.2), while the fourth wave begun with >70% of adults fully vaccinated (primary series), and correlated with the spread of Omicron subvariants BA.1 and BA.2 (10, 11). A fifth wave is developing at the time of writing, with presence of subvariants BA.4 and BA.5 (10).

Mexico began anti-SARS-CoV-2 vaccination on December, 2020, for healthcare workers and on February, 2021 for the adult population in age-groups from older to younger (8, 9). Up to April 2021, vaccination was only open to adults 60+ (11.5% of the population) and on May, June, July and August 2021, it opened for age groups 50–59, 40–49, 30–39 and 18–29 yo, which represent 10, 13, 15, and 20% of the population, respectively. Vaccination opened in May 2021 for pregnant people, in October 2021 for children 12–17 yo with severe comorbidities, in December 2021 for all children 15–17 yo and in May 2022 for those 12–14 yo; while children 5–11 yo (17% of population) will be vaccinated during July-September 2022, and children under 5 yo (8% of population) remain ineligible.

Mexico has relied on 7 COVID-19 vaccines from multiple developers: ChAdOx1 (AZD1222) from Oxford/Astra Zeneca (43.8%), BNT162b2 from Pfizer/BioNTech (25.5%), CoronaVac from Sinovac (9.9%), Gam-COVID-Vac/Sputnik V from Gamaleya Research Institute (9.9%), Ad5-nCoV from CanSino Biologics (7.0%), mRNA-1273 from Moderna (3.1%) and Ad26.COV2.S from J&J/Janssen (0.7%) (% of the initial 200 million doses received in the country until April 2022) (12). Full vaccination consisted of a single dose J&J/Janssen or CanSino, or of two doses of the rest of the vaccines, administered 4–6 weeks apart for Pfizer and Coronavac, and 9–12 weeks apart for Astra Zeneca and Sputnik V. Vaccines have been allocated as they arrive, without a strategy to serve age groups with a specific vaccine subtype, except for children <18 yo, all of whom have received BNT162b2 (Pfizer/BioNTech). Teachers and school personnel were offered immunization ahead of their age-group, in April-May 2021 with the single dose CanSino vaccine, followed by an mRNA-1273 Moderna booster 8 months later (offered on January 2022). All immunizations have been voluntary and offered at no cost to the population and no vaccine mandates are in place. Booster doses became available for adults, 5 months or more after their primary vaccination, with ChAdOx1 (Oxford/AstraZeneca, >85% of boosters administered), Sputnik V (Gamaleya) or Cansino; starting on December 2021 for those 60+, as the Omicron variant was identified in the country, and subsequently opening in January, February and March 2022, for 50–59 yo, 30–49 yo and 18+, respectively. Likely, most boosters have been heterologous, but we found no reports that specify this.

Mexico represents an interesting middle-income scenario to explore if a multi-vaccine strategy focused on immunizing and boosting the older population first, was effective to limit COVID-19 mortality during the active outbreaks caused by the Delta and Omicron variants. Here we analyzed the complete national data for the first four COVID-19 waves and correlated with the progress of anti-SARS-CoV-2 vaccination to describe how vaccination changed events per age group (cases, hospitalizations, deaths and excess deaths) during the COVID-19 epidemic in Mexico.

Methods

Ethics

The protocol describing this work was approved by IMSS ethics committee (registration IMSS-R-2021-2106-001). In all datasets patient identity was absent.

Information sources

National COVID-19 dataset

COVID-19 cases, hospitalizations and deaths were obtained from the open-access Mexican dataset updated regularly by health authorities, available at (13). The dataset includes all symptomatic COVID-19 cases, their characteristics, and outcomes, since outbreak start. It is fed nationwide by all hospital centers, public and private, and it is the source of the official COVID-19 data provided by Mexican health authorities for international surveillance. Variable descriptors for the dataset are in an auxiliary file provided by the health authority (14) and we used those definitions without modification.

We analyzed the first four COVID-19 waves, defined as cases that started symptoms up to April 30, 2022, since an increase in COVID-19 cases (2) and test positivity (15) started around May 1, 2022, marking the beginning of a fifth COVID-19 wave. Individuals with symptoms, without a SARS-CoV-2 test result, were excluded. Individuals with symptoms that tested negative to SARS-CoV-2, were not included as COVID-19 cases but were used in test positivity calculations and as a reference negative population in Figure 4D. Individuals may appear more than once in the dataset if they had COVID-19 symptoms more than once during the 27 months of study. Reinfections or vaccination status of individuals are not marked in the national data set.

Final collection of the national dataset, was conducted on July 10, 2022 (16,922,254 entries), thus patient outcomes are known until that date (10 weeks after the last date of symptom onset). With the criteria described, we included 5,757,714 COVID-19 cases (52.4% females), from Feb 2020 to April 2022, that were confirmed by SARS-CoV-2 RT-PCR (35.1%), antigen test (57.0%), both (2.1%), or clinical/epidemiological evidence (5.8%). These cases generated 681,899 hospitalizations and resulted in 325,433 deaths (38.5% females). In the same time interval, 9,442,983 individuals (54.4% females), had symptoms but tested negative.

Excess mortality

All cause excess deaths were obtained from the official report by Mexican health authorities published at (3). Final data collection was on June 27, 2022 and included the dataset updated by health authorities on May 29, 2022 that covered data until epidemiological week 13 of 2022. Excess mortality was calculated by week as the difference between total deaths and expected deaths. For expected deaths, we used the 90 percentile and a model proposed by health authorities, both reported at (3). Both calculations were similar and included in graphs.

Analysis

The national dataset was analyzed as a retrospective cohort. COVID-19 cases, hospitalizations and deaths were organized by date of symptom onset, computed per week and separated into age groups 0–19, 20–39, 40–59 and 60+ yo in R (16)/R Studio (17) with script "DatesExtractionWorking.R" that can be found at (18). No modification was operated on the database other than filtering. A computer with at least 32 Gb of RAM is required for this step. The script above is dependent on R libraries dplyr (19) and tidyverse (20). Briefly, data was first separated according to diagnosis, then by date of death, or its absence. Then, groups were filtered by age and, counts per group were added by week within the periods selected, based on week of symptom onset.

Peaks in epidemic curves were detected automatically with software Magicplot, by fitting to gaussian and verified manually (see Supplementary material for details).

Wave dates were: (1) Feb-16-2020–Sept-19-2020 (epidemiological weeks 7–37 of 2020); (2) Sept-20-2020–May-15-2021 (epi weeks 38 of 2020 to 19 of 2021); (3) May-16-2021–Nov-20-2021 (epi weeks 20-46 of 2021); (4) Nov-21-2021–Apr-30-2022 (epi weeks 47 of 2021 to 17 of 2022). Dates of start of each wave were determined by finding the point of inflection, that is the week when numbers of cases and hospitalizations increased with respect to the previous week, after 10+ weeks of descent.

The following were calculated per week: percent of cases that were hospitalized; measured case fatality rate (CFR) which was the % of identified cases that died; CFR of the hospitalized; test positivity, which was the % of positive tests from the total conducted and was verified against data per week published by health authorities (15). Vaccination coverage was calculated as (number of people vaccinated*100)/(population). Vaccines applied and people vaccinated with one or more doses, were as reported by health authorities and verified in the COVID-19 OWID data set (21), per date. Population estimates per age group to calculate rates, were obtained from populationpyramid.net (22) for 2021 (total Mexican population 130,262,220) and verified against reports by the Mexican government (23).

Results

Four COVID-19 waves in two years of epidemic in Mexico: National data

In 27 months (Feb 2020–April 2022), Mexico experienced four COVID-19 waves, with cases, hospitalizations, deaths and excess deaths peaking every 6 months, in summer and winter (Figure 1A). Up to April 30, 2022, Mexico identified officially almost 5.8 million cumulative COVID-19 cases, but high seroprevalence (24, 25), high test-positivity (Figure 1B) and high case-fatality (Figure 4A) suggest cases were under detected. Each wave happened under unique conditions, including the predominance of a particular SARS-CoV-2 variant, different mobility restrictions (more intense in the first surges and

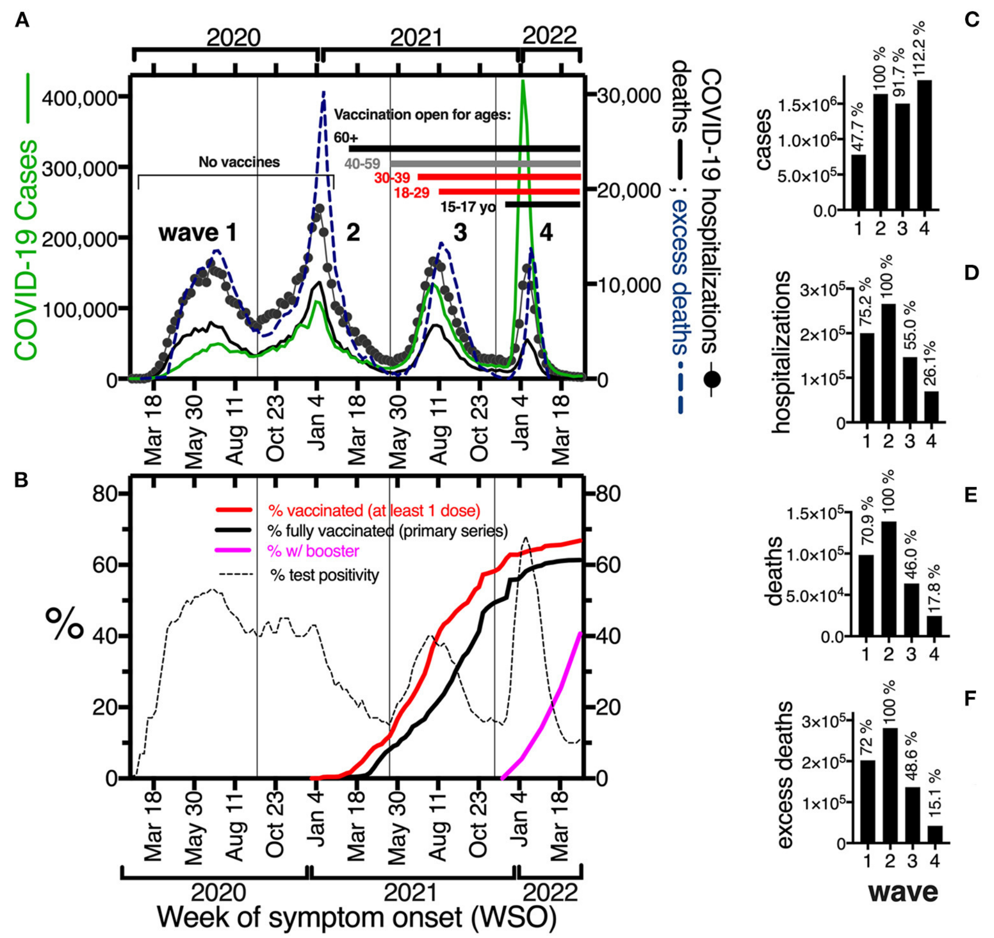

FIGURE 1
(A) Epidemic curve of COVID-19 cases (green line, left y-axis), COVID-19 hospitalizations (line with black circles) and deaths (bold black line); and all cause-excess deaths (blue discontinuous line) in the right y-axis, during the first 27 months of epidemic (Feb 2020–April 2022) in Mexico, per week of symptom onset, including all ages. **(B)** Percent test positivity for SARS-CoV-2 (discontinuous line), and percent population vaccinated with at least one dose (red line), a complete primary series (bold black line) or a complete primary series plus a booster (pink line), in the same period as in **(A)**. Vertical lines separate waves. **(C–F)** Accumulated COVID-19 cases, hospitalizations, deaths and all cause-excess deaths per wave. The percentages on top of bars were calculated using the second wave as 100%.

decreasing gradually) and likely different case-detection levels, with the lowest detection in the first wave as fewer tests were available. More important, no vaccination was available in the first two waves, and vaccination coverage grew during waves 3 and 4 (Figure 1B). Fifty million cumulative vaccine doses were administered by July 2021, 100 million by September 2021 and 200 million by April 30, 2022, when 90% of adults 18+ had at least one dose of a SARS-CoV-2 vaccine, while 59% had complete primary vaccination plus a booster. Vaccination coverage in children lagged, and around 40% of children 12–17 yo received at least one vaccine dose by April 30, 2022, while individuals 5–11 became eligible, only after the period analyzed.

To evaluate the magnitude of the SARS-CoV-2 surges and discuss the effect of vaccination, we compared the counts in each wave against the second wave, which had the most adverse outcomes (Figures 1C–F). Despite different durations (34, 27 and 23 weeks, respectively Supplementary Table 1), the last 3 waves had a similar number of detected cases, around 1.6 million; while the first wave had half as many cases (Figure 1C), related in part to less testing. In contrast, hospitalizations, deaths and excess deaths declined in waves 3 and 4 (Figures 1D–F), after vaccination.

Age-group analysis of the COVID-19 waves and the population effect of vaccination

A clearer picture of the effect of vaccination emerges when separating the analysis per age group (Figure 2). In the first two waves, older age groups had a higher case rate, while in the third wave, adult age groups inverted their positions, with lower

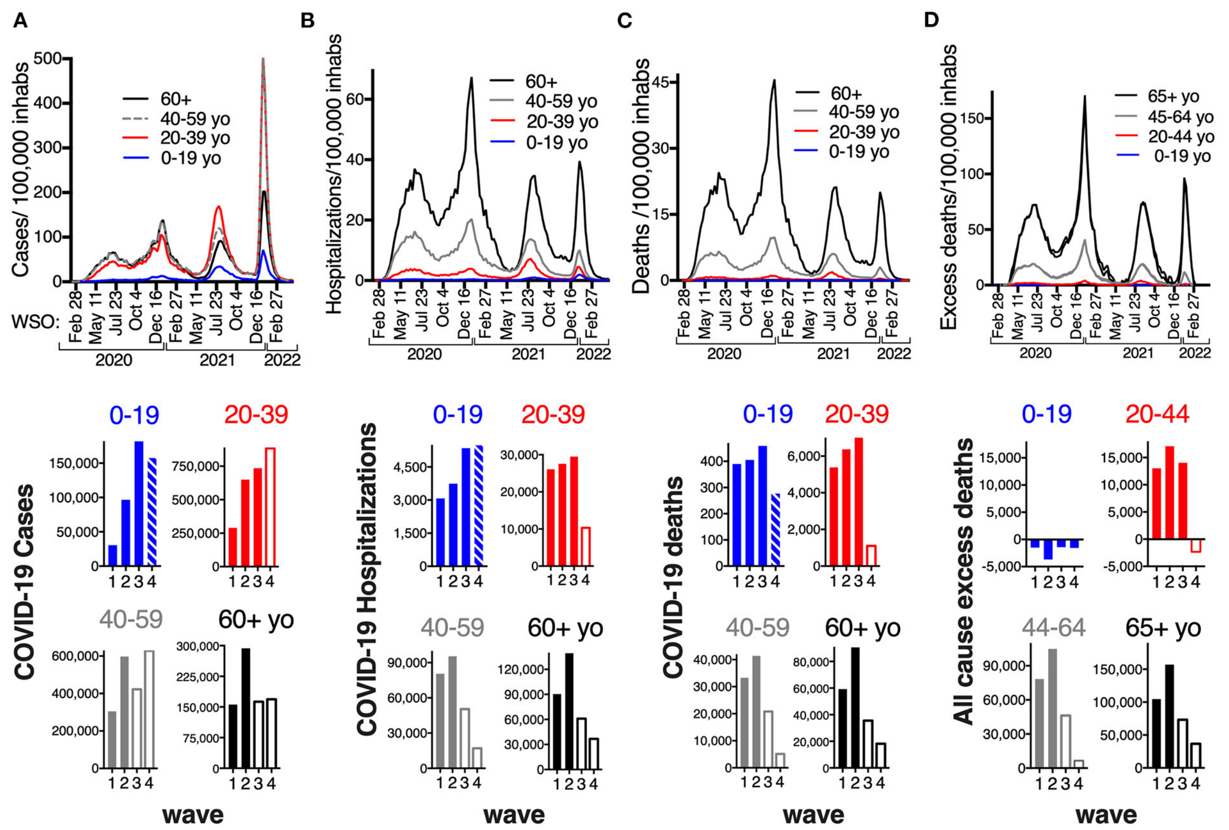

FIGURE 2
Rates per 100,000 inhabitants of COVID-19 cases **(A)**, hospitalizations **(B)**, deaths **(C)** and all-cause excess deaths **(D)**, per epidemiological week of symptom onset (WSO), per age group (0–19 yo blue; 20–39 yo red; 40–59 yo gray; 60+ black), in the first 27 months of epidemic in Mexico (Feb 2020–April 2022). Bottom: Accumulated cases hospitalizations, deaths and all cause excess deaths, per wave per age group. Bars are empty when the age-group had access to COVID-19 vaccination. The last bar in age group 0–19 represents that 15–19 yo had access to vaccination but not the rest of the children, 15–17 yo accessed first doses in December 2021; while 18–19 yo were vaccinated with the adults beginning on late August 2021, thus had the chance to complete a primary series before the fourth (Omicron) wave.

case rate in those that accessed vaccination first (Figure 2A). The older population in Mexico (60+) had the most adverse COVID-19 outcomes in all waves (Figures 2B,C), accounting for 48% COVID-19 hospitalizations and 62.5% COVID-19 deaths in the period analyzed (Supplementary Table 1). This age group was the only to access a full-vaccination primary series before the third wave (Delta) (estimated coverage 76% of the age group by the end of May 2021); while 40–59 yo were offered vaccination as the third wave developed (May-August 2021). Vaccination of just those age groups (the eldest 34% of the population) importantly reduced severe COVID-19, halving hospitalizations, deaths and excess deaths in the third wave relative to the second (Figures 1D–F), despite similar numbers of identified cases (Figure 1B).

By December 2021, when the Omicron variant colonized the country, all adult groups in Mexico had accessed vaccines and those 60+ had accessed a booster or third dose, 5–8 months after their primary series. Even with vaccine coverage >70% in adult groups, and booster coverage 50% for the 60+, a large fourth wave developed early in 2022, driven by fast Omicron (BA.1, BA.2) transmission, but with fewer adverse outcomes. Hospitalizations, deaths and excess deaths were much lower than in previous waves (26, 17, and 15% of the second wave, respectively, Figures 1D–F).

The reduction in severe outcomes in waves 3 and 4 came from the age groups that accessed vaccination (Figures 2B–D, bottom; Supplementary Table 1). In wave 3, the adult groups that had accessed vaccination (40–59 yo and 60+), had less than half of the hospitalizations and deaths relative to wave 2. In contrast, adults under 40 yo accessed first vaccine doses in the second half of the third wave, so they faced wave 3 with little to no protection from vaccines and actually had more COVID-19 hospitalizations (107%) and deaths (110%), and almost as many excess deaths (82%) as in the second wave. This group (20–39 yo) only decreased their hospitalizations and fatalities in the fourth wave, after their complete vaccination, and their excess deaths ceased (Figures 2B–D bottom).

Likewise, most children under 18 yo did not access full vaccination in Mexico until 2022, so the age group 0–19 also had more hospitalizations (143%) and deaths (113%) in the third wave (Delta) than in the second, and this pattern persisted for the fourth wave, which had 146% hospitalizations relative to the second (Figure 2B, bottom, Supplementary Table 1). First dose vaccination opened for 15–17 yo during the fourth wave, while younger children remained ineligible, so most children faced the Omicron wave without complete vaccination. However, less COVID-19 fatalities happened in 0–19 yo during the Omicron wave, than in previous waves (68.4% of the second wave, Figure 2C, bottom), related to: (1) less infant (0 yo) deaths with Omicron (Figures 3D,E); (2) less deaths in 15-19 yo (Figure 3C), and in particular in 18–19 yo (Figure 3D) that accessed complete vaccination as adults, shortly before the Omicron wave; (3) shorter wave duration. Pediatric age groups 0–14 and 15–19 (with and without vaccine access), had similar low hospitalization and death rates from COVID-19 in the first two waves, which increased in waves 3 and 4 (Figures 3B,C). The increase was larger for 15–19 yo in the third wave, but in the fourth wave, hospitalizations and fatalities were again similar between these two groups, perhaps related to the access of 15–19 yo to vaccinations shortly before the fourth wave.

In the period analyzed, there were almost half a million detected cases in children 0–19 yo, that resulted in 17,644 hospitalizations and 1,531 COVID-19 deaths (45.2% females) Of these deaths 635 (41.5%) were 0–4 yo and 748 (48.9%) 5–18 yo. Ages 0 and 1 yo accumulated the most deaths (Figure 3D) and most of the children that died from COVID were previously healthy (no comorbidities reported in 62.5% of those 0–4 yo and in 53.2% of 0–19 yo that died). COVID-19 deaths distributed similarly through pediatric ages during the first three waves, whereas in wave 4 (Omicron), there was a decrease in deaths around age 15, more prominent in ages 18+, consistent with vaccination access (Figure 3E).

Additionally, in wave 4 there was a large decrease in deaths in infants 0 yo, but not in those 1 and 2 yo who had more deaths in the fourth than in previous waves (Figures 3D,E). The decrease in infant (0 yo) fatalities could correspond to the vaccination of pregnant people that started in May 2021, and that correlated with an important decrease in COVID-19 deaths in the pregnant by the fourth wave (Figure 3F). In the period analyzed, there were 47,671 COVID-19 cases identified in pregnant people, that resulted in 7,366 hospitalizations and 377 COVID-19 deaths (CFR 0.79%; 65.5% of deaths without previous comorbidity), 50% of them during wave 3, but decreasing for wave 4, which had only 16 deaths (4.2% of total). The CFR for the pregnant was higher than for non-pregnant females of the same age (Figure 3G), resulting in a Relative Risk of death = 1.2 for being pregnant (95% CI 1.08–1.32), higher at ages 20–30 yo (Supplementary Table 2). Mortality rates in the pregnant were similar than in non-pregnant females, ranging from 6 to 100 deaths/100,000 pregnancies, and highly dependent on maternal age (Figure 3H; Supplementary Table 2).

Despite being the last population group to access vaccines, no excess mortality has been identified in children in Mexico (Figure 2D), and their population rates of hospitalization and death from COVID-19 remain lower than in adult groups (Figures 2B,C), consistent with the severity gradient that has been identified for COVID-19 with age. However, children were the only age group that did not show a drop in case fatality rate (CFR) (Figure 4A) or in the % of cases within the age group requiring hospitalization, during the Omicron wave (Figure 4B). In fact, the % of pediatric cases hospitalized grew with Omicron, surpassing the % of cases that required hospitalization in adult age-groups 20–29 and 40–59 yo, for the first time in the epidemic (Figure 4B).

The age distribution of the national COVID-19 events is driven by the population pyramid and by the age severity gradient of the disease, thus it changed only slightly before and after vaccination (Figure 4D). The curve of individuals that had symptoms but tested negative, showed no change with vaccination, while the peak of cases positive to SARS-CoV-2 switched to younger ages after vaccination and overlapped with that of individuals that tested negative (Figure 4D). After vaccination, the frequency of hospitalizations and deaths decreased at ages 40–80 and increased slightly at younger ages, again correlating with latter vaccination access of the younger half of the population. During the fourth wave, when all adults had accessed vaccination, the age distribution of hospitalizations and deaths shifted toward older ages (Figures 4E,F). However, hospitalizations in the fourth wave retained a component from ages below 35 yo, perhaps related to lower coverage of primary vaccination or boosters in the younger adults. An important increase in the frequency of hospitalizations in 0–4 yo is also seen in the fourth wave (Figure 4E). The curve of deaths in the fourth wave does not have those young-age components (Figure 4F), suggesting that most of the hospitalizations in the young result in improvement. Accordingly, the CFR of young hospitalized cases (0–19 and 20–39), remained lower than for older groups, across the four waves (Figure 4C).

Discussion

Mexico was one of the countries most affected by COVID-19 in 2020–2021 (1, 4, 5), with substantial fatalities and excess mortality. In 2020 and 2021, heart disease and COVID-19 were the first causes of death in Mexico with a narrow margin between them (26). Vaccination changed this trend and a clear decrease in COVID-19 deaths and hospitalizations is evident starting on the third wave driven by Delta SARS-CoV-2 in mid-2021, when vaccine access for the eldest third of the population resulted in a 50% decrease in COVID-19 deaths and hospitalizations. Further

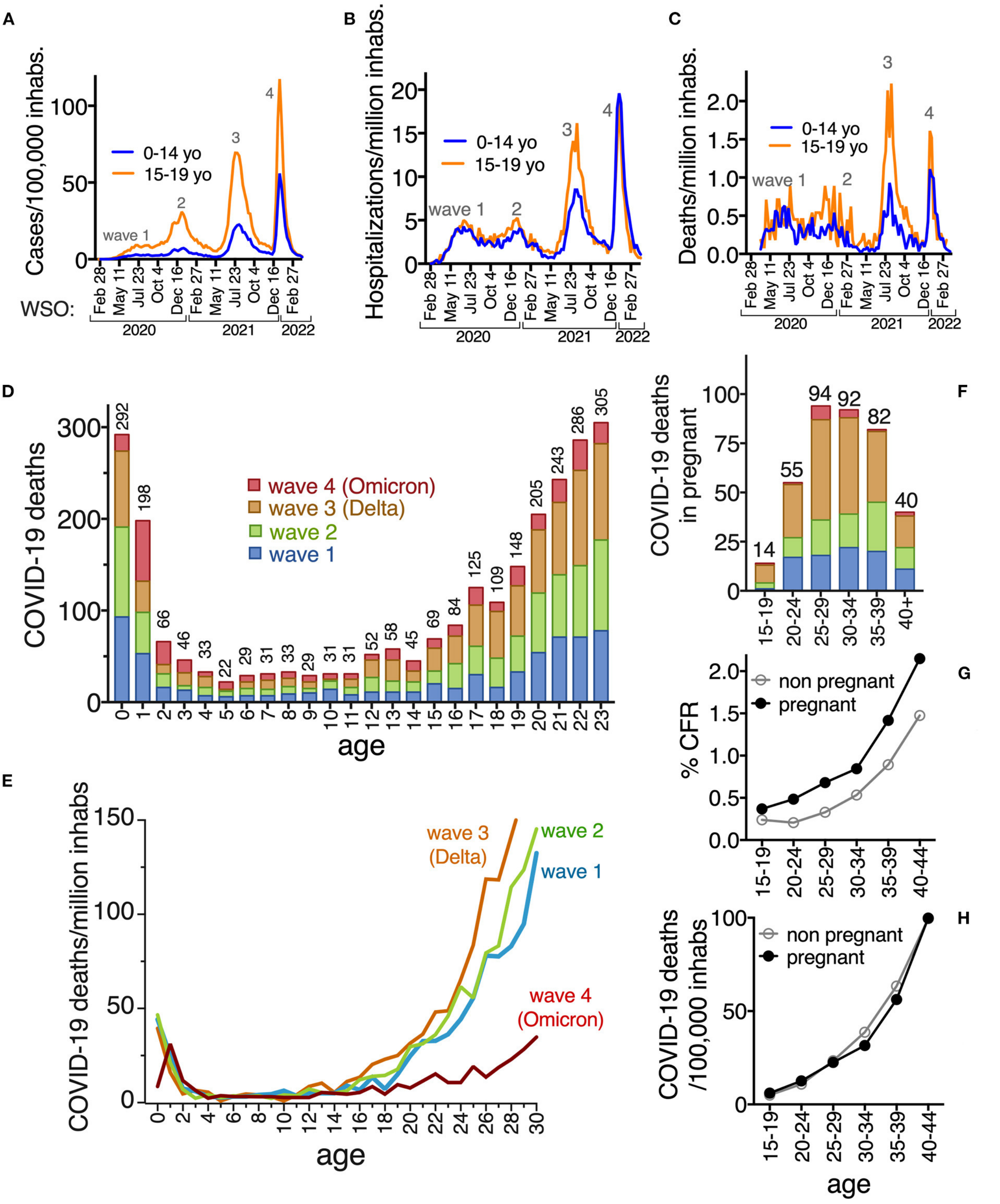

FIGURE 3
Rates of COVID-19 cases per 100,000 inhabitants **(A)**, hospitalizations **(B)** and deaths **(C)** per million inhabitants, in children 0–14 yo (blue line) that were ineligible for COVID-19 vaccinations in the period analyzed, compared to those 15–19 yo (orange line) that had access to vaccines before or during the fourth wave. **(D)** COVID-19 deaths identified in children, teens and young adults, per age, per wave and **(E)** death rates per million inhabitants comparing waves. In **(D)** the graph shows up to age 23 to appreciate that the cumulative number of deaths in infants is similar to those in 22 and 23 yo. In **(E)** the decrease in deaths in infants 0 yo during the fourth wave is obvious, and more ages were graphed, to show the decrease in fatalities after age 18 during the fourth wave. **(F)** COVID-19 deaths identified in pregnant people, by age-group and wave; **(G)** % Case fatality rate (CFR) and **(H)** deaths/100,000 inhabs in pregnant and non-pregnant. The same color code is used per wave in **(D–F)**. Numbers on top of bars are the total of deaths confirmed as COVID-19, reported in the national dataset at each age, up to April 2022 (including all four waves analyzed).

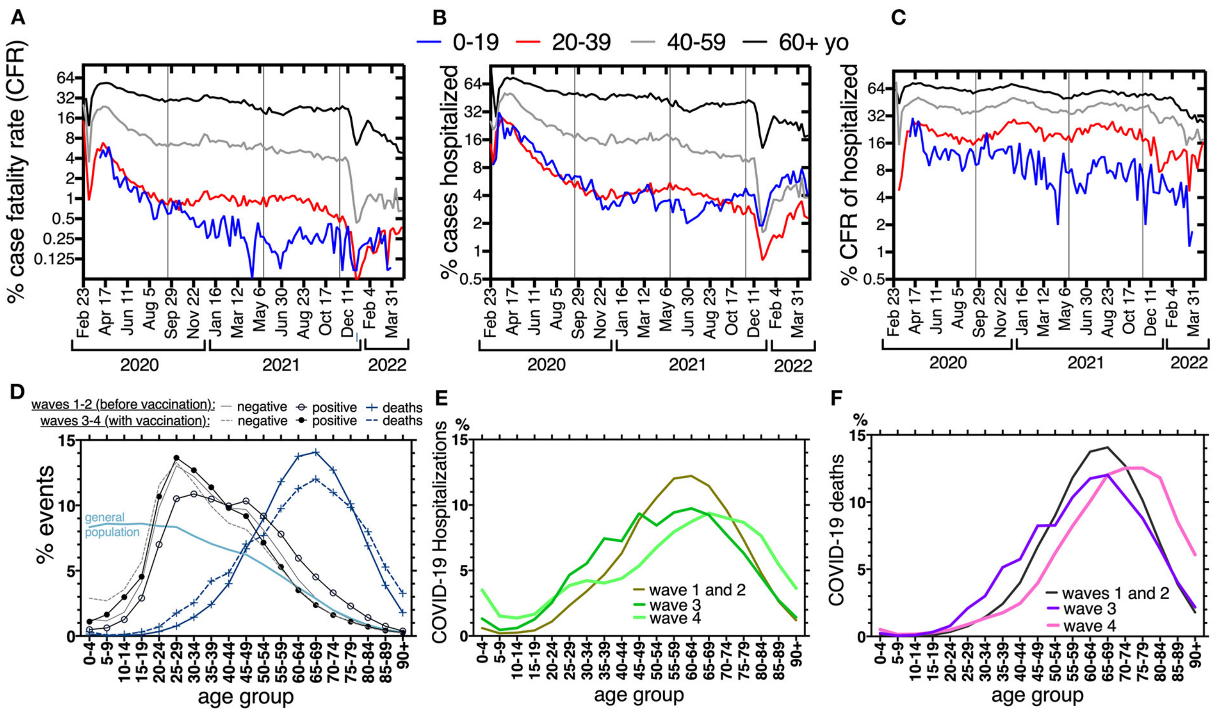

FIGURE 4
(A) Percent case fatality rate (CFR), **(B)** percent cases that were hospitalized and **(C)** percent case fatality rate of those hospitalized, per week of symptom onset, across the first four waves (Feb-2020–Apr-2022), separated by age group: 0–19 yo blue lines, 20–39 yo red lines, 40–59 yo gray lines, 60+ black lines. In **(A–C)** y-axes are log 2, to favor curve display, and horizontal lines separate the waves, like in Figures 1A,B. **(D–F)** are the percent events separated into 5-year age groups, to appreciate age distribution across the population and waves. Waves 1 and 2, before vaccines, had a similar distribution and thus are displayed together. In **(D)**, waves 3 and 4 (when vaccination of adults happened) are displayed together. In **(D)**, events are: individuals with symptoms that tested negative or positive to SARS-CoV-2 and those that died from confirmed COVID-19. The pale blue line represents the age-distribution of the population pyramid in Mexico 2021 ("general population"), for reference. In **(E,F)** only COVID-19 hospitalizations and deaths are displayed, respectively. Waves 3 and 4 are separated to appreciate the differences in distribution as vaccination progressed.

decrease was observed in 2022 during the Omicron wave when all adults had accessed vaccines, with 82% decrease in COVID-19 deaths and 85% in excess mortality compared to the second wave, despite a similar number of cases detected.

As of July 2022, >90% of the 18+, >60% of 12–17 yo and 25% of those 5 to 11 yo have received at least one dose of COVID-19 vaccines. Additionally, serology in the Mexican population suggested extensive SARS-CoV-2 circulation since 2020, in all age groups (24, 25). Thus, the population has been immunized both by vaccination and by infection/reinfection. As in other parts of the world, this immunization hasn't been enough yet to prevent further waves of SARS-CoV-2, as new variants arise. Yet a clear pattern of decreased adverse outcomes is noticeable as each age group accessed vaccination, suggesting that vaccination had a strong protective effect against hospitalization and death on the population, on top of the immunity by natural infection.

As a middle-income country, vaccination of the Mexican population has been a challenge amid international competition for vaccines and 7 different vaccines have been used, as described in the introduction. Our analysis suggests that this strategy to use vaccines from different developers, as available, has been successful to limit mortality. All of these vaccines were based on the ancestral SARS-CoV-2 but show good population effectiveness to decrease severe forms of the disease from all the variants so far, and despite the fact that only 60–68% of the vaccinated adults have received a booster, most with vaccines that do not use mRNA technology.

For 13 weeks starting on May 1, 2022, Mexico has been undergoing a fifth COVID-19 wave that seems to have reached its peak, adding almost one million more cases, but <20,000 hospitalizations (43.95% in 60+) and <2,000 deaths (76.6% in 60+), thus projecting as the least lethal wave so far, although complete data and appropriate time to discern patient outcomes is needed to analyze this accurately. The epidemiological behavior of the fifth wave suggests that the protective effect of immunization prevails.

Despite good vaccination coverage and access to boosters, the eldest individuals continue to accumulate the most adverse outcomes and are at greater risk of adverse outcomes than younger population. Thus, the most labile individuals should be alerted to limit their community exposure during high SARS-CoV-2 circulation. A limitation of our analysis is that we cannot distinguish if the individuals that died from COVID-19 were vaccinated and further studies are needed to evaluate the real-world effectiveness of the vaccines used.

At the other end of the age spectrum, the pediatric population in Mexico (except for infants 0 yo) has not yet seen a clear decrease in COVID-19 adverse outcomes, likely because their vaccination has lagged. Pediatric COVID-19 hospitalizations in Mexico almost doubled from 2020 to 2021 from 4,895 to 7,905 and the trend hasn't changed yet for 2022 which in 7 months accumulates 7,779 COVID-19 hospitalizations. Mexico has 44.4 million inhabitants 0–19 yo and 1,531 COVID-19 deaths at these ages during the first four waves, plus 46 deaths in children 0–19 added so far in the fifth wave (18 of which were in 0–4 yo). This results in a cumulative death rate of 3.6/100,000 inhabs 0–19 yo, which is roughly double that of the USA, that has 1.7 deaths/100,000 inhabs 0–18 yo [1,325 COVID-19 deaths (27) and 78 million inhabs 0–18 (28)]. Death rate from COVID-19 is higher in population 0–4 yo, currently ineligible for vaccination in Mexico, which accumulates 6 deaths/100,000 inhabs in Mexico vs. 2.4/100,000 in the USA (27). These pediatric COVID-19 death rates are orders of magnitude lower than in adults in Mexico, who have accumulated 48.8, 338.2 and 1,363.7 deaths/100,000 inhabs 20–39, 40–59 and 60+, respectively (Supplementary Table 1). Yet, COVID-19 figures in the first ten pediatric death causes in Mexico, although at lower rates than causes like accidents, cancer, congenital malformation, and neurological disease. Analyses to discern if severe respiratory infections by other pathogens persisted during the COVID-19 epidemic are lacking in Mexico. Also, MIS-C (Multisystem Inflammatory Syndrome in Children) and long COVID-19 haven't been analyzed in the Mexican population and are not registered in the national COVID-19 data base, that reports only the result of acute infections. Our analysis further suggests that vaccination of pregnant people and young people of reproductive age, resulted in a decrease of 85–90% in deaths in the pregnant and 80% in infants 0 yo, by the fourth wave.

All in-person education closed in Mexico for 17 months from March/21/2020 to August/29/2021, and its impact on the epidemic hasn't been measured. Children had less hospitalizations and deaths in the first two waves, when schools were closed, but the increase in pediatric adverse outcomes in wave 3 started months before school re-openings, when the Delta wave grew nationally (Figures 3A–C), so it seemed to respond more to community circulation of the virus than to school re-openings.

Several reports suggest that initial Omicron subvariants were clinically less severe than previous variants (29–34). In Mexico, the progress in vaccination coverage could explain the decrease in severe outcomes during the Omicron wave, and the dataset analyzed doesn't contain individual information on vaccination to correctly explore Omicron severity. However, age groups 1–14 yo without access to complete vaccination before Omicron circulation, did not experience a decrease in COVID-19 deaths during the Omicron wave. In fact, 1 and 2 yo had 50% more fatalities than in previous waves arguing against Omicron mildness. As new waves of COVID-19 sweep the country, the unvaccinated population will be at risk of severe COVID-19, thus vaccine access for all the population is crucial to prevent hospitalizations and deaths, in particular in children.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found below: https://www.gob.mx/salud/documentos/datos-abiertos-152127.

Ethics statement

The studies involving human participants were reviewed and approved by Instituto Mexicano del Seguro Social 2106. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

PC-H: conceptualization. PC-H, LD-R, JA-A, and AM-O: methodology. LD-R and IS-T: data curation. LD-R, PC-H, and IS-T: formal analysis. PC-H, GS-L, IS-T, JA-A, and FS-J: investigation. PC-H and LD-R: writing—original draft preparation. PC-H, LD-R, FS-J, RP, and GS-L: writing—review and editing. PC-H and LD-R: supervision. All authors have read and agreed to the published version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.1010256/full#supplementary-material

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Targeting COVID-19 vaccine hesitancy among nurses in Shanghai: A latent profile analysis

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Objectives: This study aims to clarify the profiles of the psychological antecedents of vaccine hesitancy among Shanghai nurses with a person-centered approach.

Methods: A population-based cross-sectional online survey was conducted on Shanghai nurses from July to August 2021 ($N = 1,928$). In the online survey, participants were asked to report their sociodemographic, the 5C vaccine hesitancy components, their knowledge level of COVID-19 vaccine and vaccination, and the COVID-19 vaccination uptake intention and attention to vaccine news. Latent profile analysis was used to reveal distinct profiles of vaccine hesitancy.

Results: The results revealed four profiles, including "believers" (68.9%; high confidence and collective responsibility), "free riders" (12.7%; similar characteristics to believers, except for a low collective responsibility), "middlemen" (14.6%; middle in all 5C constructs), and "contradictors" (3.7%; high in all 5C constructs). Compared to believers, middlemen were younger, more likely to be female, childless, less educated, held lower professional titles, had fewer years of nursing service, sometimes or never complied with recommended vaccinations, had satisfactory or poor self-assessed health status, had no work experience during the COVID-19 epidemic, and possessed greater levels of knowledge. Free riders were more likely to work in community health centers and have a lower degree than believers. Contradictors were more likely to work in community health centers, had junior college degrees or lower, and had no work experience during the COVID-19 epidemic than believers. From the highest to the lowest on vaccination intention and attention to vaccine news were believers, then free riders, contradictors, and finally middlemen.

Conclusion: This study could aid in the development of personalized vaccination strategies based on nurses' vaccine hesitancy profiles and predictors. In addition to vaccine believers, we identified other three profiles based on their 5C psychological antecedents, emphasizing the significance of establishing tailored vaccination campaigns. Further research into the prevalence of profile structure in other groups of healthcare workers is required.

KEYWORDS

COVID-19, COVID-19 vaccine, vaccine hesitancy, nurses, latent profile analysis

Introduction

The coronavirus disease 2019 (COVID-19) pandemic, which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), poses a significant threat to global public health. Since 2019, over 7.6% (576 million) of the global population has been infected with SARS-CoV-2, resulting in over 6 million deaths (1). SARS-CoV-2 infection imposes a substantial cost on human health, including musculoskeletal health complaints (2) and low back pain (3) during the acute phases, tachycardia (4), mental health disorders (5), and other sequelae during the post-acute phase. This has necessitated that health services face the dual task of managing with the increase in acute infections and providing care for COVID-19 survivors. Vaccination is a critical step in achieving COVID-19 herd immunity safely (6). The most recent research indicates that the COVID-19 vaccine is still effective in preventing moderate to severe illness and death brought on by modern variants of problems like Delta and Omicron (7, 8). However, the vaccine has not been well received and varies greatly around the world. For instance, in Central Asia, Eastern Europe, and Africa, vaccine hesitancy for the COVID-19 vaccine is more pronounced (9). Consequently, it is critical to advocate for initiatives to expand vaccination programs and increase vaccine uptake, particularly in nations and populations with low vaccine uptake and significant vaccine hesitancy (10).

Vaccine hesitancy, according to the Strategic Advisory Group of Experts (SAGE) Working Group, is defined as a delay in accepting or refusing vaccination despite the availability of vaccination services (11). More than 90% of the 194 member countries of WHO reported vaccine hesitancy during 2015–2017 (12). Vaccine hesitancy can result in lower vaccination rates, allowing for a recurrence of vaccine-preventable diseases, ultimately jeopardizing the effectiveness of immunization efforts (13). Due to the serious risks it poses to public health, the WHO listed vaccine hesitancy as one of the top 10 global health threats for 2019 (14).

Although the reasons for vaccine hesitancy differ by country and population, healthcare workers play a critical role in restoring public trust in vaccines (15) and are frequently viewed as the group with the most influence over people's vaccination (16). Nurses are not only responsible for vaccination but also spend a significant amount of time providing vaccine knowledge and health education to patients (17), and they play a critical role in promoting vaccination and reducing vaccine hesitancy in all populations (16–18). Nurses have the most direct contact with patients of any healthcare workers, and they are typically more directly confronted with the public's vaccine apprehension. However, recent studies have shown that nurses are even more hesitant about vaccines than other health professionals in Singapore (nurses: 7.4% vs. physicians: 0%) (19), Chicago (nurses: 27.0% vs. physicians or advanced practitioners: 1.7%) (20), Cape Town (nurses: 49.2% vs. physicians: 10.2%) (21), and Kuwait (nurses: 29.2% vs. physicians: 9.6%) (22). In fact, the issue of high vaccine hesitancy rates among nurses can no longer be ignored according to the data in Turkey (68.6%), Hong Kong (63%), and Israel (61%) (23–25). Vaccine hesitancy can have a negative impact on nurses' health and influence their vaccine recommendation behavior to patients, as well as enhance patients' fears and suspicions about vaccination (16).

As a complicated and dynamically shifting term, vaccine hesitancy challenges the traditional perspective of a simple dichotomization of an individual's immunization behavior into acceptance or refusal (26). Previous findings support the need for focused communication actions to address vaccine hesitancy among certain populations in various geographic cultures (27, 28). Recent studies have also classified people into subgroups depending on their vaccination beliefs, such as hesitant, confident, and trade-off clusters (29), or believers, skeptics, outsiders, contradictors, and middler profiles (30). In our study, we used the 5C model to understand the psychological antecedents of vaccination among nurses (31), which includes five dimensions of confidence (trust in vaccine efficacy, safety, and necessity, as well as in the system providing the vaccine), complacency (perception of low disease risk), constraints (perception of low vaccine availability, affordability, and accessibility), the calculation (participation in information search), and collective responsibility (willingness to vaccinate to protect others through herd immunity).

The local COVID-19 epidemic in Shanghai has been rapidly spreading since March 2022 (32), and nursing staff has become the backbone of epidemic prevention and control. Although substantial research has been carried out on vaccine hesitancy, no single study exists that adequately investigates vaccine hesitancy profiles among nurses in mainland China. Latent profile analysis (LPA) is a person-centered algorithm that will examine and identify unobserved heterogeneity in a population of nurses with vaccine hesitancy (33). In this quantitative study with an online cross-sectional survey among Shanghai nurses, we aimed to identify the following research questions: ① conduct a potential profile analysis of the psychological antecedents of nurses' vaccine hesitancy in Shanghai by LPA; ② investigate how different predictor variables predicate the profiles to which nurses belong; and ③ investigate how nurses in different profiles differ in their intentions to uptake the COVID-19 vaccine and attention to COVID-19 vaccine news.

Study methods

An exploratory, cross-sectional latent profile analysis (LPA) on vaccine hesitancy was conducted among nurses in Shanghai, China. Ethics approval was granted by the Institutional Review Board of the School of Public Health and Nursing at Shanghai Jiao Tong University (Reference number: SJUPN-202018).

Participants and data collection

Nurses from Shanghai's tertiary hospitals and community health centers (CHCs) participated in this study before the beginning of the COVID-19 booster vaccination program in China. Researchers contacted several hospitals and partnering community health centers affiliated with Shanghai Jiao Tong University School of Medicine, and nurses who volunteered to provide data for the study were recruited through advertisements. The pilot survey was first conducted in May 2021, before the formal conduct of the study. A purposive sample of 10 nurses from Shanghai was selected for the pre-survey of the study instrument. By recording the respondents' level of understanding of the content and format of the questionnaire and suggestions for modifications, we adjusted for specific situations to improve the accuracy and clarity of the questionnaire. From July to August 2021, nurses who were interested in participating in the study completed an online survey. No financial incentives are offered, and participation is entirely voluntary. We collected data *via* the Wenjuanxing website, and all participants were required to scan a QR code and provide informed consent on the survey platform before completing the questionnaire. Simplified Chinese is the language used in the questionnaire. A total of 2017 nurses completed the survey, and a final sample of 1928 was included for analysis, after deleting invalid responses. Inclusion criteria were that participants were (1) working nurses and (2) not nursing trainees or practical nurses.

Questionnaire composition

Demographic characteristics

Participants were requested to give sociodemographic information in the first section of our study, including age ($<$30 years, $\geq$30 years), sex (male, female), marital status (unmarried, married), no. of children (0, $\geq$1), workplace (tertiary hospital, community health center), education level (junior college degree or lower, bachelor degree or higher), professional title (nurse or senior nurse, supervisor or professor nurse), years of nursing service (0–10, $>$10), previous compliance with recommended vaccination (sometimes or never, always), chronic diseases (yes, no), self-assessment of health status (very good or good, satisfactory or fair), and working experience during COVID-19 epidemic (yes, no).

Psychological antecedents of vaccine hesitancy

A questionnaire based on the 5C scale was used to assess the psychological antecedents of vaccine hesitancy. The 5C scale consists of 15 items, including five subscales consisting of three items each, with subscales addressing each of the five psychological antecedents: confidence, complacency, constraint, calculation, and collective responsibility. For these items, the allowable response values range from 1 to 7 (1 = strongly disagree; 7 = strongly agree). For each subscale, average scores were generated; the higher the mean value, the more consistent the associated region is in that construct. The higher mean value of the construct indicates stronger consistency of that construct. While the original 5C scale was designed to assess vaccinations in general, we added prompts before participants completed the section to make it vaccine-specific and to focus on the COVID-19 vaccine specifically.

Since the original scale was developed in English, the Chinese version of the 5C scale was developed through cross-cultural adaptation and psychometric testing after gaining allowed approval from the original authors. The 5C scale was translated from English to Chinese using Brislin's translation approach (34). A further validation process was implemented by exploratory and confirmatory factor analysis (EFA and CFA). According to the results of the parallel study, five factors should be kept in the vaccine hesitancy measurement. KMO measure (0.888) and Bartlett's test of sphericity ($\chi^2 = 7729.676$, $P < 0.001$) further confirmed the decomposability and sufficiency of the data sample, according to EFA results. Except for the backward scoring item that was part of the collective responsibility subscale of the original scale entered into the constraint subscale, all items conformed to the original factor structure using the Oblimin rotation, with factor loadings ranging from 0.577 to 0.912. As a result, the lone reverse item was put into the constraint subscale, and the original scoring was used to create the modified Chinese 5C scale, which gave a 5-factor structure that explained 77.908 % of the total

TABLE 1 Demographic characteristics of the participating nursing staff ($N = 1,928$).

Characteristic	Number (%)
Age (years)	
20–30	909 (47.1%)
>30	1,019 (52.9%)
Sex	
Male	74 (3.8%)
Female	1,854 (96.2)
Marital status	
Unmarried	681 (35.3%)
Married	1,247 (64.7%)
No. of children	
0	904 (46.9%)
≥1	1,024 (53.1%)
Workplace	
Tertiary hospital	1,210 (62.8%)
Community health center	718 (37.2%)
Educational level	
Junior college degree or lower	608 (31.5%)
Bachelor degree or higher	1,320 (68.5%)
Professional title	
Nurse or senior nurse	1,319 (68.4%)
Supervisor or professor nurse	609 (31.6%)
Years of nursing experience	
0–10	1,048 (54.4%)
>10	880 (45.6%)
Previous compliance with recommended vaccination	
Sometimes or never	750 (38.9%)
Always	1,178 (61.1%)
Chronic disease	
Yes	196 (10.2%)
No	1,732 (89.8)
Self-assessment of health status	
Very good or good	530 (27.5%)
Satisfactory or fair	1,398 (72.5%)
Working experience during COVID-19 epidemic	
No	1,585 (82.2%)
Yes	343 (17.8%)
Vaccine-related knowledge level	
Fail	771 (40.0%)
Pass	1,157 (60.0%)

variance. The redesigned scale's CFA $(X^2)/df$ ration indicates good agreement with 2.73, while TLI (0.929), CFI (0.946), and RMSEA (0.081) goodness-of-fit indices demonstrated good fit. Supplementary material shows the detailed process.

Knowledge level of COVID-19 vaccine and vaccination

A questionnaire was developed based on the COVID-19 vaccination knowledge on the technical guidelines and expert consensus. A focus group discussion was held to choose and revise the questionnaire's items after the first draft was finished. The discussion convened two chief physicians from the Department of Infection, one chief physician from the Department of Respiratory Medicine, and two professors from the School of Public Health. After that, a pilot study revisited the updated questionnaire. A random sample of 30 nurses was pre-surveyed before the survey's official launch to ensure the questionnaire's internal consistency. The Cronbach's coefficient was 0.732. In all, the final questionnaire had 30 closed-ended items (which included vaccine type, recommended immunization practices, recommendations for populations, adverse effects, and misunderstandings) that could be answered with a simple "yes" or "no." The accurate response rate (a possible range of = 0.0–100.0%) was used to measure participants' knowledge of the COVID-19 vaccination. The correct response rates were divided into two categories: pass (≥60%) and fail (<60%).

Vaccine-related outcomes

Vaccine-related outcomes include two indicators of vaccination intention and attention to the news. The intention to take the COVID-19 vaccine was measured by a single item that asked participants on a Likert scale (0 = complete refusal; 5 = complete agreement) how likely they would be to have the COVID-19 vaccine when it is recommended for the current vaccination schedule. One question was utilized to evaluate the participants' attention to news reports about the COVID-19 vaccination. The item was assessed on a five-point Likert scale ranging from 1 (do not care at all) to 5 (care a great deal), with higher scores indicating greater interest in vaccine information.

Statistical analysis

Person-centered analysis approach, in contrast to "variable-centered" statistical methods that treat individuals as homogeneous or essentially homogeneous, focuses on studying combinations or developmental patterns of behavioral variables to produce more individually meaningful statistical results. It has been used in health and psychological behavioral research, for example, in examining the profiles of emotional

TABLE 2 Correlations of 5C indictors and outcome variables ($N = 1,928$).

	5C vaccine hesitancy indictors					Outcomes	
	Confidence	Complacency	Constraints	Calculation	Collective responsibility	Intention to COVID-19 vaccination	Attention to COVID-19 vaccine news
Median ± IR	6.33 ± 1.67	2.67 ± 2.67	1.25 ± 1.50	6.00 ± 2.00	6.50 ± 2.00		
Mean ± SD						4.55 ± 0.97	4.36 ± 0.87
Range	1–7	1–7	1–7	1–7	1–7	0–5	1–5
Confidence	1	−0.247**	−0.454**	0.397**	0.503**	0.307**	0.318**
Complacency		1	0.586**	−0.242**	−0.235**	−0.159**	−0.157**
Constraints			1	−0.315**	−0.377**	−0.268**	−0.274**
Calculation				1	0.502**	0.118**	0.267**
Collective responsibility					1	0.203**	0.280**
Intention to COVID-19 vaccination						1	0.176**
Attention to COVID-19 vaccine news							1

SD, standard derivation; IR, interquartile range. **p < 0.01.

TABLE 3 Fit statistics for profile structures.

Model	AIC	BIC	sBIC	LMR(p)	BLRT(p)	Entropy	Proportion of sample size in profile
1 profile	32,443	32,499	32,467	–	–	–	1.000
2 profiles	30,175	30,264	30,213	0.0000	0.0000	0.943	0.825/0.175
3 profiles	29,232	29,354	29,284	0.0000	0.0000	0.958	0.159/0.802/0.038
4 profiles	28,635	28,790	28,701	0.0001	0.0000	0.927	0.127/0.146/0.689/0.037
5 profiles	28,318	28,318	28,210	0.0000	0.0000	0.941	0.127/0.155/0.675/0.006/0.037
6 profiles	27,898	27,898	27,771	0.0000	0.0000	0.915	0.106/0.119/0.581/0.005/0.155/0.034

AIC, Akaike information criteria; BIC, Bayesian information criteria; sBIC, sample size–adjusted BIC; LMR, Lo-Mendell-Rubin likelihood ratio test; BLRT, bootstrapped likelihood ratio test.

labor (35), vulnerability types (36), and symptoms pattern of fatigue (37). For the objective of determining the antecedents of vaccine hesitancy, person-centered analysis would be the most appropriate sort of statistical technique. The most basic and often used approaches in this study are latent class analysis (LCA) and latent profile analysis (LPA). Latent profile analysis is to categorize individuals based on their response patterns to epiphenomenal items, allowing for the investigation of diverse groups of population attributes. The potential profile analysis (38) was used to examine the number of unobserved categories (i.e., categorical potential profiles of vaccine hesitancy), characterize the properties of the classes, and calculate the probability that each individual belongs to a given class, given that the 5C scale entries were transformed into continuous variables (39).

In the latent profile analysis, the average scores of the five dimensions of vaccine hesitancy were used as the exogenous variables to develop the model. Starting with a model with one potential class, the number of potential classes was gradually increased, and the fitness of each model was evaluated one by one to determine the best potential class model. To compare models with different numbers of classes, the Lo-Mendell-Rubin likelihood ratio test (LMR) (40) and the bootstrap likelihood ratio test (BLRT) (38) were employed as significant tests. The model with k classes is superior to the model with k∼1 classes if the LMR or BLRT is significant ($P < 0.05$) (41). Among the LPA model fit test measures are the Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), and sample size–adjusted Bayesian Information Criterion (sBIC). Usually, the lower the AIC, BIC, and sBIC values in the model, the better it fits in comparison with the previous model (42). The entropy value is frequently used to assess the classification quality of the model, and >0.80 indicates that the classification accuracy surpasses 90% (43). In addition to considering the model's fitness, the ideal model should be based on theory, integrated with previous studies, and the interpretability of data results (44).

Sociodemographic characteristics (age, sex, marital status, children, workplace, education level, professional title, years of nursing service, previous vaccination habits, chronic diseases, and working experience during the COVID-19 epidemic) and COVID-19 vaccination knowledge level were used as predictor variables, the COVID-19 vaccination intention and attention to COVID-19 vaccine news were used as outcome variables, and we utilized the R3STEP and DCON commands in Mplus to model the predictors and outcomes of the latent categorical variable (45, 46). Scores on the 5C scale did not meet the normal distribution criteria, so the median (M) and interquartile range (P25, P75) were utilized to describe them and assess them nonparametrically. Correlation analysis was carried out using Spearman's correlation coefficient *rho*. Multiple group differences were evaluated using the Kruskal–Wallis test and reported *p*-values were adjusted to account for multiple comparisons using the Bonferroni *post-hoc* test. SPSS (version 26.0) and Mplus (version 8.3) were used to analyze the data. There were no missing values discovered.

Results

Participants and correlations among variables

In this online survey, a total of 2,017 questionnaires were completed; 65 were eliminated for the following reasons: The questionnaire was unfinished ($n = 10$), or the response time was too short ($n = 55$). Unlike prior research, this study included a certain number of community nurses ($n = 718$), more representative of the nurse population, and some of the participants ($n = 343$) worked as frontline nurses during the COVID-19 epidemic. Because the 5C scales vary in their theoretical predictive aspects of vaccination intention, we checked questionnaires with repeated responses in 15 entries in extreme cases, including responses with repeated 1 ($n = 5$), 2 ($n = 2$), 6 ($n = 3$), or 7 ($n = 11$). We finally retained 1,928 cases for subsequent analysis. The characteristics of the study sample are shown in Table 1.

Correlations of study variables, including 5C vaccine hesitancy indicators and outcome variables, are shown in Table 2. On the seven-point Likert scale, participants had high scores in confidence (Median = 6.33, IR = 1.67), calculation (Median = 6.00, IR = 2.00), and collective responsibility (Median = 6.50, IR = 2.00) and low scores in complacency (Median = 2.67, IR = 2.67) and constraint (Median = 1.25, IR = 1.50). As expected, all 5C indicators were correlated with each other and all were significantly associated with COVID-19 vaccine intention. However, a positive correlation was calculated with vaccination intention ($r = 0.118$, $p < 0.01$), contradicting the original authors' hypothesis (31) but matching a study in the Hong Kong nurse population (30). In addition, the same pattern was detected for the frequency of paying attention to COVID-19 vaccine news.

Model selection

Starting with the initial model, one to six profile classes were modeled progressively when examining the data, and Table 3 shows the fitted statistics for the various latent profile structures. When five classes were retained, the information evaluation indexes AIC, BIC, and BIC decreased as the number of classes rose, the entropy values were optimal and LMR values reached significant levels. However, when five or more classes were kept, a smaller profile formed, accounting for <1% of the overall sample. Considering profiles of this site may be false (47), we did not investigate solutions with seven or more profiles further. According to the actual situation, more classes may disperse the information and result in false findings; therefore, a classification model with four profile classes is most fair (see Figure 1).

Research question 1: Profile characteristics

Chi-square tests (Supplementary Table S1) showed that there was a significant difference in the four profiles for age ($\chi^2 = 11.836$, $p = 0.008$), workplace ($\chi^2 = 38.495$, $p < 0.001$), educational level ($\chi^2 = 16.914$, $p = 0.001$), professional title ($\chi^2 = 19.622$, $p < 0.001$), previous compliance with recommended vaccination ($\chi^2 = 11.649$, $p = 0.009$), self-assessment of health status ($\chi^2 = 22.671$, $p < 0.001$), working experience during COVID-19 epidemic ($\chi^2 = 16.307$, $p = 0.001$), and vaccine-rated knowledge level ($\chi^2 = 11.994$, $p = 0.007$). However, there was no significant difference in the three subtypes for gender, marital status, no. of children, and chronic disease. When compared with those in the other profiles, nurses in the "believers" subtype tended to be those who were >30 years, those who worked in tertiary hospitals, those who had more than undergraduate degrees, supervisor or professor nurse professional titles, better previous compliance with recommended vaccination, and better self-assessment of health status, and those who worked during COVID-19 epidemic, and better vaccine-related knowledge level.

Table 4 shows the distribution of 5C indicators between four profiles. Participants with high confidence (Median = 6.67), collective responsibility (Median = 7.00), and calculation

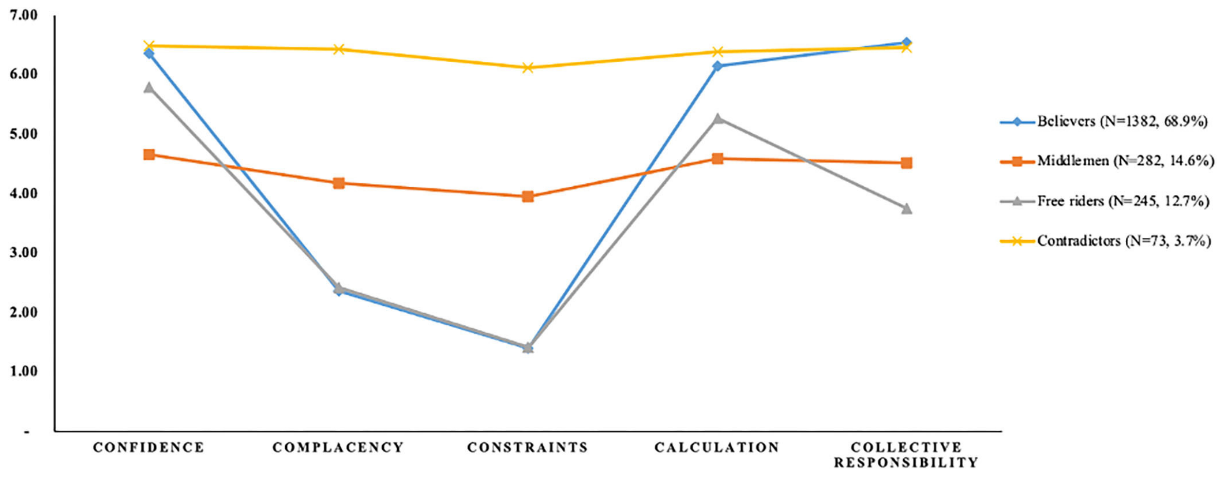

FIGURE 1
Four latent profiles with various levels of 5C indicators.

(Median = 6.33) low complacency (Median = 2.33) and constraints (Median = 1.00) were labeled as believers (*N* = 1,382, 68.9%), which was the profile of the largest portion. Believers are most likely to be vaccinated, and they will actively seek out vaccination issues, believing that vaccines are efficacious and provide optimum protection to the public. Beyond that, they have few restrictions on vaccination.

There was also a profile marked as middlemen (*N* = 282, 14.6%), with all indicators around the sample median (Median $_{confidence}$ = 5.00, Median $_{complacency}$ = 4.00, Median $_{constraints}$ = 4.00, Median $_{calculation}$ = 4.67, Median $_{collectiveresponsibility}$ = 4.50). They have mixed feelings about the efficacy of vaccines and the hazards of preventable diseases. They are apprehensive about the risks linked with vaccination, even though they can seek information and certify the herd immunity impact of vaccines to some level.

We marked high confidence (Median = 6.00) and calculation (Median = 5.33) and low other indicators (Median $_{complacency}$ = 2.33, Median $_{constraints}$ =1.00, Median $_{collectiveresponsibility}$ = 4.00) as free riders (N=245, 12.7%). They could search for information in response to vaccination questions, and they believed that vaccines are effective and had low limitations on vaccination. However, if others supply adequate protection, they could enjoy indirect protection as beneficiaries without contributing to herd immunization.

The profiles with the smallest part are contradictors (*N* = 73, 3.7%). They are high in all 5C indicators (Median $_{confidence}$ = 6.67, Median $_{complacency}$ = 7.00, Median $_{constraints}$ = 6.00, Median $_{calculation}$ = 6.33, Median $_{collectiveresponsibility}$ = 7.00). Contradictors will conduct considerable research on vaccine-related topics, and while they recognize that vaccinations are helpful, they do not believe they need vaccines to stay healthy, or they may have too many barriers to vaccination. Furthermore, they consider that immunizations do protect the population.

Research question 2: Predictors

Multinomial logistic regression was used to determine the predictors of nursing staff vaccine hesitancy profiles. Using the "believers" profile as the base outcome (reference), we obtained the following results (Table 5). We found that middlemen were younger, more likely to be female, had no children, had junior college degrees or lower, had lower professional titles, had fewer years of nursing service, sometimes or never complied with recommended vaccinations, had satisfactory or poor self-assessed health status, had no work experience during the COVID-19 epidemic, and had higher levels of knowledge than believers. Compared with believers, free riders were more likely to work in community health centers and had junior college degrees or lower. Contradictors were more likely to work in community health centers, had junior college degrees or lower, and had no work experience during the COVID-19 epidemic.

Research question 3: Outcomes

The COVID-19 vaccine-related outcomes showed the following results (see Table 6). The highest intentions for taking the COVID-19 vaccine when recommended were reported by believers (M = 4.697) and contradictors (M = 4.632), who did not significantly differ from one another. In comparison with all other profiles, middlemen had a significantly lower intention to uptake the COVID-19 vaccine (M = 3.964). A similar pattern can be observed for the frequency of paying attention to COVID-19 vaccine news. Believers (M = 4.505) and contradictors (M = 4.497) reported a significantly higher frequency of paying attention to vaccine-related news across all profiles. Middlemen were having a significantly lower frequency of following vaccine-related news than all other classes (M = 3.752).

Discussion

Before the implementation of the booster vaccination program in China, this study focused on nursing staff to understand the heterogeneity of vaccine hesitators and to provide specific evidence for targeted interventions to address vaccine hesitancy. We found a profile that was high in both confidence and collective responsibility (believers), as expected, and another profile that was high in confidence but low in collective responsibility (free riders). There were two quantitatively distinct profiles, with individuals having all 5C constructs around the median (middlemen) and all at high levels (contradictors). The study also observed differences between profiles in terms of predictors, and the profiles revealed disparities in their intention to COVID-19 vaccination and attention to COVID-19 vaccine news.

In this study, nurses had higher median score in confidence (Median = 6.33), calculation (Median = 6.00), and collective responsibility (Median = 6.50) and lower median score in complacency (Median = 2.67) and constraints (M = 1.25). The overall distribution of the five dimensions is similar to prior research on nurses in Hong Kong (30). However, our findings contradict Betsch's (31) assumptions about the structure of the calculation. They expected that individuals with superior computational skills would evaluate the risk of infection and vaccinations to make the correct choice. Therefore, those with a high level of computing ability should be risk-averse, and those with a more careful decision-making process may have a lesser intention to vaccinate. However, there is evidence that those who seek further vaccine information are more likely to be vaccinated (48). People with good computing skills should be wary about taking risks, but the link between calculation and vaccination is unclear and still needs to be further explored in different cultural contexts.

Contribution to the tailored interventions for the four profiles

Our study found that there are four types of nurses based on the 5C structure of vaccine hesitancy. Among them, the largest proportion was believers (68.9%), a group with the highest intention to vaccinate and the highest frequency of attention to vaccine-related information, which is very helpful for the smooth progress of vaccination. Therefore, it is necessary to find the differences between the other three profiles and believers and adopt targeted interventions.

Participants with all indicators around the sample median made up 14.6% of the population, who were categorized

TABLE 4 Profile characteristics of participants' responses on 5C indicators (*N* = 1,928).

5C indictors	Believers (*N* = 1,328), Median ± IR	Middlemen (*N* = 282), Median ± IR	Free riders (*N* = 245), Median ± IR	Contradictors (*N* = 73), Median ± IR	P^a-value			
					Overall	Believers vs. Middlemen	Believers vs. Free riders	Believers vs. Contradictors
Confidence	6.67 ± 1.00	5.00 ± 1.00	6.00 ± 2.00	6.67 ± 1.00	<0.001	<0.001	<0.001	1.000
Complacency	2.33 ± 2.00	4.00 ± 1.33	2.33 ± 2.17	7.00 ± 1.00	<0.001	<0.001	1.000	<0.001
Constraints	1.00 ± 0.75	4.00 ± 1.25	1.00 ± 0.75	6.00 ± 1.13	<0.001	<0.001	1.000	<0.001
Calculation	6.33 ± 1.33	4.67 ± 1.00	5.33 ± 2.17	6.33 ± 1.00	<0.001	<0.001	<0.001	0.945
Collective responsibility	7.00 ± 1.00	4.50 ± 1.00	4.00 ± 1.00	7.00 ± 1.00	<0.001	<0.001	<0.001	1.000

IR, interquartile range.

TABLE 5 Predicting pattern membership from individual characteristics.

Variables	Middlemen			Free riders			Contradictors		
	β	OR (95% CI)	*p*-value	*β*	OR (95% CI)	*p*-value	*β*	OR (95% CI)	*p*-value
Age (ref:20–30 years)									
>30 years	−0.436	0.65 (0.49, 0.85)	0.002**	−0.102	0.90 (0.66, 1.24)	0.525	−0.400	0.67 (0.41, 1.09)	0.105
Sex (ref: female)									
Male	−0.724	0.49 (0.27, 0.87)	0.016*	−0.344	0.71 (0.33, 1.53)	0.379	0.965	2.63 (0.29, 23.50)	0.388
Marital status (ref: unmarried)									
Married	−0.086	0.92 (0.69, 1.22)	0.548	−0.044	0.96 (0.69, 1.33)	0.793	0.098	1.10 (0.56, 1.84)	0.709
No. of children (ref: 0)									
≥1	−0.324	0.72 (0.55, 0.95)	0.019*	−0.225	0.80 (0.58, 1.09)	0.159	0.055	1.06 (0.65, 1.71)	0.824
Workplace (ref: community health center)									
Tertiary hospital	−0.183	0.83 (0.63, 1.10)	0.200	−0.478	0.62 (0.45, 0.85)	0.003**	−1.411	0.24 (0.15, 0.41)	<0.001***
Educational level (ref: junior college degree or lower)									
Bachelor degree or higher	−0.361	0.70 (0.53, 0.93)	0.013*	−0.340	0.71 (0.51, 0.99)	0.042*	−0.781	0.46 (0.28, 0.74)	0.002**
Professional title (ref: nurse or senior nurse)									
Supervisor or professor nurse	−0.705	0.49 (0.36, 0.69)	<0.001***	−0.080	0.92 (0.66, 1.29)	0.639	−0.384	0.68 (0.40, 1.18)	0.168
Years of nursing experience (ref: 0–10 years)									
≥10 years	−0.504	0.60 (0.46, 0.80)	<0.001***	−0.180	0.84 (0.61, 1.14)	0.262	−0.349	0.71 (0.43, 1.15)	0.164
Pervious compliance with recommended vaccination (ref: sometimes or never)									
Always	−0.471	0.62 (0.48, 0.82)	0.001**	−0.078	0.93 (0.67, 1.28)	0.635	−0.115	0.89 (0.55, 1.46)	0.648
Chronic disease (ref: no)									
Yes	0.126	1.13 (0.73, 1.75)	0.572	0.041	1.04 (0.62, 1.75)	0.878	0.255	1.29 (0.62, 2.69)	0.496
Self–assessment of health status (ref: very good or good)									
Satisfactory or fair	0.840	2.32 (1.61, 3.33)	<0.001	0.233	1.26 (0.88, 1.80)	0.200	−0.009	0.99 (0.59, 1.67)	0.975
Working experience during COVID-19 epidemic (ref: no)									
Yes	−0.556	0.57 (0.39, 0.85)	0.006**	−0.380	0.68 (0.44, 1.06)	0.089	−1.252	0.29 (0.11, 0.74)	0.010*
Vaccine-related knowledge level (ref: pass)									
Fail	−0.460	0.63 (0.48, 0.83)	0.001**	0.059	1.06 (0.77, 1.47)	0.720	0.016	1.02 (0.62, 1.67)	0.951

Values in the table are estimates from the R3STEP logistic regression analyses using Mplus. "Believers" is the reference category.
*p < 0.05, **p < 0.01, ***p < 0.001.

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TABLE 6 Results of predicting outcomes of latent profile membership.

Outcomes	Believers		Middlemen		Free riders		Contradictors		Overall χ^2	*p*-value
	Mean	*SE*	Mean	*SE*	Mean	*SE*	Mean	*SE*		
Intention to COVID-19 vaccination	4.697_{bc}	0.020	3.964_{acd}	0.087	4.423_{ab}	0.069	4.632_{b}	0.097	77.841	$P < 0.001$
Attention to COVID-19 vaccine news	4.505_{bc}	0.020	3.752_{acd}	0.064	4.244_{ab}	0.056	4.479_{bc}	0.088	137.097	$P < 0.001$

Analyses were conducted using DCON command in Mplus. The subscript letters represent that the mean value of this profile was significantly different from the mean value of the profile labeled by the subscript letter. For example, the value 3.964_{acd} indicates that the intention of taking the COVID-19 vaccine in Profile (b) was significantly different from Profile (a), Profile (c), and Profile (d).

as middlemen. They had the lowest intention of taking the COVID-19 vaccine and frequency of paying attention to vaccine news than the other three profiles. The rapid spread of the COVID-19 pandemic forced people to rapidly acquire and implement health knowledge and change their behavior (49), and the calculations were highly correlated with perceptions of disease risk and vaccination risk (31). Compared to believers, middlemen have less confidence in the efficacy and safety of the COVID-19 vaccine and are less motivated to search for information about the vaccine with a sense of collective responsibility. While the emergence of multiple social media platforms has made it simpler to acquire more information regarding the COVID-19 vaccine and vaccination, new outbreak patterns and shifting health information have hindered the proper handling and utilization of health information during a COVID-19 pandemic (50). Although younger nurses may be more proficient at using social media to get information, their lack of education and work experience makes it difficult for them to spot vaccine rumors, which add to their reduced confidence in the COVID-19 vaccine. In addition, their lack of children, lack of vaccination history, perception of their health, and lack of direct work experience with the epidemic made them less concerned about the value of the vaccine for pandemic containment. Therefore, strengthening middlemen's trust in the COVID-19 vaccine and their capacity to locate important information is crucial for nurses to perform their job as health educators and prevent the spread of the pandemic both within the hospital and in the community.

Participants with high confidence but low collective responsibility accounted for 12.7% of the population, which were named free riders. It is clear from the results that free riders had a higher intention of taking the COVID-19 vaccine and frequency of paying attention to vaccine news than middlemen but were lower than the other two profiles. Collective responsibility appears to be a more fundamental factor in free riders' decisions to get the COVID-19 vaccine than in believers. People who believe in collective responsibility advocate for individual subordination to society and feel that the collective's interests trump the individuals, which implies they will participate in more pro-social conduct (51). Our study presents a very interesting result that nurses with low education and community nurses are more inclined to be free riders. This phenomenon can be explained by the fact that lower information-seeking ability is also a characteristic of this subgroup and that information-seeking ability is positively associated with collective responsibility. Much of the information in China about the COVID-19 vaccine emphasizes societal and governmental efforts to develop the vaccine, its safety and efficacy, and the significance of coordinated efforts to stop the pandemic (52). People acquire a strong belief in their own and society's responsibility for containing the spread of COVID-19 as they seek out more information about the COVID-19 vaccine from a variety of media sources (53). However, it is of concern to us that collectivists lack confidence in their decisions compared to individualists (54). Nurses with higher levels of collectivism may be more likely to regret their previous vaccination decisions than nurses with lower levels of collectivism. Therefore, providing more transparent information to enhance the credibility of the vaccine is as important as highlighting the specific societal benefits of vaccination for nurses who bear the risk of curbing COVID-19 infections (55).

The survey results demonstrate that, despite making up the smallest fraction of these four groups, the contradictors (3.7%) are not the least likely to be vaccinated and the least likely to follow vaccine news. This group possesses the same high levels of confidence, calculation, and collective responsibility as believers, but in contrast to believers, they also demonstrate a very high level of complacency and constraints. As a result, their perspectives on the advantages and hazards of vaccination are equivocal. This could indicate a lack of concern about the COVID-19 vaccine's function in curbing the spread of the epidemic, an undue complacency about their health status, or an unwillingness to confront the limits imposed on them by vaccination barriers. As a result, making health information more available and explaining the risk of developing the disease are extremely critical in persuading these healthcare providers to be vaccinated. Furthermore, workload and shift work are barriers to vaccination and particularly affect nurses' vaccination rates (56), and it is critical to equip them with flexible immunization schedules and locations.

Implications of this study for the current situation and the future

For nurses themselves, vaccination is very important for their protection in high-risk settings. Even though the vaccination rate among Chinese nurses is high, their reluctance to uptake the COVID-19 vaccine is commonly disregarded, which may impede the advancement of continuous immunization programs. Nurses are not vaccinologists and do not know everything about vaccine development, clinical trials, etc. (57). They may not have enough information about vaccine efficacy and safety, but they are still very motivated to vaccinate for their protection and the protection of others, especially patients (58). Our study aimed to determine the psychological status of Chinese nurses regarding COVID-19 vaccination. In addition, to gain a deeper understanding, we abandoned previous studies that only explored the behavior of nursing staff to vaccinate or not to vaccinate, or the psychological state of hesitation or not to hesitate, and instead used a person-centered approach to understand the heterogeneity of nursing staff's vaccine hesitancy.

For patients and the public, our study is also relevant. Nursing staff are at the front line of safeguarding public health and are a reliable source of vaccine-related information (59), and many studies have demonstrated that pediatric nurses, obstetric and gynecological nurses, and community nurses play an important role in promoting vaccination and reducing vaccine hesitancy in different populations (17, 18, 60). Although not all nurses are directly responsible for vaccines, nurses spend far more time with patients than other medical personnel (17). Patients and the public view them as thought leaders; thus, their participation in vaccine-related health education should not be disregarded (16). They help patients understand the history and efficacy of vaccination by providing them with vaccine-related information and health education to promote public trust in vaccinations and decrease the frequency of vaccine hesitancy or refusal (60). In this study, believers had the highest readiness to vaccinate and the highest level of vaccine concern compared to the other three categories. These nurses would contribute tremendously to the seamless implementation of vaccination and immunization planning. Our findings therefore provide a factual foundation for an acceptable intervention to assist the other three subgroups of nurses who are hesitant about vaccines.

In addition, this study has other public health implications in promoting vaccination efforts. First, we found some association between the 5C model and vaccination intention among nurses in mainland China. In future, tailored immunization promotion interventions can also be developed based on testing the psychological antecedents of vaccination in other groups of healthcare workers or even the public. Second, this study was conducted before the third dose (booster) of the COVID-19 vaccine in Chinese adults. Since the COVID-19 pandemic is likely to be widespread over a long period, a person-centered approach to vaccine hesitancy at different time points in the pandemic could help control the social and economic impact of the pandemic (61). Third, this study found that it is important to further improve the science of evidence-based risk-benefit assessment of vaccines. Public communication pathways and models regarding vaccine efficacy and safety should also be actively explored in the promotion of vaccination campaigns for other vaccine types, not just for the COVID-19 vaccine, and public transparency of information should be enhanced to boost public confidence in vaccines.

Limitation

Despite the practical implications of the results of this study, there are some limitations to its generalizability. First, we used convenience sampling, which inhibits generalizability. Future studies should investigate samples from a variety of other settings to further analyze the characteristics of nurses' hesitancy to work with vaccines in the Shanghai region vs. other provinces and cities. Second, we implemented a cross-sectional design, and vaccine hesitancy is susceptible to pandemic severity. Therefore, longitudinal studies are needed to explore the long-term changes in vaccine hesitancy and the factors influencing it. Third, since participants may answer these items in a manner consistent with social expectations, the results may be biased. Fourth, our choice of the 5C model as a theoretical framework to understand participants' vaccine hesitancy issues for COVID-19 was not completed adequately, so some others such as vaccine literacy and altruistic beliefs (62, 63) can be added in future studies.

Conclusion

Overall, Shanghai nurses demonstrated a high level of confidence, calculation, collective responsibility, low complacency, and constraints with COVID-19 vaccination. By profiling the psychological antecedents of COVID-19 vaccination among nurses in Shanghai, this study identified four distinct profiles of vaccine hesitancy related to COVID-19 (named "believers," "free riders," "middlemen," and "contradictors"). We further explored the differences in sociodemographic, vaccine knowledge, vaccination intention, and attention to vaccine news among individuals between each profile. The characteristics of the latent profiles can help provide more targeted guidance for nursing managers to develop interventions that complement vaccine knowledge gained through continuing education, provide some peer or supervisory support, and thus aid nurses in reducing vaccine hesitancy and facilitating smooth vaccination and immunization planning.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the Institutional Review Board of the School of Public Health and Nursing at Shanghai Jiao Tong University (Reference number: SJUPN-202018). Participants provided informed consent to participate in the study by using an electronic informed consent form.

Author contributions

EZ: conceptualization, data curation, formal analysis, and writing—original draft. ZD: conceptualization, data curation, investigation, and writing—reviewing and editing. CW: conceptualization and writing—reviewing and editing. JH: writing—reviewing and editing. SW: conceptualization, data curation, and investigation. LZ: writing—reviewing and editing. QF: writing—reviewing and editing, project administration, and resources. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.953850/full#supplementary-material

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Psychological determinants of COVID-19 vaccine acceptance among urban slum dwellers of Bangladesh

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Introduction: Coronavirus disease 2019 (COVID-19) vaccination has emerged as a promising approach to counter the harmful impacts of the pandemic. Understanding the psychological components that may impact an individual's attitude toward COVID-19 vaccination is crucial for generating evidence-based ways to minimize vaccine hesitancy. This study determined the psychological antecedents regarding vaccine acceptance among urban slum people of Bangladesh.

Methods: From 5 July to 5 August 5, 2021, a face-to-face survey was conducted in the urban slum of two large cities in Bangladesh. The questionnaire considered socio-demographics, health-related characteristics, psychological determinants, sources of information, and conspiracy beliefs regarding COVID-19. The 5C sub-scales were used to assess psychological antecedents. Five stepwise binary logistic regression models evaluated significant predictors for confidence, complacency, calculation, constraints, and collective responsibility. Multinomial logistic regression was used to determine the relationship between psychological antecedents and vaccine acceptability.

Results: The study revealed that the slum residents with a high level of confident (89.94%), complacent (72.73%), having constraints (82.31%), calculative (84.80%), and responsible (93.30%) showed a higher vaccine acceptance rate. Higher vaccine acceptance was related to the believer in natural-made origin (85.96%) and those who rejected anti-vaccination (88.44%). The information acquired from newspapers differed significantly ($p < 0.05$), though TV or radio was the most common primary information source about COVID-19 vaccines (74.75%). The regression result revealed that marital status, education, family income, and perceived health condition were significantly associated with the 5C domains. Two psychological antecedents including complacency (OR = 3.97; $p < 0.001$) and collective responsibility (OR = 0.23; $p < 0.001$) were significantly associated with vaccine acceptance.

Conclusions: Different predictors significantly affect psychological antecedents related to COVID-19 vaccine uptake. Therefore, considering the factors, targeted actions based on the findings may help to lower vaccine reluctance and boost vaccination rates.

KEYWORDS

COVID-19, vaccine acceptance, Bangladesh, vaccine hesitancy, slum people, psychological antecedents, 5C sub-scales

Introduction

Vaccines are a material used to stimulate the development of antibodies and confer immunity against existing and emerging infectious diseases (1). Vaccines are a miracle of modern medicine. More lives have been saved due to them than any other human invention (2). The novel coronavirus disease known as COVID-19 was first detected in Wuhan, China, in late December 2019. With the rapid transmission rate, this virus spread worldwide soon thereafter. Consequently, the World Health Organization (WHO) proclaimed COVID-19 a global pandemic on 11 March 2020 (3). As of 16 March 2022, the world has experienced a catastrophic situation due to the coronavirus disease (COVID-19) that resulted in more than 460 million cases and around 6 million deaths across 220 countries (4). Since SARS-CoV-2 is a highly infectious virus that affects people worldwide, vaccines are the most significant public health intervention and the most effective technique for protecting the population against coronavirus disease 2019 (COVID-19) (5, 6).

Considering the catastrophic scenario, vaccinations are one of the most crucial public health interventions for limiting the spread of dangerous infections and their damage. The WHO estimates that vaccines have saved at least 10 million lives throughout the globe (7, 8). Vaccination helps to develop antibodies and provide immunity against the virus, which has been shown to reduce pandemic severity by reducing COVID-19 infection, hospitalization, and mortality. According to a recent study, when people's immunity reaches 67%, there is a possibility to decline in COVID-19 infections (9). It is impressive that numerous viable COVID-19 vaccines have developed in less than a year (10). Scientific and pharmaceutical companies have developed dozens of COVID-19 vaccines, including Pfizer–BioNTech, Moderna, Janssen, Sinopharm-BBIBP, Sputnik V, CoviVac, and Covaxin, to protect humans (11). However, the protection of the world's population depends on the availability of vaccine dosages and government immunization programs (10). A report demonstrated that by mid-March 2021, 380 million doses of COVID-19 vaccination had been distributed worldwide. However, the report showed that the vaccine acceptance tendency worldwide is still lagging (12). By the end of 2021, the European Union intends to have vaccinated 70% of its adult population. More than 51 million vaccine doses had been provided across the EU as of the end of 2021, with Denmark and Spain having the highest vaccination rates (13). Several high-income countries (HICs) have made significant progress, with Israel leading the way, having vaccinated half of its population by the end of February (14). However, many HICs have found it challenging to get COVID-19 vaccines due to vaccine hesitancy (11, 15). As HICs began vaccinating, new administrative issues arose, and new methods were offered to address supply hurdles, such as extending the interval between vaccine doses. On the other hand, despite their extensive expertise from the Expanded Programme on Immunization (EPI), which began in 1974, lower-middle-income countries (LMICs) may confront more extra problems than HICs (16).

A successful vaccination program depends on the extent of people's willingness to accept the vaccine, the demand for the vaccine, and their behavior toward vaccination (17, 18). However, increasing hesitancy toward vaccination limits the success of a vaccination program (19, 20); such hesitancy is defined by the delay in accepting the available vaccine (21). The WHO labeled vaccine hesitancy as a serious

Abbreviations: COVID-19, Coronavirus Disease 2019; EPI, Expanded Programme on Immunization; ROC, Receiver Operator Characteristic; LMIC, Lower-middle Income Countries; BMI, Body Mass Index.

public health threat that raised concern about the successful implementation of vaccination worldwide (22). As seen in the 2018 measles epidemic in New York City, vaccination reluctance led to continuous transmission (23). Rapid development of vaccines, conspiracy theories on vaccine origin, lack of trust in government, and religious misconceptions have been identified as major obstacles to vaccine hesitancy (24). Vaccine reluctance is context-dependent and impacted by time, location, and vaccines, as well as psychological variables (25). Studies suggest that individual attitudes regarding vaccination, in general, and COVID-19 immunization, in particular, appear to be influenced by psychological variables. This is mostly attributable to the psychological impacts of the current pandemic, which was accompanied by a deluge of information (16, 26). Therefore, it is important to analyze the psychological aspects of vaccination to determine the individual behavior toward vaccination, which might help in the development of evidence-based strategies to minimize vaccine reluctance.

Grounded on theories of vaccine hesitancy and acceptance, Betsch et al. developed and validated a vaccination tool (5C model) to explain psychological behavior toward vaccination (27). The 5C scale offers a reliable and psychologically sound approach for tracking vaccination behavior around the globe. The researchers used the 5C scale to study how anticipatory elements affect vaccination behavior as well as the deep understanding of how each person's mental depictions, attitude, and behavioral propensities are influenced by their surrounding environment and contexts. The 5C scale consisted of five psychological antecedents, including confidence, complacency, constraints, calculation, and collective responsibility (27, 28). Currently, these antecedents are widely used in high-income countries to assess vaccine hesitancy to determine the vaccination uptake rates (29). Several studies reported the psychological antecedents of the COVID-19 vaccine among different population groups in different countries, including Bangladesh (30–33); however, there is no study assessing the psychological determinants of vaccination among socioeconomically disadvantaged people using 5C scale.

Early on, there were conspiracy beliefs about the origins of the COVID-19 pandemic. These opinions were based on the idea that the virus was created by humans (34). These bad ideas also included thoughts about future vaccinations, such as charges of vaccination-enforcement conspiracies, which would be used to implant microchips in individuals to control people. Further, social media users have expressed concern about suggestions that COVID-19 vaccines could cause infertility and limit the human population increase (34, 35). Such unverified information is frequently disseminated on uncontrolled social media and other news media platforms, which might significantly influence the individual decision toward vaccination (30). Earlier studies also showed a significant correlation between conspiracy beliefs and vaccine hesitancy (30, 36).

In Bangladesh, more than 2 million people live in urban slum areas (37). Slums are characterized by inadequate healthcare services, limited educational options, limited living space, and a dearth of employment prospects (38). Being historically poor healthcare systems in Bangladesh (39), the COVID-19 pandemic compounded the plight of urban slum inhabitants who were already suffering financially and lacked access to healthcare services due to inequitable services and economics (40).

Data suggests that 75% of the slum population lives in a single room, and 45% of them suffer from infectious and parasitic diseases regularly (40), whereas only 13.9% are able to seek healthcare services from formal healthcare professionals (41). On top of that, COVID-19 has brought an additional burden to them. A study reported that slum populations are more vulnerable to COVID-19 infection than others and experience higher morbidity (42). In this situation, the slum-dwellers possible reluctance to take the COVID-19 vaccination might render them more susceptible to the virus.

Vaccine uptake determines the extent to which the population is sufficiently protected, which may vary across sub-populations such as the slum population, the ethnic minority population, and healthcare workers (43, 44). There have been a couple of studies conducted so far to determine the COVID-19 vaccine acceptance among the general population (18, 32, 45) and healthcare professionals (43) in Bangladesh. However, all these studies investigated the vaccination rates of well-educated and privileged citizens in Bangladesh. Another study in Bangladesh focused on the vaccination status of the low-income population (46); however, this study did not consider any empirical model to predict vaccination behavior. Further, none of the studies evaluated the impact of conspiracy beliefs on individual vaccination behavior. Thus, this study determined the prevalence of psychological antecedents and their associated factor toward COVID-19 vaccination using the 5C scale among urban slum dwellers in Bangladesh. The major objectives of this study were (a) to assess the psychological antecedents of COVID-19 vaccination and the factors associated with 5C domains and (b) the effect of embracing COVID-19 vaccine conspiracy beliefs on vaccine acceptance among the urban slum population in the country. Other minor objective was assessing the role of information sources in COVID-19 vaccination.

Methods

Study settings and participants

A cross-sectional survey design was employed in this study. A face-to-face survey was conducted in Bangladesh between 5 July and 5 August 2021, amid a devastating second wave of infections before the widespread vaccine was available. Individuals aged at least 18 years old without receiving their first dose of COVID-19 vaccine in urban slums in Bangladesh were

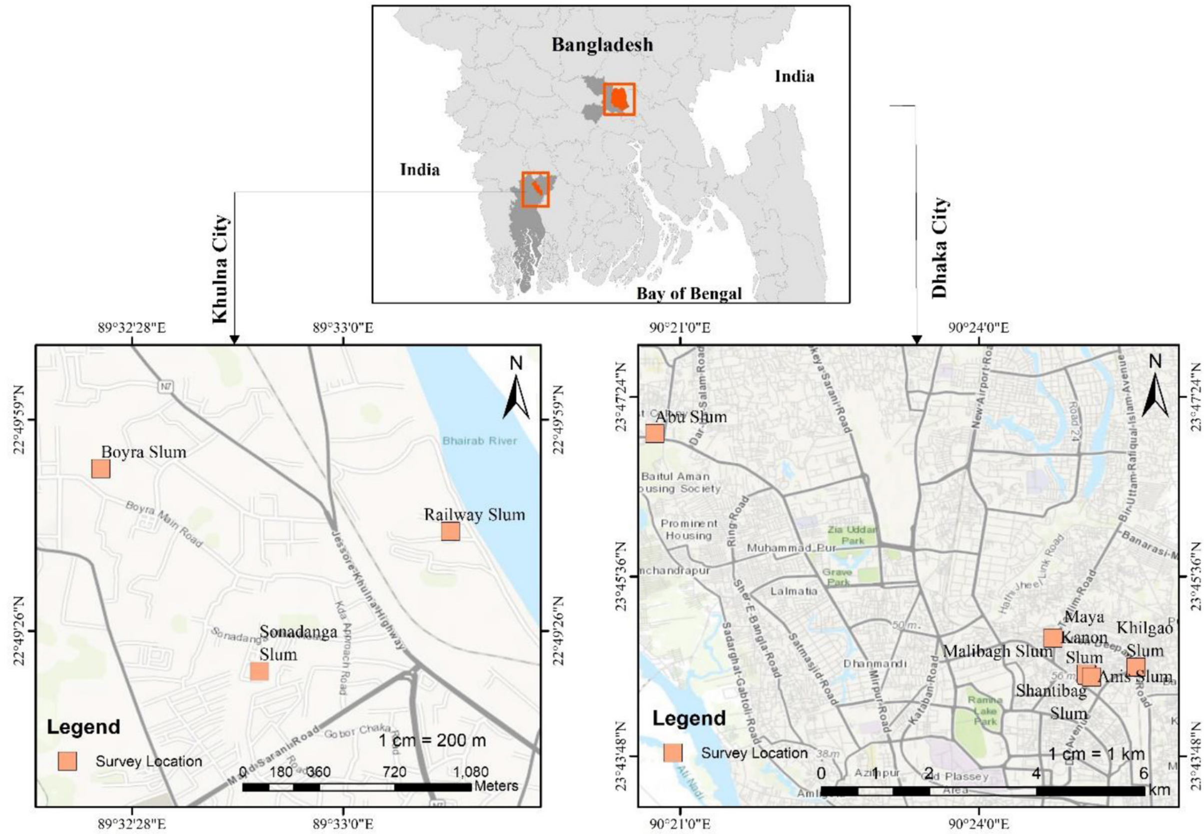


FIGURE 1
Study survey location.

included. Using a simple random sampling technique, the data were collected from urban slums (location shown in Figure 1) in Dhaka and Khulna city of Bangladesh.

Since no previous studies were available that suit our study measures, an online calculator was adopted to estimate the sample size for our research. As determined by the sample size calculator (https://statulator.com/ accessed on July 1, 2021), the minimum number of respondents is 385. The calculation were based on a 10% non-response rate, 5% precision, a 50% proportion, and a 95% confidence range for the overall slum population estimate of 2.2 million (37). Therefore, we collected 410 sample respondents from slums of two cities in Bangladesh. However, 10 participants were eliminated from the study due to prior vaccination against COVID-19. After excluding them, the final study contained 400 respondents, including 169 males and 231 females. Before completing the survey, all participants electronically consented. Therefore, participants were not needed to complete the form in its entirety. This survey did not require participants to provide their names or email addresses, ensuring that respondents could not be identified individually. Further, the research ethical clearance board of the Institute of Disaster Management, Khulna University of Engineering & Technology, Khulna, Bangladesh, approved this study.

Measures

A structured questionnaire was developed and sent to each respondent to gather data. The questionnaire elicited information on their sociodemographic and health-related features, intentions to receive a COVID-19 vaccine, 5C psychological antecedents, information sources, and conspiracy beliefs surrounding COVID-19.

Psychological antecedents

The decision to vaccinate is influenced by several factors, some of which are out of the control of the individual (such as a parent) and others within their control. There are five antecedents such as confidence, complacency, constraints, calculation, and collective responsibility, comprised of a 5C scale that determines the psychological factors of vaccination. Five psychological antecedents of vaccination are evaluated using the 5C scale, which sheds light on how the respondent's particular environment and context shape their distinctive mental representations, attitudes, and behaviors (27). The 5C scale consists of a ten-item scale (involving two items for each determinant). These items were chosen following a prior methodology established by Betsch et al. (27). The following items were used to measure confidence: (1) I am confident that public authorities decide in the best interest of the community; (2) I am entirely confident that the COVID-19 vaccine is effective. The following items were used to measure complacency: (1) It is unnecessary to get vaccinated as it cannot prevent COVID-19; (2) My immune system is robust, which protects me. The following elements were used to evaluate constraints: (1) Everyday work stress may prevent me from getting vaccinated; (2) Visiting the doctor makes me feel uncomfortable; this keeps me from being vaccinated. The calculation was evaluated based on the following criteria: (1) When I get vaccinated, I will consider whether it is effective or not; (2) Before I get vaccinated, I need to know about the details of the vaccine. Finally, the following items were used to measure collective responsibility: (1) I will take the vaccine, in that the weaker immune people will get protection; (2) COVID-19 vaccination is a collective action to prevent the spread of disease.

Source of information and conspiracy belief

Respondents were asked about the essential information sources they adopted for vaccine information. The following sources were designed as options: Social media, TV/Radio, Newspapers, Doctors/nurse/community healthcare staff, Friends/Family members, and Neighbors.

Respondent's conspiracy belief on COVID-19 and vaccine was assessed using two questions following (30). The first question was, "Do you oppose vaccination altogether?." Responses were collected as Yes, No, or No opinions. The second question was, "What is the belief about the origin of human coronavirus?." Again, responses were recorded as whether COVID-19 was naturally made from animals, manufactured, and part of a conspiracy plot and no opinion.

Willingness to accept the vaccine

A single question was used to assess the participant's willingness to receive a COVID-19 vaccination. Respondents were asked, "Will you take the Covid-19 vaccination when it becomes available?." The possible answer options were "Yes," "No," or "Not sure." Participants were divided into three groups: those who planned to take the vaccine (response = "Yes"), those who were unsure (response = "Not sure"), and those who were opposed to receiving the vaccine (response = "No").

Sociodemographic and health variables

Sociodemographic variables included gender, age, marital status, education, occupation, family type, and monthly income. Gender was assessed by asking whether male or female. Age was a continuous measure. Respondents were asked about their education level using four bins: (1) no formal education, (2) currently primary level, (2) Secondary School Certificate (SSC) level, or (3) college or higher degree. Respondents classified the family type as currently they live in a nuclear or joint family. The respondent ranked their occupation as unemployed, student or worker, day laborer, small business, or housewife. Finally, monthly income was assessed by asking for their monthly family income on $\leq$ 5,000 BDT (<58 US$), 5,001–10,000 BDT (58–115 US$), 10,001–15,000 BDT (116–173 US$), and > 15,000 BDT (>173 US$).

The health-related variables were COVID-19 test positivity, body mass index (BMI), having any long-standing illness (es), perceived health status, smoking habit, and childhood vaccination status. The COVID-19 susceptibility, presence of the long-standing condition, smoking habit, and childhood vaccination status were assessed by asking a respondent to indicate Yes or No. Body Mass Index (BMI) was calculated with the respondent's height (m^2) and weight (kg). The respondent's perceived health status was evaluated by asking them 5-items, including very good, good, fair, bad, and very bad.

Data analysis

Participants were separated into three groups according to their vaccination intentions: those who agreed to get the vaccine, those who were unsure, and those who were opposed to receiving the vaccine. The latter two categories have been merged as "undecided/unwilling." We selected two groups rather than three when doing statistical analysis on vaccination intentions to underline the possibility of differentiation between individuals who planned to accept a COVID-19 vaccine and those who did not to uncover characteristics that indicated one's desire to vaccinate. For categorical variables, Chi-square tests were employed, and Kruskal-Wallis tests were used for continuous variables. Additionally, a Chi-square test was used to examine the relationship between the sources of information, conspiracy beliefs, and vaccination intention.

Pairwise correlations between category variables were estimated using a chi-square test. The respondent's "Yes" or "No" status was determined based on their average 5C score at the cut-off points. We used five stepwise binary logistic regression models including all variables to identify the most significant factors influencing levels of confidence, complacency, calculation, constraints and collective responsibility. Statistical significance was defined as a p value of less than 0.05, and results were provided as odds ratios (OR) with 95% confidence intervals (CI). Additionally, multinomial logistic regression was used to examine the relationship between the 5C domains and willingness to receive the COVID-19 vaccination, adjusting for sociodemographic and health characteristics. To assess the effectiveness of 5C subscales in predicting COVID-19 vaccination hesitancy, we calculated the area under the receiver operator characteristic (ROC) curve (AUC).

Results

Sociodemographic characteristics

Table 1 summarizes the baseline characteristics of our study population. Out of 400 samples, 227 (56.8%) were female respondents. The mean age of the total sample was 33.43 (±11.25) years. Of the total, about 90% ($n = 360$) were married. The majority had no formal education (52.5%, $n = 210$). Most participants were day labor (29%, $n = 116$). Around 91.8% ($n = 367$) belonged to a nuclear family. About half of the participants (43.5%, $n = 174$) had a monthly family income between 5,000–10,000 BDT (US$ 58-115). More than 90% ($n = 369$) of the participants were not diagnosed with COVID-19. The mean BMI was 22.50 (±3.61). The majority (64.2%, $n = 257$) of respondents did not have a long-standing illness, and 34.5% (n = 138) reported that their health status was good. The majority (68.8%, $n = 275$) of respondents reported as being non-smokers. Around 81.1% ($n = 327$) participated in their childhood vaccination.

Prevalence of psychological antecedents of vaccination

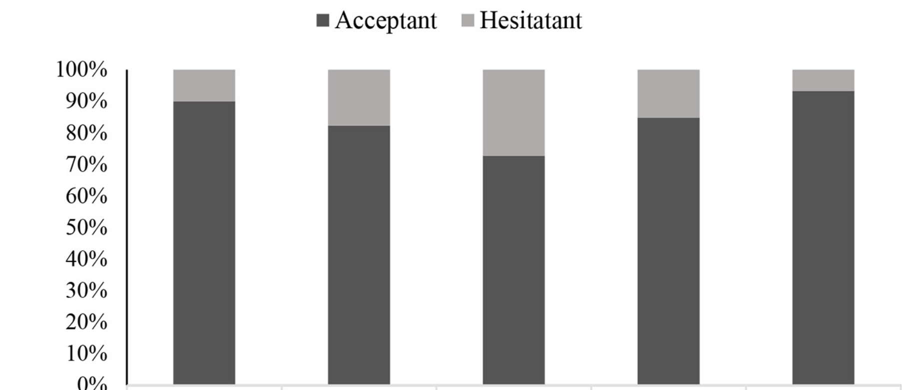
Figure 2 illustrates the psychological antecedents of vaccine acceptance among slum dwellers. Approximately 90% of respondents who said "yes" to vaccine acceptance showed confidence ($p < 0.001$, χ^2 test = 13.16) regarding COVID-19 vaccination and its effectiveness. About 72.73% were complacent ($p < 0.001$, χ^2 test = 26.67), 84.80% calculated the effectiveness and detailed information of vaccine ($p > 0.05$, χ^2 test = 3.30), and 93.30% respondents showed collective responsibility for accepting vaccines ($p < 0.001$, χ^2 test = 38.54). However, 82.31% faced constraints regarding vaccination, though they were optimistic about getting vaccinated ($p > 0.05$, χ^2 test = 0.15).

The information source of the COVID-19 vaccine and its relation to willingness to accept the vaccine

Figure 3 illustrates the information source distribution among the vaccine acceptant and hesitant groups. TV or radio was reported as the most common primary source of

TABLE 1 Descriptive statistics of respondents' intention to get vaccinated against COVID-19 ($N = 400$).

Variables	Frequency (N)	%
Sociodemographic characteristics		
Gender		
Male	173	43.2
Female	227	56.8
Age	33.43 (±11.25)	
Marital status		
Single	35	8.8
Married	360	90.0
Divorced	5	1.2
Education		
No formal education	210	52.5
Primary level	115	28.7
SSC	50	12.5
≥College	25	6.3
Occupation		
Unemployed	44	11.0
Student	14	3.5
Worker	106	26.5
Day labor	116	29.0
Small business	31	7.8
Housewife	89	22.2
Family type		
Nuclear	367	91.8
Joint	33	8.2
Monthly family income (BDT)		
≤5,000 (US$ <58)	90	22.5
5,001–10,000 (US$ 58–115)	174	43.5
10,001–15,000 (US$ 115–173)	89	22.2
>15,000 (US$ <173)	47	11.8
Health-related characteristics		
Tested positive for COVID-19		
No	369	92.2
Yes	31	7.8
BMI	22.50 (±3.61)	
Long-standing illness(es)		
No	257	64.2
Yes	143	35.8
Perceived health condition		
Very good	133	33.3
Good	138	34.5
Fair	86	21.5
Bad	26	6.5
Very bad	17	4.2
Smoking		
No smoking	275	68.8
Current smoker	108	27.0
Former smoker	17	4.2
Childhood vaccination(s)		
No	73	18.2
Yes	327	81.8



	Confidence	Constraints	Complacency	Calculation	Collective responsibility
Hesitatant	10.06	17.69	27.27	15.20	6.70
Acceptant	89.94	82.31	72.73	84.80	93.30

FIGURE 2
Psychological antecedents for acceptance of the vaccine.

information about COVID-19 vaccines (n = 299, 74.75%), followed by neighbors (n = 259, 64.75%), friends or family members (n = 228, 57%), social media (n = 116, 29 %), healthcare staff (n = 41, 10.25%), newspaper (n = 37, 9.25%), and miking (n = 6, 1.5%). Individuals who declined COVID-19 vaccination were more likely to rely on friends or family (55.66 vs. 63.01%) for vaccine information; however, the differences were not statistically significant (p = 0.351, χ^2 test). In contrast, differences in information obtained through newspapers were significant (p = 0.012, χ^2 test).

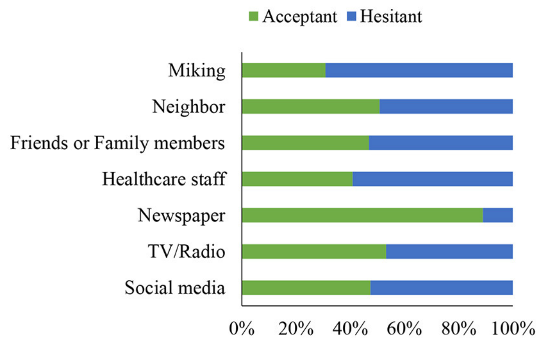


FIGURE 3
Information sources among the acceptant and hesitant groups.

Conspiracy belief on COVID-19 origin and altogether anti-vaccination and its relation to vaccine acceptance

Figure 4A demonstrates the vaccine acceptance rate based on the conspiracy belief toward COVID-19 origin. Of the total sample, 15.5% (n = 62) believed that SARS-CoV-2 had a human-made origin, while 17.5% (n = 70) believed in the natural source of the virus. However, a major portion reported no opinion (n = 268, 67%). Additionally, believing in a naturally occurring source of the virus was significantly associated (p = 0.008; χ^2 test) with a high intention to receive the COVID-19 vaccine compared to those who believed in a manufactured source of the virus and those who had no opinion on the virus's origin (85.71% vs. 67.74% vs. 83.96%).

Figure 4B illustrates the vaccine rates among the respondents based on respondents' attitudes toward altogether anti-vaccination. Only 37.50% of anti-vaccination participants (n = 12) reported an intention to receive COVID-19 vaccination, compared to 40.91% in the "no opinion" group (n = 9) and 88.44 % among those who rejected anti-vaccination (n = 306, $p < 0.001$; χ^2 test).

Univariate analysis of 5C domains with independent variables

Table 2 demonstrates the univariate analysis of the 5C domain individually predicted by the independent variables. Education level ($p < 0.01$), monthly family income ($p < 0.05$), and perceived health condition ($p < 0.05$) significantly affected the confidence regarding vaccination. Further, the COVID-19 related constraints were significantly affected by gender ($p < 0.01$), education level ($p < 0.01$), occupation status ($p < 0.01$),

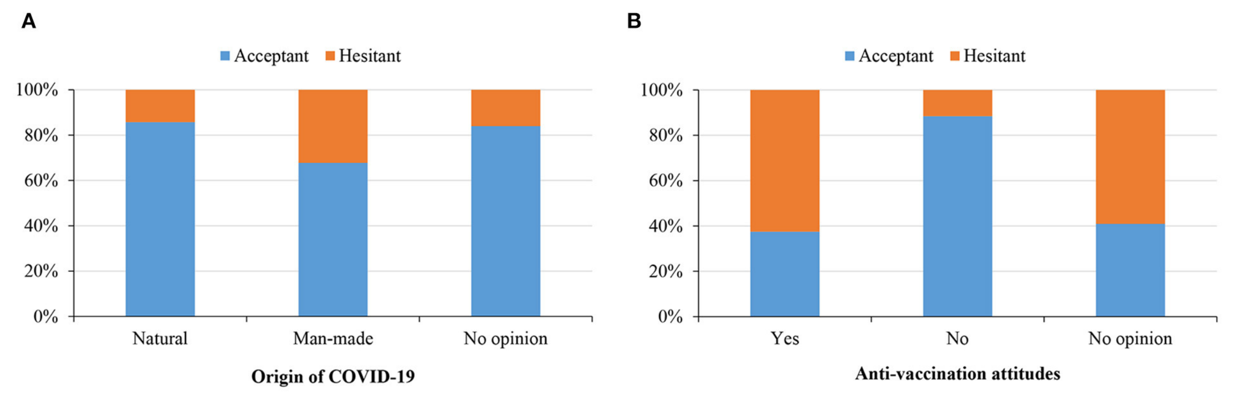


FIGURE 4
Willingness to accept vaccine based on the belief in COVID-19 origin **(A)** and attitude toward anti-vaccination **(B)**.

monthly family income ($p < 0.001$), and smoking habit ($p < 0.01$) of the participants.

The complacency domain was significantly anticipated by education level ($p < 0.001$), occupation status ($p < 0.05$), monthly family income ($p < 0.001$), and perceived health condition ($p < 0.05$). The collective responsibility was significantly predicted by the education level ($p < 0.05$), occupation status ($p < 0.05$), monthly family income ($p < 0.001$), long-standing illness ($p < 0.05$), and perceived health condition ($p < 0.01$), where only marital status was significantly related to the calculation domain ($p < 0.05$).

Predictors affecting the psychological vaccination antecedents

Table 3 presents the significant predictors affecting the psychological vaccination antecedents. Monthly family income (>15,000 BDT) was a significant predictor related to the confidence antecedent (OR = 0.42; 95% CI: 0.20–0.89). Having a monthly family income between 5,001–10,000 BDT (US$ 58–115) (OR = 0.25; 95% CI: 0.12–0.50) and having a monthly family income >15,000 BDT (>US$ 173) (OR = 0.26; 95% CI: 0.11–0.62) were significantly associated with vaccination constraints. The significant complacency antecedent predictors were: primary level of education (OR = 0.55; 95% CI: 0.33–0.1), college or higher level of education (OR = 0.29; 95% CI: 0.09–0.96), and having 10,001–15,000 BDT (US$ 115–173) family income (OR = 0.35; 95% CI: 0.17–0.69). Being married was a significant predictor for the calculation domain (OR = 0.43; 95% CI: 0.20–0.91). The significant collective responsibility predictors were: monthly family income (>15,000 BDT, > US$173) (OR = 3.18; 95% CI: 1.34–7.54) and who perceived health condition was fair (OR = 0.47; 95% CI: 0.24–0.94).

Association between 5C psychological antecedents with COVID-19 vaccine acceptance

Table 4 summarizes the association between 5C psychological antecedents and willingness to accept COVID-19 vaccine. The respondents with a complacency was significantly associated with a high intention to receive a vaccine (OR = 3.97; 95% CI = 1.87–8.42, $p < 0.001$). On the other hand, the respondents with no collective responsibility showed low intention toward vaccine acceptance (OR = 0.23; 95% CI = 0.11–0.49, $p < 0.001$). Additionally, amid all covariates, gender and age, and perceived health condition were related to low intention to vaccine acceptance (OR = 0.22; $p < 0.05$, OR = 0.95; $p < 0.05$, and OR = 0.66; $p < 0.05$, respectively).

ROC analysis of the 5C subscales

Figure 5 illustrates the ROC analysis of the 5C psychological antecedents. The ROC analysis disclosed that four domains, except complacency, appeared to be placed above the reference line. The highest AUC was found for collective responsibility (0.701). Beyond this, the AUC of confidence, calculation, and constraints were 0.616, 0.559, and 0.512, respectively. The lowest AUC was denoted in the case of the complacency subscale (0.334).

Discussion

Summary of the major findings

COVID-19 vaccine hesitancy has been globally a matter of concern (47). Despite multiple logistic efforts and national education programs, this issue continues to be a significant

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TABLE 2 Univariate analysis of 5C domains.

Variables	Confidence N (%)			Constraints N (%)			Complacency N (%)			Calculation N (%)			Collective responsibilitys N (%)		
	Yes	No	*p*-value	Yes	No	*p*-value	Yes	No	*p*-value	Yes	No	*p*-value	Yes	No	*p*-value
Sociodemographic characteristics															
Gender			0.147			**0.002****			0.976			0.967			0.104
Male	66 (39.1)	103 (60.9)		127 (48.8)	46 (32.9)		95 (43.2)	78 (43.3)		88 (43.3)	85 (43.1)		98 (47.1)	75 (39.1)	
Female	107 (46.3)	124 (53.7)		133 (51.2)	94 (67.1)		125 (56.8)	102 (56.7)		115 (56.7)	112 (56.9)		110 (52.9)	117 (60.9)	
Age	31.75 ± 11.06	34.65 ± 11.26	0.192	34.01 ± 10.76	32.34 ± 12.07	0.052	34.75 ± 11.10	31.81 ± 11.25	0.119	33.38 ± 11.46	33.47 ± 11.06	0.239	32.38 ± 10.71	34.56 ± 11.73	0.769
Marital status			0.955			0.105			0.503			**0.047***			0.897
Single	14 (8.3)	21 (9.1)		19 (7.3)	16 (11.4)		20 (9.1)	15 (8.3)		24 (11.8)	11 (5.6)		19 (9.1)	16 (8.3)	
Married	153 (90.5)	207 (89.6)		236 (90.8)	124 (88.6)		196 (89.1)	164 (91.1)		176 (86.7)	184 (93.4)		186 (89.4)	174 (90.6)	
Divorced	2 (1.2)	3 (1.3)		5 (1.9)	0 (0.0)		4 (1.8)	1 (0.6)		3 (1.5)	2 (1.0)		3 (1.4)	2 (1.0)	
Education			**0.004****			**0.001****			**0.000*****			0.382			**0.041***
No formal education	71 (42.0)	139 (60.2)		155 (59.6)	55 (39.3)		137 (62.3)	73 (40.6)		99 (48.8)	111 (56.3)		96 (46.2)	114 (59.4)	
Primary level	59 (34.9)	56 (24.2)		65 (25.0)	50 (35.7)		52 (23.6)	63 (35.0)		64 (31.5)	51 (25.9)		64 (30.8)	51 (26.6)	
SSC	27 (16.0)	23 (10.0)		28 (10.8)	22 (15.7)		24 (10.9)	26 (14.4)		25 (12.3)	25 (12.7)		32 (15.4)	18 (9.4)	
≥ College	12 (7.1)	13 (5.6)		12 (4.6)	12 (9.3)		7 (3.2)	18 (10.0)		15 (7.4)	10 (5.1)		16 (7.7)	9 (4.7)	
Occupation			0.124			**0.001****			**0.015***			0.129			**0.025***
Unemployed	18 (10.7)	44 (11.0)		28 (10.8)	16 (11.4)		32 (14.5)	12 (6.7)		24 (11.8)	20 (10.2)		19 (9.1)	25 (13.0)	
Student	5 (3.0)	14 (3.5)		6 (2.3)	8 (5.7)		5 (2.3)	9 (5.0)		6 (3.0)	8 (4.1)		8 (3.8)	6 (3.1)	
Worker	47 (27.8)	106 (26.5)		61 (23.5)	45 (32.1)		61 (27.7)	45 (25.0)		64 (31.5)	42 (21.3)		66 (31.7)	40 (20.8)	
Day labor	38 (22.5)	116 (29.0)		94 (36.2)	22 (15.7)		68 (30.9)	48 (26.7)		52 (25.6)	64 (32.5)		56 (26.9)	60 (31.3)	
Small business	17 (10.1)	31 (7.8)		21 (8.1)	10 (7.1)		12 (5.5)	19 (10.6)		18 (8.9)	13 (6.6)		21 (10.1)	10 (5.2)	
Housewife	44 (26.0)	89 (22.3)		50 (19.2)	39 (27.9)		42 (19.1)	47 (26.1)		39 (19.2)	50 (25.4)		38 (18.3)	51 (26.6)	
Family type			0.279			0.331			0.298			0.649			0.760
Nuclear	158 (93.5)	209 (90.5)		236 (90.8)	131 (93.6)		199 (90.5)	168 (93.3)		185 (91.1)	182 (92.4)		190 (91.3)	177 (92.2)	
Joint	11 (6.5)	22 (9.5)		24 (9.2)	9 (6.4)		21 (9.5)	12 (6.7)		18 (8.9)	15 (7.6)		18 (8.7)	15 (7.8)	
Monthly family income			**0.033***			**<0.001*****			**<0.001*****			0.314			**<0.001*****
≤5,000	33 (19.5)	57 (24.7)		70 (26.9)	20 (14.3)		64 (29.1)	26 (14.4)		38 (18.7)	52 (26.4)		37 (17.8)	53 (27.6)	

(Continued)

TABLE 2 (Continued)

Variables	Confidence N (%)			Constraints N (%)			Complacency N (%)			Calculation N (%)			Collective responsibilitys N (%)		
	Yes	No	*p*-value	Yes	No	*p*-value	Yes	No	*p*- value	Yes	No	*p*-value	Yes	No	*p*-value
5,001–10,000	71 (42.0)	103 (44.6)		123 (47.3)	51 (36.4)		100 (45.5)	74 (41.1)		93 (45.8)	81 (41.1)		77 (37.0)	97 (50.5)	
Alone	36 (21.3)	53 (22.9)		42 (16.2)	47 (33.6)		35 (15.9)	54 (30.0)		46 (22.7)	43 (21.8)		59 (28.4)	30 (15.6)	
10,001–15,000															
>15,000	29 (17.2)	18 (7.8)		25 (9.6)	22 (15.7)		21 (9.5)	26 (14.4)		26 (12.8)	21 (10.7)		35 (16.8)	12 (6.3)	
Health-related characteristics															
Tested positive for COVID-19			0.678			0.217			0.252			0.784			0.482
No	157 (92.9)	212 (91.8)		243 (93.5)	126 (90.0)		206 (93.6)	163 (90.6)		188 (92.6)	181 (91.9)		190 (91.3)	179 (93.2)	
Yes	12 (7.1)	19 (8.2)		17 (6.5)	14 (10.0)		14 (6.4)	17 (9.4)		15 (7.4)	16 (8.1)		18 (8.78)	13 (6.8)	
BMI	22.70 ± 4.21	22.35 ± 3.11	0.582	22.77 ± 3.74	22.00 ± 3.33	0.123	22.74 ± 3.64	22.22 ± 3.56	0.450	22.33 ± 4.05	22.68 ± 3.10	0.283	22.43 ± 4.09	22.57 ± 3.02	0.410
Long-standing illness(es)			0.253			0.818			0.362			0.743			**0.003****
No	114 (67.5)	143 (61.9)		166 (63.8)	91 (65.0)		137 (62.3)	120 (66.7)		132 (65.0)	125 (63.5)		148 (71.2)	83 (43.2)	
Yes	55 (32.5)	88 (38.1)		94 (36.2)	49 (35.0)		83 (37.7)	60 (33.3)		71 (35.0)	72 (36.5)		60 (28.8)	109 (56.8)	
Perceived health condition			**0.031***			0.881			**0.024***			0.889			**0.001****
Very good	66 (39.1)	67 (29.0)		90 (34.6)	43 (30.7)		73 (32.3)	60 (33.3)		67 (33.0)	66 (33.5)		83 (39.9)	50 (26.0)	
Good	63 (37.3)	75 (32.5)		87 (33.5)	51 (36.4)		63 (28.6)	75 (41.7)		71 (35.0)	67 (34.0)		76 (36.5)	62 (32.3)	
Fair	27 (16.0)	59 (25.5)		55 (21.2)	31 (22.1)		54 (24.5)	32 (17.8)		46 (22.7)	40 (20.3)		37 (17.8)	49 (25.5)	
Bad	7 (4.1)	19 (8.2)		18 (6.9)	8 (5.7)		17 (7.7)	9 (5.0)		12 (5.9)	14 (7.1)		8 (3.8)	18 (9.4)	
Very bad	6 (3.6)	11 (4.8)		10 (3.8)	7 (5.0)		13 (5.9)	4 (2.2)		7 (3.4)	10 (5.1)		4 (1.9)	13 (6.8)	
Smoking			0.116			**0.001****			0.873			0.073			0.110
No smoking	123 (72.8)	152 (65.8)		162 (62.3)	113 (80.7)		149 (67.7)	126 (70.0)		144 (70.9)	131 (66.5)		136 (65.4)	139 (72.4)	
Current smoker	37 (21.9)	71 (30.7)		84 (32.3)	24 (17.1)		61 (27.7)	47 (26.1)		47 (23.2)	61 (31.0)		65 (31.3)	43 (22.4)	
Former smoker	9 (5.3)	8 (3.5)		14 (5.4)	3 (2.1)		10 (4.5)	7 (3.9)		12 (5.9)	5 (2.5)		7 (3.4)	10 (5.2)	
Childhood vaccination (s)			0.825			0.674			0.630			0.117			0.071
No	30 (17.8)	43 (18.6)		49 (18.8)	24 (17.1)		42 (19.1)	31 (17.2)		31 (15.3)	42 (21.3)		31 (14.9)	42 (21.9)	
Yes	139 (82.2)	188 (81.4)		211 (81.2)	116 (82.9)		178 (80.9)	149 (82.8)		172 (84.7)	155 (78.7)		177 (85.1)	150 (78.1)	

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. Significant coefficients are shown in bold.

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TABLE 3 Factors affecting the psychological antecedents ($N = 400$).

Predictors	Confidence	Constraints	Complacency	Calculation	Collective responsibility
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Sociodemographic characteristics					
Gender					
Male		Ref.			
Female		0.73 (0.36–1.47)			
Age					
Marital status					
Single				Ref.	
Married				**0.43* (0.20–0.91)**	
Divorced				0.81 (0.79–0.14)	
Education					
No formal education	Ref.	Ref.	Ref.		Ref.
Primary level	0.72 (0.32–1.73)	0.61 (0.36–1.04)	**0.55* (0.33–0.1)**		1.08 (0.65–1.80)
SSC	1.39 (0.57–3.39)	0.71 (0.39–1.48)	0.76 (0.38–1.57)		1.49 (0.70–3.16)
≥ College	1.40 (0.52–3.74)	0.60 (0.19–1.86)	**0.29* (0.09–0.96)**		1.65 (0.49–5.45)
Occupation					
Unemployed		Ref.	Ref.		Ref.
Student		0.76 (0.16–3.63)	0.57 (0.12–2.84)		0.76 (0.15–3.78)
Worker		1.02 (0.46–2.26)	0.75 (0.32–1.73)		1.92 (0.86–4.26)
Day labor		2.08 (0.89–4.82)	0.58 (0.26–1.31)		1.13 (0.52–2.46)
Small business		2.25 (0.75–6.75)	0.46 (0.15–1.31)		1.10 (0.37–3.30)
Housewife		01.21 (0.52–2.83)	0.45 (0.19–1.03)		0.78 (0.34–1.76)
Monthly family income					
≤5,000	Ref.	Ref.	Ref.		**Ref.**
5,001–10,000	0.51 (0.23–1.11)	0.61 (0.32–1.14)	0.59 (0.33–1.06)		0.96 (0.52–1.59)
10,001–15,000	0.55 (0.27–1.10)	**0.25*** (0.12–0.50)**	**0.35** (0.17–0.69)**		1.94 (0.99–3.81)
>15,000	**0.42* (0.20–0.89)**	**0.26** (0.11–0.62)**	0.48 (0.21–1.09)		**3.18** (1.34–7.54)**
Health-related characteristics					
Long-standing illness(es)					
No					Ref.
Yes					0.97 (0.55–1.71)
Perceived health condition					
Very good	Ref.		Ref.		Ref.
Good	1.33 (0.44–4.02)		0.67 (0.68–1.12)		0.66 (0.39–1.13)
Fair	1.12 (0.37–3.38)		1.10 (0.60–2.00)		**0.47* (0.24–0.94)**
Bad	0.69 (0.22–2.15)		0.96 (0.38–2.48)		0.35 (0.12–1.01)
Very bad	0.53 (0.14–2.06)		1.15 (0.32–4.14)		0.31 (0.08–1.23)
Smoking					
No smoking		Ref.			
Current smoker		1.71 (0.80–3.64)			
Former smoker		1.66 (0.39–7.01)			

OR, Odds Risk; CI, Confidence Interval; Only significant variables ($p < 0.05$) in univariate analysis were considered for the five-stepwise binary logistic regression analysis, significant coefficients are shown in bold, $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

threat to the COVID-19 vaccine coverage in the coming days (10). In such a global scenario, the socially disadvantaged people, in particular, urban slum residents, are in vulnerable conditions to access vaccines. However, they should be prioritized for the COVID-19 vaccine as they are susceptible to infection because of their poor and unhygienic living condition. Understanding

TABLE 4 Multinomial logistic regression results determine the association between 5C domains and willingness to accept the COVID-19 vaccine.

	B	SE	Sig.	OR	95% CI	
					Lower bound	Upper bound
Confidence (Ref. = Yes)	−0.392	0.365	0.282	0.67	0.33	1.38
Constraint (Ref. = Yes)	−0.553	0.378	0.144	0.57	0.27	1.21
Complacency (Ref. = Yes)	1.380	0.384	**0.000*** **	3.97	1.87	8.42
Calculation (Ref. = Yes)	−0.522	0.339	0.123	0.59	0.31	1.15
Collective responsibility (Ref. = Yes)	−1.444	0.374	**0.000*** **	0.23	0.11	0.49
Gen	−1.509	0.557	**0.007** **	0.22	0.07	0.66
Age	−0.052	0.017	**0.003** **	0.95	0.92	0.98
Marital	0.973	0.686	0.156	2.65	0.69	10.15
Edu	0.129	0.251	0.607	1.14	0.69	1.86
Occupation	0.107	0.110	0.333	1.11	0.89	1.38
Family type	0.405	0.593	0.494	1.50	0.47	4.79
Monthly income	−0.130	0.205	0.526	0.89	0.59	1.31
COVID-19 positive tested	0.656	0.700	0.349	1.93	0.49	7.59
BMI	0.049	0.053	0.350	1.05	0.95	1.17
Long-standing illness	0.211	0.434	0.627	1.24	0.53	2.88
Perceived health condition	−0.424	0.207	**0.041***	0.66	0.44	0.98
Smoking status	−0.719	0.439	0.102	0.49	0.21	1.15
Childhood vaccination	0.708	0.393	0.071	2.03	0.94	4.38

SE, Standard Error; OR, Odds Risk; CI, Confidence Interval; Only significant variables ($p < 0.05$) in univariate analysis were considered for the multinomial logistic regression analysis, significant coefficients are shown in bold, $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

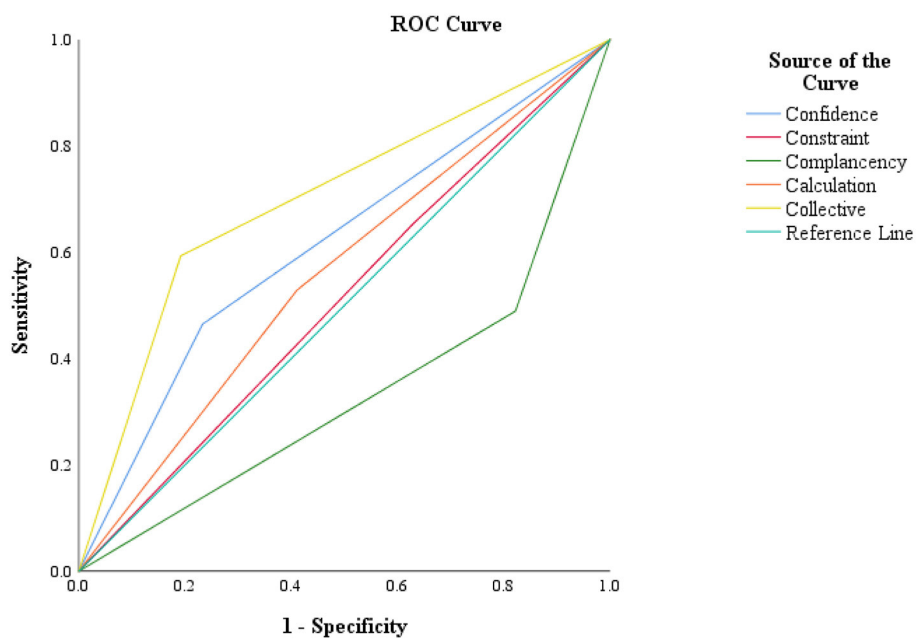

FIGURE 5
Receiver operating characteristic (ROC) analysis for 5C subscales in COVID-19 vaccine acceptance screening.

the psychological components that may impact an individual's attitude toward COVID-19 vaccination is crucial for generating evidence-based ways to minimize vaccine hesitancy (30). Given the dearth of research on psychological determinants of vaccine acceptance, this study explored the psychological determinants of COVID-19 vaccine acceptance among urban slum residents in Bangladesh.

The present study explored the psychological antecedents of COVID-19 vaccine acceptance among urban slum people of two large cities in Bangladesh using the 5C sub-scale. Our findings show that most of the slum dwellers who were confident, complacent, calculative, and responsible showed a higher vaccine acceptance rate. The slum residents those obtained vaccine information from the newspaper were highly willing to accept the COVID-19 vaccine. A high percentage of slum people who believe that coronavirus originated naturally and disagree with anti-vaccination were highly inclined to receive the COVID-19 vaccine. The regression results show that gender, marital status, education level, occupation status, monthly family income, long-standing illness, perceived health condition, and smoking behavior were significantly associated with 5C domains by different degrees. Further, two of the five psychological antecedents, including complacency and collective responsibility, were significantly associated with the vaccine acceptance rate to different degrees. Furthermore, the study found the highest AUC for the collective responsibility domain from ROC analysis.

Our results reveal that the majority of the slum residents had a greater level of confidence, calculation, and collective responsibility to be vaccinated. A similar finding was observed among migrants, another vulnerable population in Shanghai, China, where three in fourth respondents showed higher confidence levels in vaccine safety and effectiveness (48). In contrast, some constraints might be responsible for lessening the vaccine uptake, such as family dynamics and gender, geographical and technological barriers, and socioeconomic reasons (49). The respondents had a high level of calculation of information regarding the effectiveness and more details about the vaccine. The more people were found calculative, the more they hesitated toward vaccination (32). An earlier study in 13 Arab countries found that Sudan and Egypt had the highest calculation, which refers to assessing the benefits and risks of vaccination before making a decision (50). Amnesty International reported that the high calculation level is attributable to a lack of clear strategy and transparency for vaccination distribution, as well as insufficient vaccine information provided to local media and Egyptian authorities, and a limited awareness campaign (51). Our study also found a high level of collective responsibility, emphasizing the importance of herd immunity in controlling the spread of COVID-19. This thought increases the number of individuals willing to accept vaccines. Many recent studies have reported higher collective responsibility in line with our study findings (30, 32, 50, 52, 53).

Information sources also anticipated the acceptance of the COVID-19 vaccine. Three in fourth respondents supported TV or radio as the most common primary information source of vaccination information. However, vaccine acceptance seemed higher in the group that mentioned newspapers as a primary source. That might be for their high trust in the newspaper. One study conducted in Germany found that the participants who turned to the local newspaper for information were more likely to vaccinate, and the source positively affected vaccine intention (54).

Moreover, our study suggests that respondents who think the virus originated naturally had a greater acceptance rate for the COVID-19 vaccination. A similar finding was observed in research conducted in Kuwait, where more than 90 percent of healthcare professionals were favorable to vaccination acceptance and believed in the natural origin of COVID-19 (30). In addition, about eight out of every one hundred slum inhabitants in this survey were anti-vaccination, with over two-thirds demonstrating vaccine hesitancy. At the same time, approximately 90% of respondents who were not part of the anti-vaccination group anticipated high vaccine acceptance. These results were consistent with a prior study conducted in Kuwait (30).

In this study, the 5C psychological antecedents were influenced by the predictors, including being married, having primary and college-level education, earning 10,001–15,000 BDT or more per month, and having good health. A recent multinational study considering 13 Arab countries found that males, being of advanced age, educated, being a healthcare professional, having had COVID-19, or having an infected relative or one that died from COVID-19 as significant predictors regarding the 5C domains (50). Our study found that high-income slum people were less likely to be confident about vaccination. One possible explanation could be that aid from the government and non-government organizations might be a crucial factor in developing confidence in public authorities that affect residents' vaccination behavior (55). An earlier study also reported that higher trust and satisfaction in authorities were related to 1.95 times higher intention to be vaccinated (18).

Our findings suggest that people with higher income were less likely to have limitations toward vaccine uptake. In other words, low-income people were more likely to face restrictions on vaccination because of their loss of work hours or workdays. The majority of the respondents were workers and day laborers in our study. They need to earn daily to meet their daily needs, even a tiny amount (56). In addition, a study found that around 60% of those who received a second dose of the vaccine had various severe side effects, including fever, headache, myalgia, and general malaise (57). Fear of working days lost due to side effects of vaccination might impede the intention to vaccinate. Married participants in the present study were less likely to be calculative toward immunization. Their desire to vaccinate to protect their family members might make them less calculative. Our study found that primary and above college education and medium income levels were less likely to show complacency antecedents. A similar outcome was reported previously where people with post-graduate were less complacent (50). Furthermore, they believe economic and political uncertainty may contribute to people's complacency with vaccines. Finally, people with a high level of family income and good health showed varying levels of collective responsibility. In this research, the high-income group was positively related to collective responsibility. People with fair health, as opposed to very good health, were less inclined to consider collective responsibility. Respondents with fair, poor, or very poor health may be concerned about the side effects of vaccination rather than considering collective responsibility.

Low levels of complacency and high levels of collective responsibility were linked with COVID-19 vaccination acceptability among the slum dwellers. Prior research on Bangladeshi adults supported these results (32). This research found that more collective responsibility considerably decreased vaccination hesitancy, but greater complacency significantly increased vaccine hesitancy. Conversely, reduced complacency and more collective responsibility were positively related to high vaccination intent seen among nurses (52). Individuals with a complacent attitude usually believe that vaccination is unnecessary since their immune systems are capable of protecting them from infection. It was observed that the Chinese thought they did not need to be vaccinated since they were physically well, which affected their intention to get vaccinated (58).

The ROC analysis for all of the psychological domains in this study suggests that four of the 5C sub-scales, with the exception of complacency, might be useful in predicting COVID-19 vaccine uptake. Similar results have been found among Kuwaiti healthcare professionals, with the exception of the math sub-scale. Similar findings have been reported in healthcare workers of Kuwait; however, their exception was for the calculation sub-scale (30).

Implications of the study

The notable implication of this study is that the application of 5C psychological antecedents would assist in understanding the confidence, complacency, constraints, calculation, and collective responsibility of slum dwellers toward COVID-19 vaccine acceptance. Beyond this, sociodemographic predictors significantly affect this 5C and are a solid addition to this study. While vaccine development and availability are essential to accomplish herd immunity against the pandemic, the study will assist local public health representatives design targeted vaccine intervention programs regarding vaccination coverage successes. Recognizing the variables and determinants of COVID-19 vaccine uptake would help increase the efficiency of these rollout campaigns.

Strength and limitations of the study

This study investigated the COVID-19 vaccine acceptance among the slum people of two large cities in Bangladesh, using a large and diverse representative sample. Slum people are considered a backward community because of their socioeconomic vulnerability (40). Therefore, exploring their intention to vaccination will be an efficient addition to public health concerns. Moreover, a significant strength of this study was adopting the 5C sub-scale for evaluating the psychological determinants of vaccinations. The scale has an admissible discriminatory power with its identified cutoff score to anticipate the psychological antecedents regarding COVID-19 vaccine acceptance (59). However, there are some limitations to this study. We could not draw causal connections between variables of interest because of the cross-sectional study design. However, the association between psychological antecedents and vaccine acceptance can be tracked over time in longitudinal studies, which may help researchers determine how health-related policies affect these factors. Besides, the study's findings were based on self-reported data that introduced information bias.

Further, our sample is disproportionately female since most study participants were housewives found in their homes at the time of data collection instead of the income person. Finally, we considered only two large cities, including the capital city; however, we could not include the slum areas of the entire country. The nationwide representative samples should be focused on in future research.

Conclusions and recommendations

The study investigated the psychological antecedents of COVID-19 vaccination acceptability among slum dwellers in two Bangladeshi cities. Vaccine acceptance was higher among slum inhabitants who were confident, complacent, calculated, and collectively responsible. Further, individuals who received information from the newspaper were more inclined to accept the COVID-19 vaccine. Similarly, more significant percentages of slum dwellers believed coronaviruses were naturally occurring and refused to get vaccinated. Marital status, education, family income, and perceived health condition significantly predicted the 5C domains. Two antecedents, complacency, and collective responsibility, were significantly associated with vaccine acceptance.

These results might assist policymakers in developing appropriate measures for increasing vaccine acceptance among the urban slum population of Bangladesh. Government activities and laws, the media, and healthcare organizations should play a vital role in influencing the public's attitude regarding COVID-19 vaccinations to maximize vaccination acceptance. To convince the public to vaccinate against COVID-19, several social actors, the great majority of whom are often marginalized from mainstream politics and health policy, would need to collaborate. In addition, vaccination reluctance might be reduced with an effective communication campaign that debunks COVID-19 vaccination conspiracy theories. This may be achieved by highlighting the need to communicate clear information *via* reliable sources (e.g., scientists and scientific journals) and fact-checking the statements made on television, newspapers, and social media platforms. Finally, the Government of Bangladesh should initiate public health education programs among the urban slum population to increase their basic health literacy, with a larger focus on the perception of vaccination benefits and disease severity.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Research Ethical Clearance Board of the Institute of Disaster Management, Khulna University of Engineering & Technology, Khulna, Bangladesh. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

MP: conceptualization, methodology, formal analysis, writing—original draft, review and editing. MB: conceptualization, survey development, data curation, and writing—original draft. SA: conceptualization, survey development, and writing—original draft. MeH, FI, SR, MN, and MaH: conceptualization, survey development, data collection, and data curation. MZH and AD: conceptualization and survey development. MRH, AR-M, FS, SN, and SS: writing—review and editing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Effectiveness of Pfizer/BioNTech and Sinopharm COVID-19 vaccines in reducing hospital admissions in prince Hamza hospital, Jordan

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Background: There is a need to establish the effectiveness of the coronavirus disease 2019 (COVID-19) vaccines in reducing COVID-19-related hopitalization of patients in Jordan. As the vaccination program accelerates, it is important to determine whether the vaccines' effectiveness (VE) has successfully reduced the number of acute cases admitted to hospital.

Methods: To determine the efficacy of Pfizer-BioNTech and Sinopharm COVID-19 vaccines among Jordanian patients admitted to Prince Hamza hospital, a single center case-control study was performed. The study analyzed the hospitalization rates of vaccinated ($n = 536$) and unvaccinated ($n = 585$) individuals across the 2-month period from February 6 to April 6, 2022. The cases were patients who tested positive for SARS-CoV-2 ("case-patients"), whilst the control group were hospital patients who did not test positive for SARS-CoV-2 ("control-patients").

Results: This study found that among 1,121 total participants (561 cases and 560 control), the overall vaccine effectiveness (VE) among the participants was 84% (95% CI 79–88%). VE was higher in females (88%, 95% CI 84–93%) than in males (77%, 95% CI 67–84%) ($p < 0.001$), and it was highest in those between the ages of 18 and 28-years-old (95%, 95% CI 86–98%). For patients with pre-existing conditions, including chronic heart disease, chronic lung disease, and diabetes, VE was higher compared to patients with no comorbidities, though the difference was not statistically significant. Finally, in comparing all vaccinated participants, VE was higher for those who received the Pfizer vaccine (VE = 92%, 95% CI 88–94%) (OR 0.08, 95% CI 0.06–0.12) than for those who received the Sinopharm vaccine (VE = 67%, 95% CI 52–78%) (OR 0.33, 95% CI 0.22–0.48); ($p = 0.011$).

Conclusion: Overall, Pfizer and Sinopharm vaccines were found to be effective in limiting hospitalizations for acute cases of coronavirus among Jordanian adult's patient's cohort between February 6 and April 6, 2022, especially among patients with comorbidities.

KEYWORDS
COVID-19, hospital admission, Pfizer, Sinopharm, Jordan

Introduction

In December 2019, the acute respiratory syndrome coronavirus (SARS-CoV-2) emerged in China and rapidly spread across the world, jumpstarting a global pandemic that has persisted (1). As scientists and medical professionals all over the world have turned their attention to fighting COVID-19, a multitude of medications have been proposed with therapeutic capability, including Camostat, Darunavir, Ivermectin, Remdesivir, Resveratrol, and Ritonavir (2, 3). Moreover, a considerable efforts are being made globally to develop safe and effective vaccines against coronavirus as a primary prophylactic intervention.

Many companies have introduced candidate vaccines, each with various indications, contraindications, and adverse events, but ultimately all providing differing levels of efficacy in preventing infection, acute outcomes, and death as a result of coronavirus infection (4). Therefore, evaluating the effectiveness of authorized vaccinations is vital. At the time that the data for this study was collected, Jordan was undergoing its third wave of coronavirus, which has been attributed to the highly transmittable Omicron variant. As of March 23, 2022, the number of positive cases was recorded to be 1,689,314, and there were 14,003 deaths, and the situation has only escalated since (5). For a country with approximately 10 million people, this rate of infection and death toll represents a significant portion of the population. The government has consequently enforced stricter safety measures to combat the outbreak (6). Furthermore, while the Ministry of Health in Jordan launched a national vaccination campaign on December 23, 2020, inviting everyone who lives in the country to register for free coronavirus vaccinations, only about 4.41 million (∼43.2%) of the population have been fully vaccinated at this point.

One of the several studies that have considered explanations for the country's low vaccination population found that misinformation and conspiracy theories, primarily ones that discredit the vaccine's ability to reduce rates of hospitalization, have had a negative impact on vaccine administration among Jordanians (7). As this may be a major impediment in Jordanians' willingness to receive the vaccination, determining various vaccines' effectiveness in limiting rates of hospitalization due to acute cases of coronavirus is paramount for the country's overall competency in managing the pandemic. Therefore, this study will compare the most commonly administered vaccines among Jordanian adults admitted to one governmental hospital in Jordan—the mRNA Pfizer-BioNTech vaccine and the inactive Sinopharm vaccine—to determine their overall efficacy in limiting hospitalization.

Methodology

Study design

To consider each vaccine's effectiveness in preventing coronavirus-related hospitalizations among sample of Jordanians patients, this study used a retrospective case-controlled analysis of 1,121 adults over the age of 18 years who were hospitalized at Prince Hamza Hospital in Jordan between February 6 and April 6, 2022. Prince Hamzah Hospital is the main isolation and treatment center for COVID-19 in Jordan. The sample consisted of patients who tested positive for SARS-CoV-2 and had also received either the Pfizer-BioNTech or the Sinopharm vaccination. The control group was comprised of patients who were admitted to the hospital but did not test positive for SARS-CoV-2. Any individuals with immune compromising conditions were excluded from the pool.

The pool of hospitalized patients due to coronavirus consisted of individuals who had both a positive test for SARS-CoV-2 within 10 days of symptom onset and a diagnosis of a clinical syndrome that signals an acute case of coronavirus, which includes ≥1 of the following: fever, cough, shortness of breath, loss of smell, requiring respiratory support, or new pulmonary findings on chest imaging consistent with pneumonia. The control group consisted of patients who were hospitalized without an indication of acute coronavirus and who tested negative for SARS-CoV-2.

Data collection

A standardized medical record review provided demographic information including age, gender, medical history, SARS-CoV-2 vaccination status, and other patient characteristics. Specific details of patients' SARS-CoV-2 vaccine administrations, including dates and vaccine suppliers, were supplied through source verification of documents like vaccine cards or hospital records.

Classification of vaccination status

Patients' vaccination status was categorized based on the number of vaccine doses received before the reference date (i.e., the date of symptom onset for coronavirus-positive patients), ("case-patients"), and the date of hospitalization for coronavirus-negative patients ("control-patients"). All hospitalized patients were determined to be either "fully vaccinated" or "unvaccinated." Because both Pfizer and Sinopharm SARS-CoV-2 vaccinations were administered as a two-dose series and protective immunity is not expected immediately after the first dose, participants were only considered "fully vaccinated" fourteen days after receipt of the second vaccine dose (8). Subsequently, patients who had received no vaccine before the reference date were considered "unvaccinated." All other vaccine scenarios, including those who received the first dose less than fourteen days before the reference date were excluded from the study. This included patients who received vaccinations from vaccine suppliers other than Pfizer-BioNTech or Sinopharm, vaccines that were not authorized in Jordan, patients who received vaccine doses from different suppliers, or patients who only received one dose. Patients who had previously contracted coronavirus were also excluded from the study.

Statistical analysis

By comparing the vaccination status of case patients and control patients, VE was calculated using the following expression: VE = (1–odds ratio) × 100% (9). The 95% confidence intervals (CI) were determined using the formula $1–CI_{OR}$, where CI_{OR} is the confidence interval of the odds ratio estimates.

VE estimates were stratified by age group, designated in 10-year increments (18–28, 28–38, 38–48, 58–68, and >68-years-old), SARS-CoV-2 vaccine supplier (Pfizer-BioNTech or Sinopharm), and the following underlying medical conditions: diabetes mellitus, chronic lung disease, chronic cardiovascular disease, and obesity. Characteristics of cases and controls were compared by employing chi-square tests or Fisher's exact tests for categorical variables and Student's t-test or Wilcoxon rank-sum tests for continuous variables.

Hashemite University and Prince Hamza Hospital's Ethics Service Committee granted ethical approval for this case study (reference number 5/3/2020/2021).

Results

A total of 186 patients, who were hospitalized at Prince Hamza Hospital between February 6 and April 6, 2022, were excluded from this study. Of these, 36 had an immune compromising condition, 66 had received ≥1 vaccine dose other than a Pfizer-BioNTech or Sinopharm vaccine, and 84 did not meet other eligibility criteria. The remaining 1,121 recorded patients included 561 case-patients and 560 control-patients. Overall, 585 (52%) patients were unvaccinated and 536 (47.5%) were vaccinated. Of those who were vaccinated, 205 (18%) were fully vaccinated with the Sinopharm vaccine and 331 (29.5%) were fully vaccinated with the Pfizer-BioNTech vaccine (Figure 1). Demographically, 51.4% of all participants were female while the remaining 48.6 % were male. The median age of the participants was 58-years-old. While most cases occurred in individuals between the ages of 38 and 68-years, 22.6% of recorded cases were individuals below the age of 38-years and 14% of cases were individuals over the age of 68 (Table 1). The age distribution among vaccinated and non-vaccinated groups aligned approximately equally, revealing an appropriate parallel from which to draw accurate conclusions between the control and test groups.

The medical record review concluded that 52% of case-patients and 45.7% of control-patients had at least one underlying condition ($p > 0.001$). The most prevalent underlying conditions reported for both case-patients and control-patients, respectively, were chronic heart disease (22%; 21%) and diabetes (27%; 21.4%) (Table 1). Finally, the median time between the final vaccine dose and symptom onset was 23 weeks for case-patients (IQR 15.3, 32.5) and 23.5 weeks for control-patients (IQR 14.7, 32.1).

The risk of coronavirus infection among vaccinated groups was 0.28 (149/536) while the risk of coronavirus infection among unvaccinated groups was 0.7 (418/585), suggesting a risk ration of 0.4 and odd ration of 0.16 (95% CI 0.12–0.21). VE among hospitalized patients included in the sample was 84% (95 CI 79–88%). In terms of VE by supplier, those who had received the Pfizer-BioNTech vaccine had a higher VE rate (VE = 92%, 95% CI 88–94%) (OR 0.08, 0.06–0.12) than the Sinopharm vaccine (VE = 67%, 95% CI 52–78%) (OR 0.33, 95% CI 0.22–0.48) ($p = 0.011$). Additionally, the risk of coronavirus infection among patients who received the Pfizer-BioNTech was 0.22 compared to 0.36 among those who received the Sinopharm vaccination.

Demographically, point estimates were higher for people ages 18–28-years-old (95%; 95% CI 86–98%) than any other age range. For those with comorbidities, VE was higher for patients with underlying cardiovascular disease (90.0%; 95% CI 83–94%), chronic lung disease (92%; 95% CI 84–96%), and diabetes mellitus (88%; 95% CI 81–93%) compared with patients who had no underlying conditions (Table 2).

While the Pfizer-BioNTech vaccine's effectiveness against infection increased only after the first twenty weeks following the vaccination, the Sinopharm vaccine markedly decreased 4 weeks after the final dose was administered (Figure 2).

Discussion

An essential element of managing the COVID-19 pandemic involves vaccines. Our study indicates that two doses of Pfizer-BioNTech or Sinopharm vaccines at least fourteen days after administration provided significant reduction in coronavirus-associated hospitalizations at Prince Hamza Hospital in Jordan. Based upon the hospitalization rates of patients in our patient cohort, it is evident that Sinopharm (VE 92%) is less effective than Pfizer-BioNTech (VE 67%) These results are consistent with previous studies, in particular, those done during the period between March and July, and February and August 2021, which

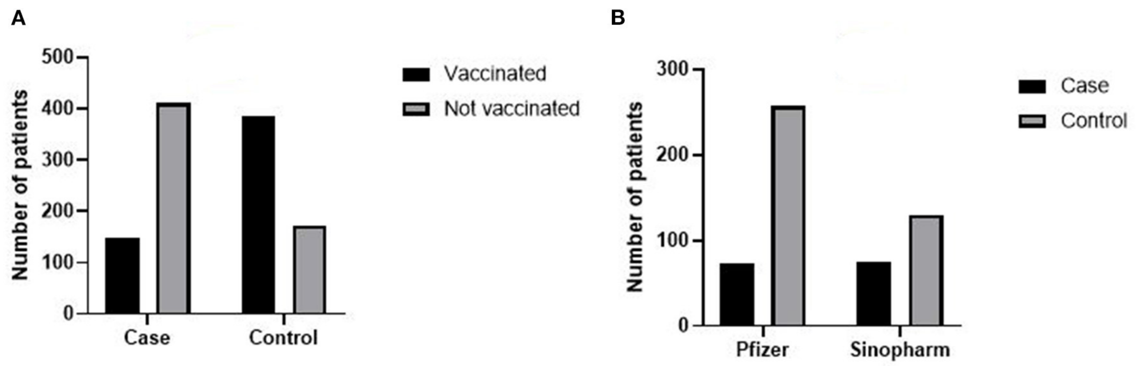

FIGURE 1
(A) Number of vaccinated and non-vaccinated patient among cases and control group case and control patient included in this study. **(B)** Number of patient vaccinated with Pfizer and Sinopharm COVID-19 vaccination among cases and control.

TABLE 1 Characteristics of Jordanian hospitalized COVID-19 case-patients and controls.

Characteristic	Cases ($n = 561$)	Control ($n = 560$)	*P*
Age group			
18–28	43	50	0.32
28–38	84	78	0.07
38–48	101	93	0.1
48–58	148	134	0.24
58–68	106	119	0.49
>68	79	86	0.014
Gender			
Male	256	288	0.97
Female	305	272	0.91
Underlying medical conditions			
Chronic cardiovascular disease	123	117	0.23
Chronic lung disease	17	19	0.29
Diabetes mellitus	153	120	0.37

showed the VE of Pfizer-BioNTech and Sinopharm against hospitalization rates to be 86% (95% CI = 82–88%) (10, 11), and 79.6% (95% CI 77.7–81.3%) (12).

On the other hand, this study finds that the VE is lower than in some other assessments in preventing hospitalization due to coronavirus. These other case studies, which examined the same vaccination suppliers as this study, suggested that the VE for fully vaccinated individuals to be 96% (95% CI 49–99%) among adults who received Pfizer-BioNTech vaccines and 81% (95% CI 88–93%) among adults who received the Sinopharm vaccines (13, 14). This study of a sample of hospitalized Jordanians occurred between February 7 and April 7, 2022, when the dominant SARS-CoV-2 variant was considered to be Omicron. This variant surpassed the former Delta variant as the dominant circulating virus in Jordan early in January 2022. Several studies targeted the Delta variant specifically, possibly accounting for the observed differences in VE values among other studies. For that reason, it is critical to interpret VE results cautiously and draw careful comparisons to other vaccine-effectiveness studies conducted in other contexts.

The findings of this study revealed that although both vaccines alleviated the risk of being hospitalized, each offered a different level of protection. For instance, patients given the Pfizer-BioNTech formula exhibited comparatively modest attenuation of VE, and they were more protected than their counterparts, whom received the Sinopharm vaccine, but their protection levels fell significantly. Furthermore, it supports other emerging evidence to suggest that, while VE waning is an expected result following the second dose of both Pfizer-BioNTech and Sinopharm vaccines (15–17), the Sinopharm vaccine in particular is less effective against the Omicron variant, as its initial effectiveness steadily declines 1 month following the second dose (18).

Our findings can be contextualized against several other studies vaccines' efficiency levels. For instance, an assessment of registries in Sweden indicated a sharp fall in vaccine efficacy against the risk of being hospitalized after 25 weeks (19). Meanwhile, Feikin, Higdon (20) conducted a systematic evaluation, which determined that in the 6-month post-vaccination period, vaccine efficacy against the acute risk of disease fell by 9.7 percentage points (95% CI 5.9–14.7). According to Mateo-Urdiales, Alegiani (21), the fall in vaccine efficacy became less evident at the 6-month mark, although researchers found a hint of a possible decrease in relation to the rising Delta variant cases at the conclusion of the follow-up phase.

TABLE 2 Vaccine effectiveness of Pfizer-BioNTech and Sinopharm vaccines against COVID-19 hospitalization overall and by subgroup.

Subgroup	Vaccinated cases	Vaccinated control	Odds ratio (95% CI)	Vaccine effectiveness (95% CI)	
	Patient/total case patient (%)	Patient/total control patient (%)			
Overall	149/561 (27.7)	387/560 (72.3%)	0.16 (0.12–0.21)	84% (79–88%)	$P < 0.0001$
18–28	6/45 (13%)	38/50 (76%)	0.05 (0.02–0.14)	95% (86–98%)	$P < 0.0001$
28–38	23/84 (27%)	58/81 (71.6%)	0.15 (0.08–0.30)	85% (70–92%)	$P < 0.0001$
38–48	24/101 (23.7%)	63/90 (70%)	0.13 (0.07–0.25)	87% (75–93%)	$P < 0.0001$
48–58	52/141 (36.8%)	89/130 (968.4%)	0.27 (0.16–0.45)	73% (55–84%)	$P < 0.0001$
58–68	27/112 (24%)	78/121 (64.5%)	0.185 (0.10–0.31)	81% (69–90%)	$P < 0.0001$
>68	17/78 (21.8%)	61/88 (69%)	0.12 (0.06–0.25)	88% (75–94%)	$P < 0.0001$
Sinopharm	75/205 (36.5%)	130/205 (63.5%)	0.33(0.22–0.48)	67% (52%—78%)	$P < 0.0001$
Pfizer	74/331 (22.3%)	257/331 (77.7%)	0.08 (0.06–0.12)	92% (88–94%)	$P < 0.0001$
Chronic cardiovascular disease	51/200 (14%)	113/146	0.10 (0.06–0.17)	90% (83–94%)	$P < 0.0001$
No chronic cardiovascular disease	98/361	274/414	0.19 (0.14–0.26)	81% (74–86%)	$P < 0.0001$
Chronic lung disease	27/108	86/107	0.08 (0.04–0.16)	92% (84–96%)	$P < 0.0001$
No chronic lung disease	122/453	301/453	0.17 (0.14–0.28)	83% (72–86%)	$P < 0.0001$
Diabetes mellitus	56/205	103/135	0.12 (0.07–0.19)	88% (81–93%)	$P < 0.0001$
No Diabetes mellitus	93/356	284/407	0.15 (0.11–0.21)	85% (81–89%)	$P < 0.0001$
Obesity by body mass index	30/113	74/107	0.16 (0.09–0.29)	84% (71–91%)	$P < 0.0001$
No obesity	119/448	313/453	0.16 (0.12–0.22)	84% (82–88%)	$P < 0.0001$
Gender					
Male	71/256 (27.7%)	180/288 (62.5%)	0.23 (0.16–0.33)	77% (67–84%)	$P < 0.0001$
Female	78/305 (25.5%)	207/272 (76%)	0.12 (0.07–0.16)	88% (84–93%)	$P < 0.0001$

Echoing the findings of Niessen et al. (22), we found higher VE in patients with comorbidities than in patients without comorbidities. In Niessen and Knol's study, a subgroup analysis of various comorbid conditions found partial and full vaccination of COVID-19 patients conferred some protection for all the comorbidities evaluated. Excluding immune compromised patients, the estimated VE for full vaccination exceeded 96% (95% CI 77–99) for comorbid patients, whereas the VE in patients without comorbidities was 93% (95% CI 82–98) (22). However, these results contradict other research, which found reduced VE in diabetic patients (23), and those with more than one comorbidity (24). For example, Yelin et al. (25) found a negative association between VE and the chronic comorbidities of COPD, immunosuppression, hypertension and type 2 diabetes. However, according to Pellini et al. (28), the efficacy and safety of COVID-19 vaccines in comorbid patients are comparable to that of non-comorbid patients. One explanation proposed by Godbout and Drolet (29) that could account for our findings is that comorbid patients had less social interaction than patients without underlying conditions had. The difference in the number of contacts between the two populations prior to the Christmas 2020/2021 holidays was statistically significant (comorbid contacts = 2.9 (95% CI 2.5–3.2) vs. non-comorbid contacts = 3.9 (95% CI 3.5–4.3); $P < 0.001$) (26).

Our study found that the maximum VE occurred in patients aged 18–28-years-old (95%; 95% CI 86–98%). This finding is similar to those reported by other researchers, who found the antibody response to be greater in younger people than in older people (27–29). However, these finding are not unanimous, as Salmerón Ríos, Mas Romero (30) did not detect any relationship between antibody response and age, though their findings could be limited by its sample, which was of residents in long-term care facilities. The participants in that study ranged in age from 65 to 99-years-old (mean 82.9 years) and by virtue of being in long-term care, had various disabilities and frailties. The majority of the studies found that a subset of pro-inflammatory B cells increased and the quality of memory B cells and plasma cells was affected, which resulted in a reduced humoral immune response (28). Furthermore, the rate of change in titers of antibodies

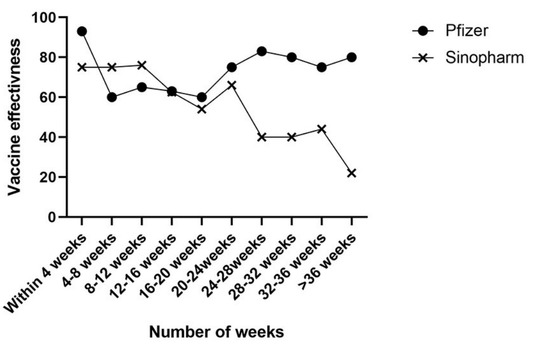

FIGURE 2
Change in vaccine effectiveness based on number of week after 2 dose Pfizer and Sinpoharm COVID-19 vaccination.

in people <50-years-old were appreciably lower than those of people older than fifty (29). Although there was a marked difference in the antibody response after first dose of COVID-19 vaccine, the response diminished over time; this effect was more pronounced following the second dose (29, 31). The vaccine-initiated antibody response has implications for COVID-19 vaccination programs, indicating that to maintain the response in older people, multiple boosters are required (32). These findings also emphasize the benefits of implementing strategies and individualized vaccination programs that can minimize the age-related inadequacies of the COVID-19 vaccines (33).

In a comparison of the sexes, we found VE was greater in females than males; this observation may be attributed to hormonal differences between the sexes. It is recognized that estradiol in females promotes adaptive and innate immune responses, whereas these same responses are dulled by testosterone in males; therefore, the antibody response is greater in females than males (34). Notarte, Ver (35) also noted that the humoral response and adverse events due to the COVID-19 mRNA vaccines is greater in females.

An important finding reported by Ma, Hao (36) is that replication of the SARS-CoV-2 virus can be inhibited directly by estrogen. The hormone limits the incidence of SARS-CoV-2 infection modifying cell metabolism genes, thereby sustaining cell integrity and enhancing metabolic function. Conversely, immune cell activity and androgen receptors are subdued by testosterone, which reduces inflammation and stimulates anti-inflammatory responses. Consequently, compared to males, females have an innate physiologic lead when initiating immune responses to infections (36).

Limitations of this study include diversity of the sample pool, identification of the virus variant, and antibody measurements. First, this study did not consider children, immune compromised adults, or individuals who tested positive for coronavirus but were not hospitalized. Second, supplier-specific effectiveness among a variety of virus variants could not be determined as variants were largely unknown. Thirdly, our study is disadvantaged by inconsistent serological undertakings at admission. This means we could not assess immune status prior to hospitalization; nor could we quantify vaccine-induced antibody levels to correlate with vaccine effectiveness. This information would have enabled us to develop deeper and broader knowledge about the effectiveness of the vaccines.

Further, estimates of vaccine effectiveness could be compounded by certain behavioral measures that were not considered in this study. For example, the use of non-pharmaceutical interventions, including mask use, social distancing, and exposure risks have been found to be useful in preventing coronavirus infection, much apart from one's vaccination status (37).

In conclusion, this study demonstrated that Pfizer-BioNTech and Sinopharm vaccines were effective in reducing the rate of hospitalization among a sample of 1,121 adult Jordanians patients between February 7 and April 7, 2022. Vaccines were found to be particularly effective for patients with comorbidities and younger age groups. In addition, this research emphasizes the importance of monitoring vaccine effectiveness over time, rather than at an isolated moment. It reiterates the useful and increasingly relevant role served by booster doses in restoring high levels of protection that were observed early in the vaccination roll out. Understanding vaccine effectiveness by vaccine supplier can guide individual choices and policy recommendations regarding the continued administration of coronavirus vaccines, as well as subsequent boosters in providing substantial and significant protection against coronavirus hospitalization. Moving forward, this study hopes to add to the ongoing research and increasing information around preventative measures to fight coronavirus. Future research that explores the interdependence of age, comorbidities, serostatus, and sex and the relationships between them with humoral responses is warranted. Also, studies could compare the extent and nature of humoral responses of other COVID-19 vaccines, such as Johnson & Johnson, and Moderna (mRNA 1273), and the vaccines evaluated in this study.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by Hashemite University and Prince Hamza Hospital's Ethics Service Committee (reference number 5/3/2020/2021). The patients/participants provided their written informed consent to participate in this study.

Author contributions

HA-M was responsible for the study design, analyzed data, and wrote the manuscript. KA, EA, YA, and ZA responsible for data collection and co-wrote the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.1008521/full#supplementary-material

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Immunogenicity and safety of SARS-CoV-2 vaccine in hemodialysis patients: A systematic review and meta-analysis

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Rationale and objective: COVID-19 vaccination is the most effective way to prevent COVID-19. For chronic kidney disease patients on long-term dialysis, there is a lack of evidence on the pros and cons of COVID-19 vaccination. This study was conducted to investigate the immunogenicity and safety of COVID-19 vaccines in patients on dialysis.

Methods: PubMed, MEDLINE, EMBASE, and the Cochrane Library were systemically searched for cohort, randomized controlled trials (RCTs), and cross-sectional studies. Data on immunogenicity rate, antibody titer, survival rate, new infection rate, adverse events, type of vaccine, and patient characteristics such as age, sex, dialysis vintage, immunosuppression rate, and prevalence of diabetes were extracted and analyzed using REVMAN 5.4 and Stata software. A random effects meta-analysis was used to perform the study.

Results: We screened 191 records and included 38 studies regarding 5,628 participants. The overall immunogenicity of dialysis patients was 87% (95% CI, 84-89%). The vaccine response rate was 85.1 in hemodialysis patients (HDPs) (1,201 of 1,412) and 97.4% in healthy controls (862 of 885). The serological positivity rate was 82.9% (777 of 937) in infection-naive individuals and 98.4% (570 of 579) in patients with previous infection. The Standard Mean Difference (SMD) of antibody titers in dialysis patients with or without previous COVID-19 infection was 1.14 (95% CI, 0.68–1.61). Subgroup analysis showed that the immunosuppression rate was an influential factor affecting the immunogenicity rate ($P < 0.0001$). Nine studies reported safety indices, among which four local adverse events and seven system adverse events were documented.

Conclusions: Vaccination helped dialysis patients achieve effective humoral immunity, with an overall immune efficiency of 87.5%. Dialysis patients may experience various adverse events after vaccination; however, the incidence of malignant events is very low, and no reports of death or acute renal failure after vaccination are available, indicating that vaccine regimens may be necessary.

Systematic review registration: https://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42022342565, identifier: CRD42022342565.

KEYWORDS

COVID-19 vaccine, dialysis, immunogenicity, end stage kidney disease (ESKD), system review, meta-analysis

Introduction

Since the rapid transmission and wide variability of the novel coronavirus, developing a highly effective vaccine against the stubborn pathogen has become vital (1). Several SARS-CoV-2 vaccines have been developed and are currently administered to people worldwide to achieve effective immunity (2). According to a cohort study in Chile involving 10.2 million people, inactivated vaccines were effective at preventing COVID-19 as well as reducing the incidence of severe disease and death (3). The latest clinical trials have demonstrated that they can effectively reduce morbidity and mortality and the incidence of adverse events in a healthy population (4, 5). Vaccination against COVID-19 raises the hope that humans can defeat the disease.

Patients with end-stage renal disease (ESRD) rely on hemodialysis (HD), peritoneal dialysis (PD), and other renal replacement therapies to facilitate the removal of toxins and metabolic waste from the body to compensate for a patient's dysfunctional kidneys and maintain the body's water and acid-base balance. Multiple complications are often associated with dialysis, of which diabetes mellitus and hypertension are the most closely related (6). Additionally, advanced age, diabetes, hypertension, and smoking are all risk factors for COVID-19 (7, 8). Furthermore, the long-term use of immunosuppressants and the loss of immune proteins caused by the increase in renal basement membrane permeability jointly led to immunosuppression in dialysis patients. In such situations, HDPs were at a higher more at risk of COVID-19 infection, and may lead to adverse outcomes (9). Therefore, it can be assumed that dialysis patients benefit from an effective vaccine. However, for immunocompromised patients, inadequate immune efficacy after other vaccination such as hepatitis B vaccine has raised concern of the efficacy and safety of COVID-19 vaccines (10, 11). Currently, the benefits and costs of COVID-19 vaccination for immunocompromised populations still remain controversial.

Given the higher infection rate and lower resistance to virus than healthy individuals, the risks of vaccination in HDPs should be considered (12). After all, it remains to be seen whether patients with an immune deficiency can produce an adequate immune response against the virus. Furthermore, patients with impaired immunity risk experiencing uninformed health problems due to the toxicity of the vaccine itself. Therefore, more convincing evidence regarding the efficacy and safety of COVID-19 vaccines in hemodialysis patients is needed. This study was aimed to summarize available evidence on the efficacy and safety of COVID-19 vaccines in HDPs and to guide clinical practice.

Methods

A systematic review and meta-analysis were performed strictly per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). This meta-analysis has been recorded in the International Prospective Register of Systematic Reviews (PROSPERO) database (ID: CRD42022342565).

Search strategy

PubMed, MEDLINE, EMBASE, and Cochrane Library databases were searched for relevant articles published between January 1st, 2020 and September 30th, 2021, with medical subject headings (MeSH) terms and the corresponding entry terms. Additional search details can be found in the Supplementary materials. To conduct a comprehensive search, the references listed in the retrieved studies were reviewed for comparison.

Study selection

Prospective cohort studies, randomized controlled trials (RCTs), and cross-sectional studies investigating the immunogenicity of COVID-19 vaccines in patients undergoing maintenance hemodialysis were included. Studies reporting adverse events and vaccine safety were also included. Studies that reported immunogenicity only in peritoneal dialysis patients and kidney transplant recipients and non-English studies were excluded. Reference management software, Endnote, was used to find and remove duplicate literatures.

Data extraction

As part of the data extraction procedure, the literature was independently screened, and the included studies' titles, abstracts, and full text were checked. Patient characteristics, such as age, sex, rate of previous immunosuppression, Body Mass Index (BMI), and vaccination protocols, including doses and interval between vaccines, were extracted. In addition, the post vaccination humoral response, antibody titer, and rate of adverse events were collected regarding the outcomes. A consensus regarding the differences between the research selection and data extraction was reached through consultation.

Risk of bias assessment

The risk of bias in the included studies was assessed using the risk of bias in non-randomized studies of interventions (ROBINS-I) (13). There were seven Bias domains included in this scale, each of which was accessed to be "low," "moderate," "serious," "critical," and "no information." The opinions of five reviewers were combined and a consensus was reached on these controversial points.

Data synthesis and analysis

RevMan 5.4 and Stata software were used to conduct the analysis. This study pooled antibody titers, seropositivity, and adverse events in hemodialysis patients who received COVID-19 vaccines as the outcome indices. According to a previously published formula, some data with only median (IQR) coverage to mean ± SD for further analysis was converted (14). This meta-analysis was performed in REVMAN 5.4 and Stata using a random-effects model. A $\geq$ 50% value of the I^2 statistic was considered substantially heterogeneous for the pooled estimate. A sensitivity analysis was conducted to identify potential sources of heterogeneity by excluding studies with a high risk of bias. Subgroup analysis was performed to identify age, immunosuppression, dialysis vintage, the prevalence of diabetes, doses, the timing for detecting, continents and vaccine types to clarify the causes of heterogeneity.

Results

Study selection and population characteristics

In this paper, 78, 50, 63, and one potentially eligible article was collected by searching PubMed, EMBASE, MEDLINE, and Cochrane Library, respectively. After reviewing the titles and abstracts, 105 duplicate studies and 32 irrelevant studies were excluded. After reviewing the full text to further determine the study's eligibility, studies whose subjects did not meet the requirements and did not address the results of interest were excluded. Finally, a total of 38 studies investigating immunogenicity, with nine studies investigating vaccine safety, were included (Figure 1). Table 1 summarizes the data extracted from the selected studies (15–52).

Among the 38 included studies, 20 were prospective observational studies, four were retrospective studies, and one was a cross-sectional study (13 studies did not state the research types). Thirty-seven of the included studies reported the seropositivity rate in hemodialysis patients 1–8 weeks after receiving COVID-19 vaccine. On average, 17 of 38 studies compared the immunogenicity of dialysis patients with that of healthy volunteers. Seven studies examined the immunogenicity of dialysis patients with or without prior COVID-19. Six vaccine types (BNT162b2, AZD1222, mRNA-1,276, ChAdOx, BBV152, and Ad26.COV2. S) were studied to determine their immunological effects in HD patients.

The security of COVID-19 vaccines was evaluated by including indices of new infections, survival rates, and adverse events. Two studies reported the rate of new infections, three reported survival rates, and nine reported a variety of local and systemic adverse events.

Risk of bias assessment

Thirty-eight non-randomized studies were assessed by the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) (13). Among the 38 studies, 22 were rated as having a low risk of bias, 10 as moderate risk, and four as severe risk. Two other studies were classified as "no information" due to insufficient data (Supplementary Table S1).

Most questions in the included studies were precise and relevant to the goals of this study. Moreover, most studies collected data according to a previously developed protocol. In some studies, the reasons for exclusion were not specified. Several studies did not indicate how objective endpoints were evaluated and how the study size was calculated.

Immunogenicity of HD patients after receiving COVID-19 vaccine

A single-group meta-analysis of seropositivity rates of hemodialysis patients 2–8 weeks after vaccination revealed overall immunogenicity of 87% (95 CI, 84–89%) with high heterogeneity of $I^2 = 89.8\%$, as illustrated in Figure 2.

As shown in Figure 3, the vaccine response rate in hemodialysis patients (HDPs) was significantly higher than

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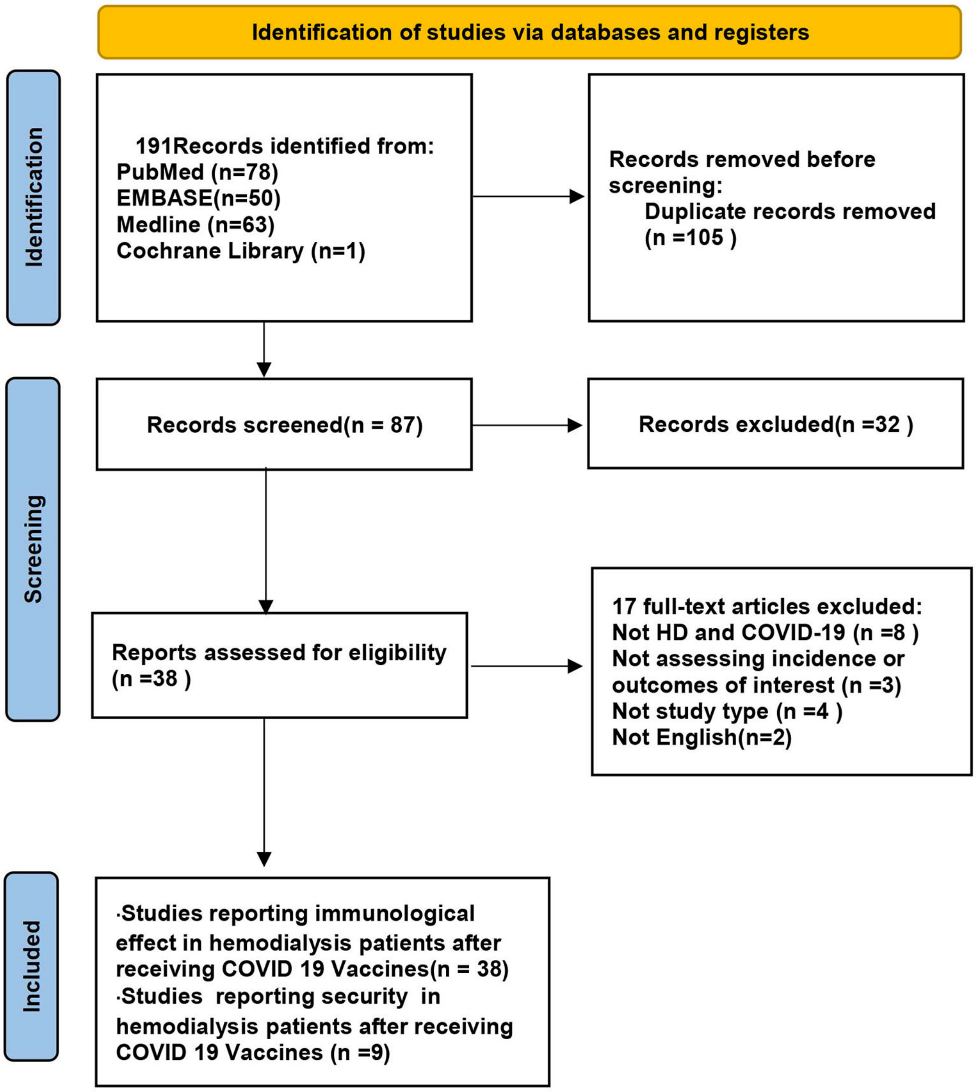

FIGURE 1
Study select progress of identification of studies via databases and registers.

that in healthy control groups (HCs). In HDPs, seropositivity was achieved in approximately 85.1% (1,201 out of 1,402) cases, whereas in HCs, it was achieved in 97.4% (862 out of 885) cases.

As shown in Figure 4, the seropositive conversion rate in patients without prior infection was lower than in patients with prior infection. It was 82.9% (777 of 937) in infection-naive patients and 98.4% (570 of 579) in patients with previous infections. Furthermore, antibody titers were compared among dialysis patients with and without prior COVID-19 infection, and the SMD was 1.14 (95% CI, 0.68–1.61), indicating that patients with prior infection are more likely to develop antibodies (Figure 5).

Sensitivity analysis

A sensitivity analysis was performed on the included studies by excluding individual studies. After removing each study from the analysis, the seropositivity rate showed no significant difference in the degree of heterogeneity. However, in terms of antibody titer, sensitivity analysis showed that heterogeneity was significantly reduced when one of the studies, Anand et al. (13), was removed. There was a change in the standard mean difference from 1.06 (95% CI, 0.56–1.57) to 1.24 (95% CI, 1.11–1.38), with a reduction in heterogeneity from 95 to 5% (Supplementary Figure S1). This may be because the study was performed in the early phase of vaccine rollout, with the elderly population and patients with complications being prioritized.

TABLE 1 Characteristics of included studies.

Study	Country	Population	Prior COVID infection	Age (Mean± SD)	Male (%)	BMI (kg/m^2)	Diabetes mellitus N(%)	Immuno-suppression N (%)	Dialysis vintage (months)	Name of vaccine	Dose	Criteria for positive response
Agur et al. (15)	Israel	HD/PD	NO	71.57 ± 12.87	33.6	26.69 ± 5.51	70 (57.4%)	NR	39.73 ± 32.59	BNT162b2	2	Anti-spike antibody >50 AU/ml
Anand et al. (16)	USA	HD	Mixed	NR	NR	NR	NR	NR	NR	BNT162b2	2	NR
Attias et al. (17)	France	HD	NO	71 ± 11.5	78.0	NR	33 (58%)	NR	NR	BNT162b2	2	Anti-spike antibody signal-to-cutoff <1
			YES	69 ± 13.5	77.0		7 (54%)					
Bertrand et al. (18)	France	KTRs/HD	NO	71.2 ± 16.4	51.0	NR	NR	NR	NR	BNT162b2	2	Anti-spike antibody >50 AU/ml
Billany et al. (19)	UK	HD	Mixed	62.1 ± 12.2	59.6	NR	43 (45.7%)	10 (10.6%)	NR	BNT162b2 /AZD1222	1	Anti-spike antibody >1 RLU/ml
Broseta et al. (20)	Spain	HD	NO	67.1 ± 16.0	67.9	NR	26 (33.3%)	NR	94.26 ± 127.75	mRNA-1273	2	Anti-spike antibody >50 AU/ml
Chan et al. (21)	USA	HD	NO YES	70 ± 11	93.0	NR	20(49%)	NR	NR	mRNA-1273	2	Anti-N IgG > 1.39, Anti-RBD IgG > 1.0
					100.0		15(75%)					
Clarke et al. (22)	UK	HD	Mixed	NR	NR	NR	NR	NR	NR	BNT162b2 /ChAdOx	2	NR
Cserep et al. (23)	UK	HD	NO	73 ± 11.67*	60.0	NR	31 (37%)	NR	NR	BNT162b2	2	NR
Danthu et al. (24)	France	HD/KTRs/HC	NO	73.5 ± 12.8	59.0	26.8 ± 5	42(53.8%)	NR	NR	BNT162b2	2	antibody>13 AU/ml
Duarte et al. (25)	Portugal	HD	NO	75.1 ± 11.7	59.5	NR	19 (45.2%)	NR	NR	BNT162b2	2	NR
		PD		60.5 ± 10.7								
Ducloux et al. (26)	France	HD/PD	Mixed	NR	NR	NR	NR	NR	NR	BNT162b2	2	Antibody >50 AU/ml
Espi et al. (27)	France	HD/HC	NO	64.9 ± 15.2	65.0	26.5 ± 6.5	37 (35%)	13 (12%)	50.7 ± 60.7	BNT162b2	2	Anti-RBD IgG > 1 AU/ml
Fernando and Govindan (28)	India	HD	NO	NR	NR	NR	NR	NR	NR	AZD1222 /BBV152	2	IgG anti-spike protein >0.8 U/mL
Frantzen et al. (29)	France	HD	NO	71.3 ± 12.7*	70.0	NR	90 (37%)	1(4.1%)	NR	BNT162b2	2	Anti-spike antibody >15 U/ml
Goupil et al. (30)	Canada	HD/HC	NO	70 ± 14	77.0	NR	72 (55%)	22 (16%)	45.6 ± 44.4	BNT162b2	1	NR
			YES	76 ± 12	53.0	NR	7 (37%)	1 (5%)	40.8 ± 38.4			

(Continued)

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TABLE 1 (Continued)

Study	Country	Population	Prior COVID infection	Age (Mean± SD)	Male (%)	BMI (kg/m^2)	Diabetes mellitus N(%)	Immuno-suppression N (%)	Dialysis vintage (months)	Name of vaccine	Dose	Criteria for positive response
Grupper et al. (31)	Israel	HD/HC	NO	74 ± 11	75.0	27.2 ± 4	35 (63%)	1 (2%)	38 ± 37	BNT162b2	2	Anti–spike antibody >50 AU/ml
Jahn et al. (32)	Germany	HD/HC	NO	68 ± 8.83*	43.1	NR	NR	NR	62.7 ± 66.0	BNT162b2	2	Antibody ≥13.0AU/mL
Labriola et al. (33)	Belgium	HD/HC	Mixed	80.7 ± 10.0*	44.0	NR	14 (41%)	NR	NR	BNT162b2	2	Anti-SARS-CoV-2 N >1.0 or anti-SARS-CoV-2 RBD >0.8 U/mL
Lacson et al. (34)	USA	HD	NO	68 ± 12	53.0	NR	NR	NR	58.1 ± 54.3	mRNA-1273 / BNT162b2	2	Antibody ≥2.0
Lesny et al. (35)	Germany	HD	NO	69.3 ± 17.4*	55.6	27.9 ± 4.3*	6 (26.1%)	3 (13.0%)	29.7 ± 29.2*	BNT162b2 /AZD1222	1	SARS-CoV-2 spike IgG ≥ 50 AU mL
Longlune et al. (36)	France	HD	NO	64 ± 14	68.8	NR	33(29.5%)	NR	39 ± 40	BNT162b2	2	Spike antibody signal-to-cutoff [S/CO] >1
Mulhern et al. (37)	USA	HD	Mixed	NR	NR	NR	NR	NR	NR	Ad26.COV2.S / mRNA-1273	2	Spike antibody signal-to-cutoff [S/CO] >1
Rincon et al. (38)	Germany	HD/HC	NO	71.3 ± 14.6*	70.0	NR	19(46.3%)	NR	66.0 ± 64.5*	BNT162b2	2	NR
Sattler et al. (39)	Germany	HD/KTRs/HC	NO	67.39 ±11.88	65.4	NR	12 (46.15%)	NR	82.4 ± 60.8	BNT162b2	2	NR
Schrezenmeier et al. (40)	Germany	HD/HC	NO	74 ± 12.4*	69.4	NR	16(44.4%)	NR	64.0 ± 64.9*	BNT162b2	2	Spike antibody signal-to-cutoff [S/CO] >1
Simon et al. (41)	Austria	HD	NO	67 ± 8.67*	55.0	NR	31(38.3%)	9(11.1%)	NR	BNT162b2	2	Antibody> 29 AU/mL
Speer et al. (42)	Germany	HD/HC	NO	78.7 ± 14.8*	60.0	25.3 ± 5.4*	6 (20%)	NR	37.3 ± 45.9*	BNT162b2	2	NR
Speer et al. (43)	Germany	HD/HC	NO	72.75 ± 10.25*	55.0	NR	14 (64%)	NR	84.0 ± 114.1*	BNT162b2	2	NR
Speer et al. (44)	Germany	HD	NO	83 ± 5.4*	63.0	26.0 ± 4.6*	18 (42%)	8 (19%)	50.0 ± 47.6*	BNT162b2	2	A semi-quantitative index of>1

(Continued)

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TABLE 1 (Continued)

Study	Country	Population	Prior COVID infection	Age (Mean± SD)	Male (%)	BMI (kg/m^2)	Diabetes mellitus N(%)	Immuno-suppression N (%)	Dialysis vintage (months)	Name of vaccine	Dose	Criteria for positive response
Strengert et al. (45)	Germany	HD/HC	NO	69 ± 18	58.0	NR	22 (27.16%)	10 (12.34%)	NR	BNT162b2	2	NR
Stumpf et al. (46)	Germany	HD/HC	NO	67.6 ± 14	65.1	27.5 ± 5.7	430(34.2%)	63(5%)	68.4 ± 67.2	mRNA-1273 / BNT162b2	2	NR
Torreggiani et al. (47)	France	HD/HC	NO	68.89 ± 14.86	59.0	NR	NR	NR	30.8 ± 34.9	BNT162b2	2	NR
Tylicki et al. (48)	Poland	HD	NO	69.3 ± 10.5	61.5	25.7 ± 5.3*	34 (37.4%)	6 (6.6%)	36.0 ± 34.7	BNT162b2	2	NR
			YES	65.7 ± 12.4	65.7	25.1 ± 4.5*	5 (14.3%)	2 (5.7%)	44.3 ± 52.6	BNT162b2	2	
Weigert et al. (49)	Portugal	HD/HC	NO	64 ± 49.4	67.8	NR	NR	NR	NR	BNT162b2	2	NR
Yanay et al. (50)	Israel	HD /PD/HC	NO	69.7 ± 12	63.0	NR	NR	NR	40.8 ± 34.0	BNT162b2	2	Anti-spike antibody >15 AU/ml
Yau et al. (51)	Canada	HD/HC	NO	73.7 ± 13.6	61.0	NR	45 (59%)	4 (5%)	35.2 ± 27.2	BNT162b2	2	NR
Zitt et al. (52)	Austria	HD	NO	67.6 ± 14.8	68.0	NR	NR	NR	NR	BNT162b2	2	NR

* Data are converted from the median (IQR) according to the formula in the article. Estimating the sample mean and standard deviation from the sample size, median, range, and/or interquartile range.

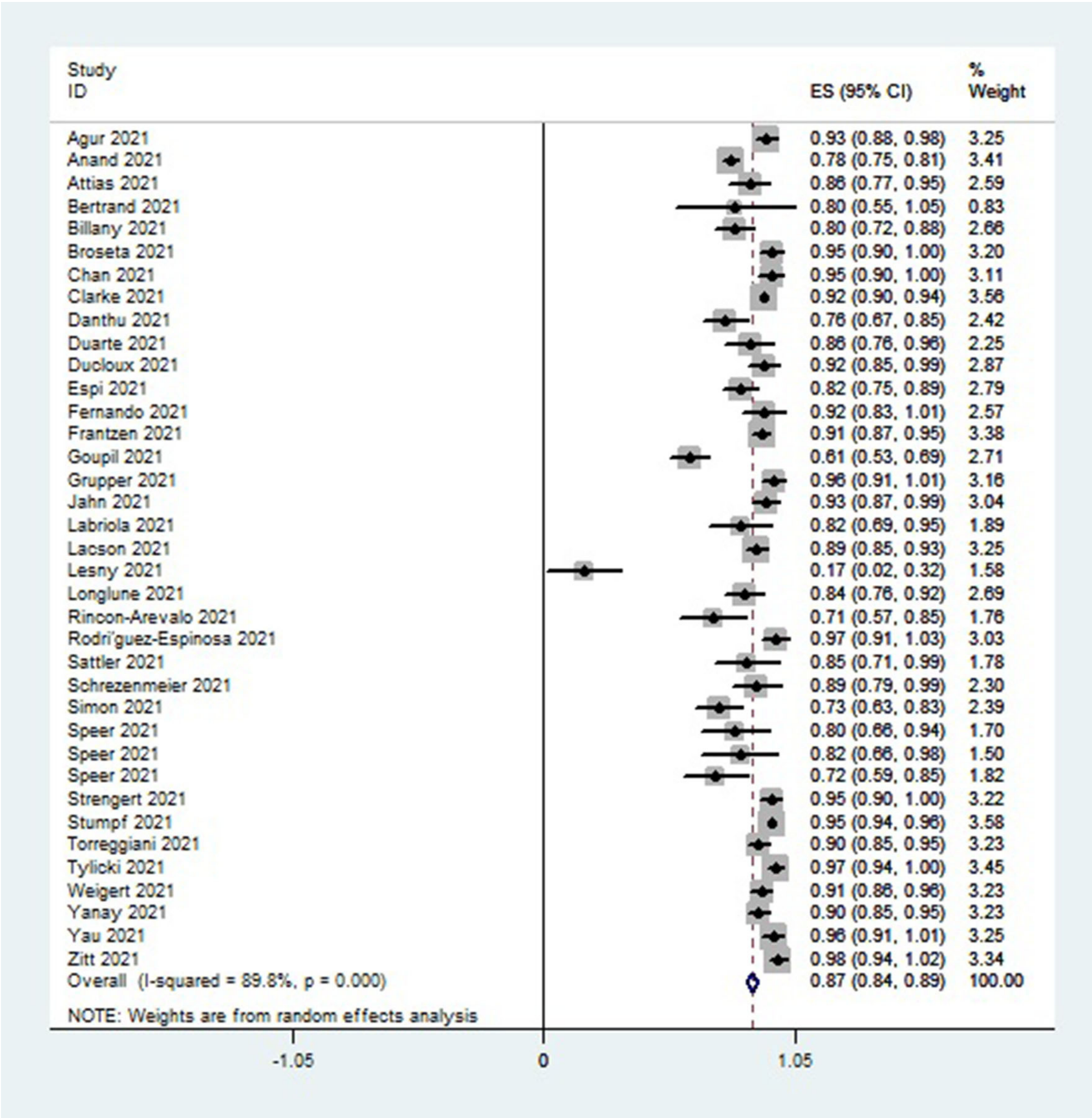

FIGURE 2
Forest plot of the immune response rate of HD patients who received COVID 19 vaccines, as obtained using Stata.

Subgroup analysis

A subgroup analysis was performed for age, immunosuppression, dialysis vintage and, the prevalence of diabetes, doses, the timing for detecting, continents and vaccine types to clarify the causes of heterogeneity to identify the possible sources of heterogeneity. Accordingly, low immunosuppression was defined as a rate <10% and high immunosuppression as a rate of 10%. As a result, the population with low immunosuppressive drug utilization rates is more likely to develop immunity to the virus (Figure 6). When studies were grouped according to doses, serological positivity was significantly higher in patients who received two doses of the vaccine than in those who did not complete two doses (Supplementary Figure S2). In addition, the forest plot of the age subgroups (Supplementary Figure S3) revealed no difference between the young (<70 years of age) and old (>70 years of age) groups. A further division was made between dialysis duration <36 months and dialysis duration ≥36 months. No statistically significant difference in dialysis vintage was observed (Supplementary Figure S4). Additionally, there was no significant correlation between the prevalence of

Study or Subgroup	HDP Events	HDP Total	Healthy Control Events	Healthy Control Total	Weight	Odds Ratio M-H, Random, 95% CI
Danthu 2021	59	75	7	7	2.7%	0.24 [0.01, 4.43]
Espi 2021	87	106	30	30	2.9%	0.07 [0.00, 1.26]
Goupil 2021	91	140	19	20	5.5%	0.10 [0.01, 0.75]
Grupper 2021	54	56	95	95	2.5%	0.11 [0.01, 2.42]
Jahn 2021	67	72	16	16	2.7%	0.37 [0.02, 7.07]
Labriola 2021	28	34	40	45	14.1%	0.58 [0.16, 2.10]
Lesny 2021	4	23	8	14	10.1%	0.16 [0.03, 0.72]
Rincon-Arevalo 2021	31	40	35	35	2.8%	0.05 [0.00, 0.84]
Schrezenmeier 2021	32	36	41	44	9.4%	0.59 [0.12, 2.80]
Speer 2021	24	30	18	18	2.7%	0.10 [0.01, 1.93]
Speer2 2021	14	17	46	46	2.5%	0.04 [0.00, 0.91]
Strengert 2021	77	81	34	34	2.7%	0.25 [0.01, 4.76]
Stumpf 2021	176	200	38	39	5.6%	0.19 [0.03, 1.47]
Torreggiani 2021	114	127	132	132	2.9%	0.03 [0.00, 0.54]
Weigert 2021	130	143	136	143	25.6%	0.51 [0.20, 1.33]
Yanay 2021	144	160	132	132	2.9%	0.03 [0.00, 0.56]
Yau 2021	69	72	35	35	2.6%	0.28 [0.01, 5.57]
Total (95% CI)		**1412**		**885**	**100.0%**	**0.25 [0.15, 0.40]**
Total events	1201		862			

Heterogeneity: Tau² = 0.00; Chi² = 15.68, df = 16 (P = 0.48); I² = 0%
Test for overall effect: Z = 5.67 (P < 0.00001)

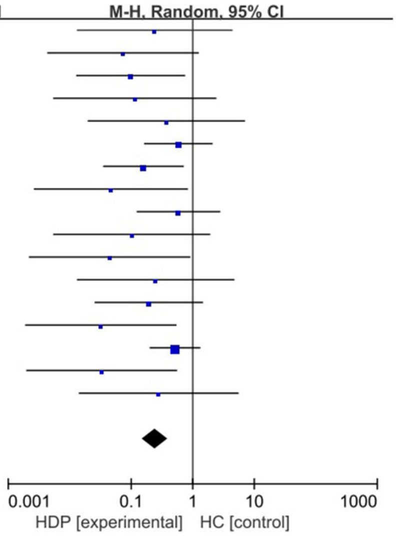

FIGURE 3
Forest plot of the positive immunity rate of HD patient vs. healthy control groups after receiving COVID 19 vaccines.

Study or Subgroup	COVID-19 history(+) Events	COVID-19 history(+) Total	COVID-19 history(-) Events	COVID-19 history(-) Total	Weight	Odds Ratio M-H, Random, 95% CI
Attias 2021	12	12	43	52	4.8%	5.46 [0.30, 100.48]
Chan 2021	20	20	38	41	4.5%	3.73 [0.18, 75.71]
Clarke 2021	15	15	40	45	4.7%	4.21 [0.22, 80.73]
Ducloux 2021	16	19	75	131	24.8%	3.98 [1.11, 14.33]
Goupil 2021	9	10	19	24	7.8%	2.37 [0.24, 23.36]
Labriola 2021	35	35	87	91	4.7%	3.65 [0.19, 69.60]
Tylicki 2021	463	468	475	553	48.8%	15.21 [6.10, 37.90]
Total (95% CI)		**579**		**937**	**100.0%**	**7.43 [3.93, 14.07]**
Total events	570		777			

Heterogeneity: Tau² = 0.00; Chi² = 5.01, df = 6 (P = 0.54); I² = 0%
Test for overall effect: Z = 6.16 (P < 0.00001)

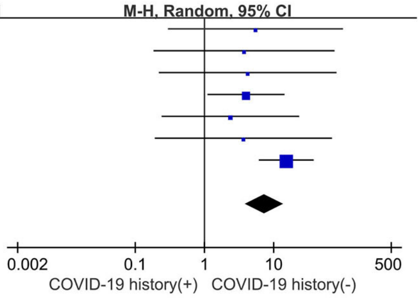

FIGURE 4
Forest plot of the immune response rate of HD patients with or without previous COVID-19 infection.

Study or Subgroup	COVID-19 history(+) Mean	COVID-19 history(+) SD	COVID-19 history(+) Total	COVID-19 history(-) Mean	COVID-19 history(-) SD	COVID-19 history(-) Total	Weight	Std. Mean Difference IV, Random, 95% CI
Anand 2021	107.73	94.22	610	67.63	103.09	553	19.2%	0.41 [0.29, 0.52]
Chan 2021	55.05	9.81	20	26.71	24.36	41	14.8%	1.34 [0.76, 1.93]
Clarke 2021	3,120.67	3,494.99	468	281.33	446.7	553	19.1%	1.19 [1.05, 1.32]
Ducloux 2021	9,409	16,412.68	15	1,137.67	1,772.82	45	14.5%	0.99 [0.38, 1.61]
Goupil 2021	90	160.19	19	4.67	3.75	131	15.7%	1.52 [1.01, 2.03]
Tylicki 2021	4,560	5,086.2	35	416.67	375.14	91	16.6%	1.54 [1.10, 1.97]
Total (95% CI)			**1167**			**1414**	**100.0%**	**1.14 [0.68, 1.61]**

Heterogeneity: Tau² = 0.29; Chi² = 98.51, df = 5 (P < 0.00001); I² = 95%
Test for overall effect: Z = 4.83 (P < 0.00001)

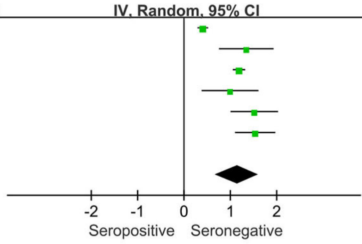

FIGURE 5
Forest plot of the antibody titer of HD patients with or without previous COVID-19 infection.

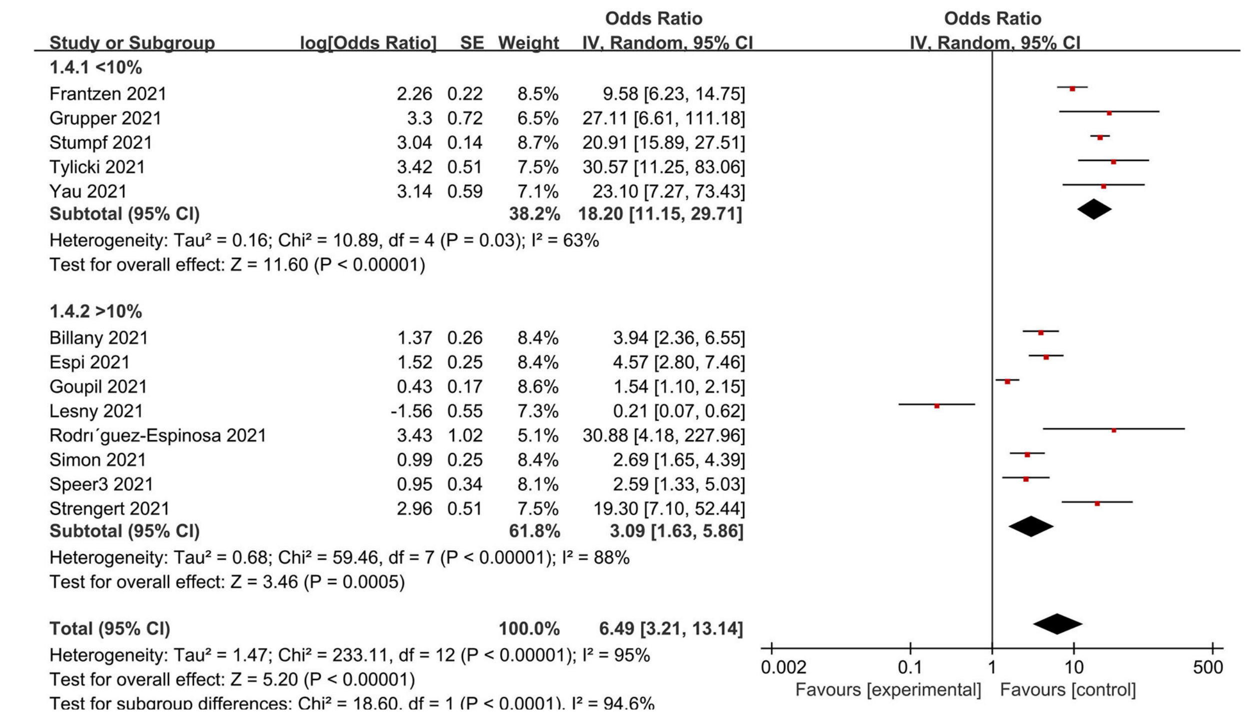

FIGURE 6
Subgroup analysis of immunosuppressant utilization rate.

diabetes mellitus and the serum positivity rate of the population (Supplementary Figure S5). Further studies showed that factors such as the type of vaccine, the time of testing after vaccination, and country and region were not the sources of heterogeneity in results (Supplementary Figures S6–S8).

Safety and adverse events

Nine studies examined the safety indices and adverse events following vaccination (20, 25, 33, 38, 41, 42, 47–49). The survival rate of dialysis patients receiving vaccination was high, and there were few deaths due to COVID-19. An extremely low rate of newly acquired infections was observed.

The following local adverse events were observed: pain at the injection site, redness, bruising, and swelling (Table 2). Pain at the injection site was the most common adverse event, accounting for 25% (95 CI, 11–40%), while other local reactions were sporadic (Supplementary Figure S9). Most adverse reactions were mild-to-moderate.

System adverse events that occurred less frequently were summarized (Table 3), which included fatigue, headaches, fevers, chills, nausea, diarrhea, muscle aches, and joint pain. The most common system adverse reaction was fatigue, accounting for 11% of all adverse reactions (95% CI, 6–18%) (Supplementary Figure S10).

Discussion

This review summarized recent studies on the efficacy and safety of COVID-19 vaccine in dialysis patients, so as to provide scientific guidance for clinical vaccination and application. It highlights that the vaccines elicited an adequate immune response in most patients, indicating it to be a sturdy shield to protect patients from the virus, despite the lower immunogenicity rates compared to healthy populations, which is consistent with many previous studies (15, 18, 20).

The low immunogenicity rate as well as inadequate innate and adaptive immune responses in dialysis patients is caused by a combination of reasons (53). In terms of pathogenesis, the progression of CKD is closely related to the dysfunction of autoimmune system, as the deposition of immune complexes will cause damage to the basement membrane. For current therapeutic interventions, the high rate of prolonged immunosuppressant use can hinder adaptive immune responses and contribute to COVID-19 severity (54). A retrospective study concluded that COVID-19 disease is more severe in patients taking prior immunosuppressive medications as the data showed that patients with COVID-19 having prior immunosuppressive therapy had significantly greater mortality, longer lengths of hospitalization, and longer ICU stays (55). Based on our subgroup analysis, a negative correlation between immunosuppression and immune response was found.

TABLE 2 Local adverse events in dialysis patients after vaccine administration.

Study	Population	Sample size	New infection *N* (%)	Survival rate (%)	Pain at the injection site (%)	Redness (%)	Local bruising (%)	Swelling (%)
Cserep et al. (23)	HD	83	0	100%	NR	NR	4 (4.8%)	2 (2.4%)
Fernando and Govindan (28)	HD	42	2 (4.76%)	97.6%	NR	NR	NR	NR
Longlune et al. (36)	HD	82	0	NR	15 (18.3%)	NR	NR	NR
Simon et al. (41)	HD	81	NR	NR	NR	NR	NR	NR
Speer et al. (44)	HD	43	NR	NR	4 (9.3%)	NR	NR	NR
Strengert et al. (45)	HD	81	NR	100%	NR	NR	NR	NR
Yanay et al. (50)	HD/PD	160	6 (3.75%)	NR	NR	NR	NR	NR
Yau et al. (51)	HD/HC	70	NR	NR	30 (42.9%)	6 (8.6%)	NR	6 (8.6%)
Zitt et al. (52)	HD	48	NR	NR	16 (33.4%)	NR	NR	NR

TABLE 3 System adverse events in dialysis patients after vaccine administration.

Study	Population	Sample size	Fatigue (%)	Headache (%)	Fever and chills (%)	Nausea or vomiting (%)	Diarrhea (%)	Muscle ache (%)	Joint pain (%)
Cserep et al. (23)	HD	83	9 (10.8%)	7 (8.4%)	3 (3.6%)	NR	1 (1.2%)	NR	NR
Fernando and Govindan (28)	HD	42	NR	NR	NR	NR	NR	NR	NR
Longlune et al. (36)	HD	82	15 (18.3%)	NR	7 (8.5%)	NR	NR	NR	NR
Simon et al. (41)	HD	81	NR	NR	NR	NR	NR	NR	NR
Speer et al. (44)	HD	43	2 (4.6%)	2 (4.6%)	NR	NR	NR	1 (2.3%)	NR
Strengert et al. (45)	HD	81	NR	NR	NR	NR	NR	NR	NR
Yanay et al. (50)	HD/PD	160	NR	NR	NR	NR	NR	NR	NR
Yau et al. (51)	HD/HC	70	15 (21.4%)	NR	9 (12.9%)	6 (8.6%)	3 (4.2%)	NR	6 (8.5%)
Zitt et al. (52)	HD	48	2 (4.2%)	2 (4.2%)	2 (4.2%)	0 (0%)	1 (2.1%)	1 (2.1%)	2 (4.2%)

Accordingly, the higher the rate of herd immunosuppression, the lower the immune response. This may explain why the response rate of dialysis patients is lower than that of healthy individuals. Additionally, the dialysis procedures make it inevitable to lose some immune protein factors in the process of dialysis. Furthermore, the characteristics of multiple complications in dialysis patients will also cause the low immunogenicity rate.

The characteristics of the dialysis population may contribute to immunogenicity acquisition as well. Several factors have been reported to be associated with immune responses, including age (30, 32), body mass index (BMI) (15), previous immunosuppression (24, 36), dialysis vintage, and diabetes prevalence (19). To validate the conclusions of previous studies, we performed subgroup analyses of age, dialysis vintage and diabetes prevalence, but the data obtained did not support us to draw similar conclusions. Additionally, data on BMI was collected, the mean of which was quite similar, fluctuating around 27 kg/m^2; thus, subgroup analyses of this type of data were not performed. From our perspective, large sample studies and sufficient data are needed to support the effects of these factors.

Vaccination schedules also affect the rate of immunogenicity in patients. Taking vaccine dose, type and testing time into consideration, the data revealed that the immune response rate was correlated with the dose rather than vaccine type and timing of detecting, which was consistent with previous reports (26, 28, 35).

In the current study, the immune response rate was higher in patients with a prior infection than in patients who had not been infected. With respect to the first immune response, the second immune response is characterized by a shorter incubation period, increased antibody levels, and a more extended maintenance period, which can explain the difference between the immune responses of patients with and without infection histories (56).

Vaccine safety studies are few, and statistics are lacking. Based on available data, the survival rate of COVID-19 vaccinated patients was close to 100%, although some patients still developed new infections (<5%) (23, 28, 35, 50). The most commonly reported adverse event is local pain at the injection site. Previous studies have also reported redness, local bruising, and swelling (23, 36, 44, 51, 52). System adverse events included fatigue, headache, fever and chills, nausea or vomiting, diarrhea, muscle aches, and joint pain, among which fatigue was the most common (23, 36, 44, 51, 52). Based on the data analysis, occasional adverse events do not threaten dialysis patients' safety.

The review has certain limitations. The literature included in this systematic review mainly included the data of the first two doses of COVID-19 vaccine. With the continuous development of COVID-19 vaccine, booster doses have been carried out and obtained in many countries. The discussion of the booster doses was lacking in this study. With the development of multi-center, large-sample studies worldwide, more comprehensive summaries are expected.

Overall, this system review focused on the effect and safety of COVID-19 vaccines. From the perspective of this study, dialysis patients in stable health conditions are encouraged to receive vaccines. For dialysis patients, COVID-19 vaccination is more beneficial than risky. Although malignancies occasionally occur, these adverse effects have little impact on health, and the antibodies produced by the vaccines can effectively protect the body against the virus. Of note, in order to obtain sufficient immune protection for these special individuals, alternative strategies need to be innovated and developed.

Conclusion

Overall, the systematic meta-analysis confirmed the positive effects of COVID-19 vaccine in dialysis patients. Although it is less efficient than in healthy people, it can protect the patient's body from the virus to some degree. Furthermore, it can be concluded that the vaccine is safe for dialysis patients due to the low incidence of adverse events and absence of life-threatening incidents.

Considering our viewpoint, it could be a reasonable option for dialysis patients in stable condition to receive COVID-19 vaccine, which can prevent the transmission of the virus. However, strict post-vaccination observation is necessary to ensure the safety of patients and to avoid the occurrence of serious malignant events. Therefore, an optimal treatment plan should be discussed comprehensively based on the patient's specific characteristics for patients who have used immunosuppressants for an extended period.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

Author contributions

RP, YM, and SX contributed equally to the intellectual content during manuscript drafting and took responsibility for the accuracy and integrity of the materials, performed the statistical analysis, and drafted of the manuscript. RP and ZY designed the study protocol. RP and YM performed the electronic database search. YM, SX, HW, and ZD screened the citations retrieved from electronic searches. ZY, JJ, HQ, RP, YM, SX, ZD, and HW weighed on the bias of the studies, consulted on discrepancies during screening, and data extraction. RP, YM, SX, HW, and ZD performed data extraction, synthesis, and interpretation. ZY, JJ, and HQ supervision and obtained funding. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.951096/full#supplementary-material

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Tolerance for three commonly administered COVID-19 vaccines by healthcare professionals

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Importance: Most healthcare institutions require employees to be vaccinated against SARS-CoV-2 and many also require at least one booster.

Objective: We determine the impact of vaccine type, demographics, and health conditions on COVID-19 vaccine side effects in healthcare professionals.

Design: A COVID-19 immunity study was performed at the 2021 American Association for Clinical Chemistry Annual Scientific meeting. As part of this study, a REDCap survey with cascading questions was administered from September 9, 2021 to October 20, 2021. General questions included participant demographics, past and present health conditions, smoking, exercise, and medications. COVID-19 specific questions asked about SARS-CoV-2 vaccine status and type, vaccine-associated side effects after each dose including any boosters, previous infection with COVID-19, diagnostic testing performed, and type and severity symptoms of COVID-19.

Results: There were 975 participants (47.1% male, median age of 50 years) who completed the survey. Pfizer was the most commonly administered vaccine (56.4%) followed by Moderna (32.0%) and Johnson & Johnson (7.1%). There were no significant differences in vaccine type received by age, health conditions, smoking, exercise, or type or number of prescription medications. Side effects were reported more frequently after second dose (e.g., Moderna or Pfizer) (54.1%) or single/only dose of Johnson & Johnson (47.8%). Males were

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significantly more likely to report no side effects ($p < 0.001$), while females were significantly more likely to report injection site reactions ($p < 0.001$), fatigue ($p < 0.001$), headache ($p < 0.001$), muscle pain ($p < 0.001$), chills ($p = 0.001$), fever ($p = 0.007$), and nausea ($p < 0.001$). There was a significant upward trend in participants reporting no side effects with increasing age ($p < 0.001$). There were no significant trends in side effects among different races, ethnicities, health conditions, medications, smoking status or exercise. In multivariate logistic regressions analyses, the second dose of Moderna was associated with a significantly higher risk of side effects than both the second dose of Pfizer and the single dose of Johnson & Johnson.

Conclusions and relevance: Younger people, females, and those receiving the second dose of Moderna had more COVID-19 vaccine side effects that per self-report led to moderate to severe limitations. As reported in other studies, the increase in side effects from Moderna may be explained by higher viral mRNA concentrations but be associated with additional protective immunity.

KEYWORDS

COVID-19, SARS-CoV-2, vaccine, Moderna, Pfizer, Johnson and Johnson, side effects

Introduction

The availability of vaccines against COVID-19 has changed the course of the pandemic and reduced disease severity (1, 2). In late 2020, several vaccines against the spike protein of SARS-CoV-2 were granted Emergency Use Authorization by the FDA. Both Pfizer (BNT162b2) and Moderna (mRNA-1273), mRNA vaccines, and Johnson & Johnson (J&J), an adenovector, were commonly administered in the United States. Healthcare professionals (HCP) were one of the first populations to be vaccinated leading to many fully vaccinated (e.g., two doses of Moderna or Pfizer or one dose of J&J) HCP by the spring of 2021. Vaccine boosters were available to certain high-risk populations in the summer of 2021 and routinely recommended for adults in the fall of 2021. Following the Centers for Medicare and Medicaid Services mandates, healthcare institutions require employees to be vaccinated against SARS-CoV-2 (3).

Most surveys in the literature assess the attitudes of HCP toward COVID-19 vaccination (4–10). In France and Belgium ~30% of HCP were reluctant to receive vaccinations, primarily because of safety concerns (4). Alley et al. (5) reported that in Australia, women and those without a bachelor's degree were less willing to get vaccinated. In Great Britain, non-white, younger adults with lower education and/or unconfirmed past infection were less likely to get vaccinated (7). Many HCP were concerned about vaccine efficacy, safety, side effects, and speed of vaccine development. Results of these surveys have been utilized to develop targeted education on the benefits of vaccination. Despite targeted education, misinformation remains one common cause of continued vaccine hesitancy (11).

Surveys on vaccine side effects have also been published (12–18). Common side effects to the Pfizer vaccine included soreness, fatigue, myalgia, headache, chills, fever, joint pain, nausea, muscle spasm, sweating, and dizziness (12). Ahsan et al. (13) reported that female HCP and those with known allergies were more likely to report side effects. A study performed in Poland demonstrated a higher rate of side effects with the first dose of AstraZeneca when compared to either dose of Pfizer (18). However, to our knowledge, a survey comparing the side effects of the three most common vaccines administered in the U.S. (Pfizer, Moderna, J&J), and the impact of demographics and health conditions on the risk of side effects, has not been performed. Further, our participants represented a healthy, fully vaccinated, middle-aged, and geographically diverse population. We, therefore, conducted this survey and present our findings in this paper.

Materials and methods

Study design and participants

A COVID-19 immunity study (CIS) sponsored by the American Association for Clinical Chemistry (AACC) occurred between September 9, 2021 and October 20, 2021. AACC is a global organization with more than 8,000 members from 105 countries including over 5,000 members from the United States. AACC members were informed via email, social media [including Twitter, Facebook, and the Artery—an AACC online discussion platform with 11,000 active participants (8,000 members and 3,000 non-members able to access only the COVID forum)], or both about enrolling in the study which included a health questionnaire survey and blood draw. The survey portion was designed to gather information from HCP about COVID-19 vaccination and its side effects. The study was approved by the University of Maryland Institutional Review Board. Participants <18 years old and pregnant women were excluded from study participation. The blood draw portion of the study was performed independently of the survey, had different objectives and will be reported in a separate study.

CIS survey

The survey was administered through REDCap and contained questions about participant demographics, general health, medications, history of COVID-19, and COVID-19 vaccination status (Supplementary Table 1). The participant's medications were categorized according to the FDA guidelines (Supplementary Table 2) (19).

Statistical analysis

The survey data was retrieved from the REDCap at the end of the survey period. Basic demographic information and COVID-19 specific questions were analyzed. Of those vaccinated, comparisons were made between participants who received Pfizer, Moderna, and J&J vaccines using Kruskal-Wallis rank sum tests (for continuous data) or chi-squared tests (for categorical data). Due to the heterogeneity and relatively small sample size, participants who received other or unknown vaccine types were not included in the analysis. We focused on typical side effects as described in the CDC and FDA guidelines (20, 21). Health conditions were recorded by detailed disease types; however, they were analyzed at the higher disease category level (e.g., neurological disease) to provide adequate statistical power in each group. Analysis of medication categories was performed if 20 or more participants reported taking a medication in that category.

Logistic regression models were fit to predict the presence of individual side effects after the single dose of J&J and the second dose of Pfizer and Moderna; those doses were completed vaccinations and associated with the highest rate of side effects (referred to as the second/single dose in results). The sensitivity model was adjusted for age, sex, race, ethnicity, self-reporting of overweight, cancer, autoimmune, lung, or other disease, self-reported antidepressant, respiratory tract agent or sex hormone medications, or over-the-counter agents, and previous positive COVID-19 RT-PCR or rapid antigen test. Adjustments for the other health conditions and medication categories, and self-reported healthy, exercise status, and smoking history were considered, but not included in the multivariate model because they were not significant univariate predictors of any side effects. A tertiary model included interactions between vaccine type and both sex and age (in three categories). Odds ratios (OR) for having each side effect were calculated for all comparisons (i.e., Moderna vs. Pfizer, Moderna vs. J&J and Pfizer vs. J&J).

In the logistic regression models, we compared the 932 subjects vaccinated with Pfizer, Moderna, or J&J. For Pfizer and J&J, the risk of any side effects was approximately 50%. Therefore, with at least 80% power, we were able to discover increases in the likelihood of side effects with OR $\geq$ 1.195 (or decreases $\leq$ 0.836).

Results

Participant demographics, health conditions, and COVID-19 specifics

Of the 1,012 participants who completed the informed consent to answer the health questionnaire survey, 975 completed the survey. Table 1 displays participant demographics, general health, and COVID-19 questions. 47.1% of the participants were male. The median age of the participants was 50 [interquartile range (IQR) 40–59] [male median age 51 (IQR 40–60), female median age 49 (IQR 39–58)]. Most participants were living in the United States (87.4%), Caucasian (77.4%) and non-Hispanic/non-Latino (83.1%). The most common health condition was obesity (17.7%). Nearly all participants (99.1%) responded "yes" when asked if they considered themselves generally healthy (question 19 in Supplementary Table 1). Most had no smoking history (85.9%) and exercised regularly (72.0%). Many participants were taking prescription medications (17.0%), OTC medications/vitamins (19.5%), or both (36.3%) with cardiovascular agents (25.5%) and antidepressants (11.1%) being the most common prescription medications.

Per self-report, 16.1% of participants had previously suspected or known COVID-19 (48% of those had positive RT-PCR or antigen test). Of the 157 participants reporting previous COVID-19, 121 (77.1%) reported symptoms from the infection, 56 (46.3%) of which led to mild-moderate limitation of activities and 34 (28.1%) of which led to severe limitation of activities including three hospitalizations; one requiring non-invasive ventilation.

The majority of participants (89.3%) were tested for SARS-CoV-2 at some point with a median of one test (IQR = 1–2) and a positivity rate of 11.2% (Table 1). Of all the SARS-CoV-2 testing performed 62.8% was RT-PCR and 30.2% was a rapid antigen test. However, the positive tests were RT-PCR (49.5%), rapid antigen (18.0%), and antibody (30.6%). Of the nine participants who reported multiple positive results, four had a positive PCR result followed by multiple positive serology results, four had positive serology result(s) followed by a positive PCR result, and one had two positive PCR results 13 days apart. Participants reported

TABLE 1 Survey participant demographics, general health conditions, and COVID-19 questions.

Category*	Demographic and general health condition	Participants ($n = 975$)
Sex	Male, No. (%)	459 (47.1)
Age	Median (IQR)	50 (40–59)
Country	United States, No. (%)	852 (87.4)
	Canada, No. (%)	21 (2.2)
	Colombia, No. (%)	16 (1.6)
	Mexico, No. (%)	13 (1.3)
	Germany, No. (%)	11 (1.1)
	Other, No. (%)	62 (6.4)
Race	Caucasian, No. (%)	755 (77.4)
	African American/Black, No. (%)	54 (5.5)
	Asian, No. (%)	89 (9.1)
	Native Hawaiian/Pacific Islander, No. (%)	6 (0.6)
	Unknown/Other/Prefer not to say, No. (%)	71 (7.3)
Ethnicity	Hispanic and/or Latino, No. (%)	116 (11.9)
	Non-Hispanic/Non-Latino, No. (%)	810 (83.1)
	Prefer not to reply, No. (%)	49 (5.0)
Health conditions	Overweight or Obesity, No. (%)	173 (17.7)
	Diabetes, No. (%)	58 (5.9)
	Autoimmune disorder, No. (%)	52 (5.3)
	Cancer, No. (%)	50 (5.1)
	Cardiovascular disease, No. (%)	49 (5.0)
	Lung disease, No. (%)	28 (2.9)
	Neurological conditions, No. (%)	11 (1.1)
	Cerebrovascular disease or Stroke, No. (%)	9 (0.9)
	Immunodeficiency, No. (%)	8 (0.8)
	Thalassemia, No. (%)	6 (0.6)
	Liver disease, No. (%)	5 (0.5)
	Solid organ or Blood stem cell transplant, No. (%)	4 (0.4)
	Substance use disorder, No. (%)	4 (0.4)
	Chronic kidney disease, No. (%)	1 (0.1)
	Other, No. (%)	92 (9.4)
	No past or present health conditions, No. (%)	573 (58.8)
Healthy (Per report)	Yes, No. (%)	966 (99.1)
Smoking	Past, No. (%)	121 (12.4)
	Current, No. (%)	16 (1.6)
	No, No. (%)	838 (85.9)
Exercise	Yes, No. (%)	702 (72.0)
	Hours/Week median (IQR)	5 (3–7)
Medications	None, No. (%)	265 (27.2)

(Continued)

TABLE 1 (Continued)

Category*	Demographic and general health condition	Participants ($n = 975$)
	Prescriptions only, No. (%)	166 (17.0)
	OTC/Vitamins only, No. (%)	190 (19.5)
	Both, No. (%)	354 (36.3)
Category*		
Number of prescriptions	Median (IQR)	1 (0–2)
Number of OTC/Vitamins	Median (IQR)	1 (0–2)
Types of prescription medications	Cardiovascular agents, No. (%)	249 (25.5)
	Antidepressants, No. (%)	108 (11.1)
	Hormonal agents (thyroid), No. (%)	83 (8.5)
	Respiratory tract agents, No. (%)	66 (6.8)
	Blood glucose regulators, No. (%)	63 (6.3)
	Hormonal agents (sex hormones/modifiers), No. (%)	62 (6.4)
	Gastrointestinal agents, No. (%)	50 (5.1)
	Genitourinary agents, No. (%)	23 (2.4)
Previous COVID infection	Yes (confirmed or suspected), No. (%)	157 (16.1)
	Symptomatic, No. (%)	121 (77.1)
	Severe limitations and/or hospitalization, No. (%)	34 (28.1)
Previous COVID testing (per participant)	Yes, No. (%)	871 (89.3)
	Number, median (IQR)	1 (1, 2)
	Any positive (per participant), No. (%)	98 (11.2)
	Multiple positives, No. (%)	9 (9.1)
Total tests (per test)	All types reported	1,642
	Rapid Antigen Test, No. (%)	496 (30.2)
	RT-PCR, No. (%)	1,032 (62.8)
	Antibody, No. (%)	81 (4.9)
	Unknown, No. (%)	33 (2.0)
	Positive test reported, No. (%)	111 (6.7)
	Rapid Antigen Test, No. (%)	20 (18.0)
	RT-PCR, No. (%)	55 (49.5)
	Antibody, No. (%)	34 (30.6)
	Unknown, No. (%)	2 (1.8)
COVID vaccination	None, No. (%)	9 (0.9)
	Pfizer X2, No. (%)	545 (56.4)
	Moderna X2, No. (%)	309 (32.0)
	J&J X1, No. (%)	69 (7.1)
	AstraZeneca X2, No. (%)	20 (2.1)

(Continued)

TABLE 1 (Continued)

Category*	Demographic and general health condition	Participants ($n = 975$)
	Other, No. (%)	23 (2.4)
COVID booster	Any booster, No. (%)	70 (7.2)
	Pfizer, No. (%)	57 (81.4)
	Moderna, No. (%)	11 (15.7)
	J&J, No. (%)	2 (2.9)
COVID vaccination side effects	Yes (after first dose/single dose), No. (%)	355 (36.7)
	Yes (after second dose), No. (%)	483 (54.1)
	Yes (after booster), No. (%)	36 (51.4)
Post vaccination	Exposure, No. (%)	147/966 (15.2)
	Tested Positive, No. (%)	31/966 (3.2)
	Rapid Antigen Test, No. (%)	5 (16.1)
	RT-PCR, No. (%)	11 (35.5)
	Antibody, No. (%)	2 (6.5)
	Not reported, No. (%)	13 (41.9)

J&J, Johnson & Johnson; OTC, over the counter.
*Refer to Supplementary Table 1 for specific questions asked in each category.

low rates of post-vaccination exposure (15.2%) with 3.2% testing positive.

Participant demographics and health conditions by vaccine type

The majority of participants received two doses of the Pfizer vaccine (56.4%), while 32.0% received two doses of Moderna and 7.1% received one dose of J&J (Table 1). The remaining 4.5% received a different vaccine or combination of vaccines, were not fully vaccinated (e.g., only one dose of Moderna) or did not know which vaccine(s) they received (Table 1). At the time of the survey, only 70 (7.2%) participants had received a booster.

Compared to both Pfizer and J&J, Moderna was more frequently administered to males (53.0%; $p = 0.04$) and participants in the United States (94.4%; $p = 0.007$) (Table 2). Participants from Colombia more frequently received Pfizer than Moderna or J&J ($p = 0.007$). Compared to Pfizer or Moderna, J&J was administered to a higher percentage of participants in Mexico ($p = 0.02$). Participants who received J&J were less likely to report that they were healthy (97.7%) as compared to Pfizer (99.1%) and Moderna (100%) ($p = 0.03$). There were no significant differences in vaccine type received by age, health conditions, smoking, exercise, or type or number of prescription medications.

SARS-CoV-2 vaccine side effects by vaccine type

Participants who received J&J were more likely to have previously had COVID-19 ($p = 0.006$) and experienced a higher likelihood of side effects after the single dose ($p = 0.003$), particularly fatigue ($p < 0.001$), muscle pain ($p < 0.001$), chills ($p = 0.003$), and fever ($p = 0.006$). These side effects led to mild-moderate ($p < 0.001$) or severe ($p < 0.001$) limitation of activities (Table 3). Whereas, Moderna had the highest rate of injection site reactions after the first dose ($p = 0.001$). When compared to the second dose of Pfizer, the second dose of Moderna had a higher rate of side effects ($p < 0.001$) which included injection site reactions ($p = 0.04$), chills ($p < 0.001$), fever ($p < 0.001$), and nausea ($p = 0.04$) which led to mild-moderate limitation of activities ($p < 0.001$). More participants received the Pfizer booster ($p = 0.004$). Although the incidence of most side effects was higher after the Moderna booster than Pfizer, the differences were not significant. There were no significant differences in post-vaccination exposure among the three vaccine types.

SARS-CoV-2 vaccine side effects by demographics and health conditions

Side effects were reported more frequently after second dose (e.g., Moderna or Pfizer) (54.1%) (Table 1) or single dose of J&J (47.8%) (Table 3), therefore in this section we report participant side effects in all participants receiving the second/single dose as a group as well as the side effects per vaccine type. Males were significantly more likely to report no side effects ($p < 0.001$), while females were significantly more likely to report injection site reactions ($p < 0.001$), fatigue ($p < 0.001$), headache ($p < 0.001$), muscle pain ($p < 0.001$), chills ($p = 0.001$), fever ($p = 0.007$), and nausea ($p < 0.001$) (Figure 1A). There were no significant differences in moderate or severe limitations between males and females. Results were similar when Pfizer and Moderna were analyzed separately (Supplementary Figure 1). However, there was no longer a significant difference between males and females for no side effects, muscle pain, or fever for participants who received Moderna. Females who received Pfizer were more likely to report severe limitations ($p = 0.02$).

There was a significant upward trend in participants reporting no side effects with increasing age ($p < 0.001$) (Figure 1B). Conversely, there was a significant downward trend in side effects with increasing age for fatigue ($p < 0.001$), headache ($p < 0.001$), muscle pain ($p < 0.001$), chills ($p < 0.001$), fever ($p < 0.001$), nausea ($p = 0.03$), and severe limitations ($p = 0.008$). There was no significant trend in injection site reactions or moderate limitations among the age groups. Results were similar when Pfizer and Moderna were analyzed separately

TABLE 2 Participant demographics and health conditions by vaccine type.

Category*	Demographic	Pfizer ($n = 545$)	Moderna ($n = 309$)	J&J ($n = 69$)	χ^2 statistic† (df)	*P*-value†
Age	Median (IQR)	50 (41–59)	50 (40–60)	49 (38–57)	1.92 (2)	0.38
Sex	Male, No. (%)	240 (44.0)	164 (**53.0**)	33 (47.8)	**6.46 (2)**	**0.04**
Country	United States (including Puerto Rico), No. (%)	483 (88.6)	293 (**94.8**)	60 (87.0)	**10.01 (2)**	**0.007**
	Canada, No. (%)	11 (2.0)	6 (1.9)	0 (0.0)	1.40 (2)	0.49
	Colombia, No. (%)	14 (**2.6**)	0 (0.0)	0 (0.0)	**9.85 (2)**	**0.007**
	Mexico, No. (%)	7 (1.3)	1 (0.3)	3 (**4.3**)	**7.85 (2)**	**0.02**
	Germany, No. (%)	8 (1.5)	1 (0.3)	0 (0.0)	3.40 (2)	0.18
	Other, No. (%)	22 (4.0)	8 (2.6)	6 (8.7)	5.67 (2)	0.06
Race	Caucasian, No. (%)	431 (79.0)	244 (78.9)	53 (76.8)	8.47 (10)	0.58
	African American/Black, No. (%)	31 (5.6)	17 (5.5)	3 (4.3)		
	Asian, No. (%)	49 (8.9)	30 (9.7)	6 (8.6)		
	Native Hawaiian/Pacific Islander, No. (%)	3 (0.5)	3 (0.9)	0 (0.0)		
	Unknown/Other/Prefer not to say, No. (%)	31 (5.6)	15 (4.8)	7 (10.1)		
Ethnicity	Hispanic and/or Latino, No. (%)	56 (10.3)	31 (10.0)	12 (17.4)	4.60 (4)	0.33
	Non-Hispanic/Non-Latino, No. (%)	469 (86.1)	262 (84.8)	54 (78.3)		
	Prefer not to reply, No. (%)	20 (3.7)	16 (5.2)	3 (4.3)		
Health Conditions	Overweight or Obesity, No. (%)	102 (18.7)	53 (17.1)	11 (15.9)	0.53 (2)	0.76
	Diabetes, No. (%)	37 (6.7)	15 (4.8)	3 (4.3)	1.66 (2)	0.44
	Autoimmune disorder, No. (%)	31 (5.6)	17 (5.5)	4 (5.7)	0.01 (2)	>0.99
	Cancer, No. (%)	28 (5.1)	17 (5.5)	3 (4.3)	0.16 (2)	0.92
	Cardiovascular disease, No. (%)	31 (5.6)	11 (3.5)	2 (2.8)	2.54 (2)	0.28
	Lung disease, No. (%)	16 (2.9)	10 (3.2)	2 (2.8)	0.06 (2)	0.97
	Neurological conditions, No. (%)	5 (0.9)	3 (0.9)	2 (2.8)	2.29 (2)	0.32
	None, No. (%)	312 (57.2)	177 (57.2)	47 (68.1)	3.09 (2)	0.21
Healthy (Per report)	Yes, No. (%)	540 (99.1)	309 (100)	**67 (97.1)**	**6.74 (2)**	**0.03**
Smoking	Past, No. (%)	72 (13.2)	39 (12.6)	4 (5.8)	3.26 (4)	0.52
	Current, No. (%)	9 (1.7)	6 (1.9)	1 (1.4)		
	No, No. (%)	464 (85.1)	264 (85.4)	64 (92.8)		
Exercise	Yes, No. (%)	394 (72.2)	229 (74.1)	53 (76.8)	0.81 (2)	0.66
	Hours/Week median (IQR)	5 (3–7)	5 (3–7)	5 (4–6)	0.61 (2)	0.74
Medications	None, No. (%)	145 (26.6)	81 (26.2)	17 (24.6)	4.92 (6)	0.55
	Prescriptions only, No. (%)	96 (17.6)	53 (17.2)	8 (11.6)		
	OTC/Vitamins only, No. (%)	103 (18.8)	56 (18.1)	20 (28.9)		
	Both, No. (%)	201 (36.9)	119 (38.5)	24 (34.8)		
Number of prescriptions	Median (IQR)	1 (0–2)	1 (0–2)	0 (0–2)	0.77 (2)	0.68
Number of OTC/Vitamins	Median (IQR)	1 (0–2)	1 (0–2)	1 (0–2)	1.04 (2)	0.59
Types of prescription medications	Cardiovascular agents, No. (%)	150 (27.5)	80 (25.8)	13 (18.8)	2.42 (2)	0.30
	Antidepressant, No. (%)	62 (11.3)	31 (10.0)	10 (14.4)	1.19 (2)	0.55
	Hormonal agents (thyroid), No. (%)	48 (8.8)	30 (9.7)	3 (4.3)	2.02 (2)	0.36
	Respiratory tract agents, No. (%)	37 (6.7)	24 (7.7)	4 (5.7)	0.46 (2)	0.79
	Blood glucose regulators, No. (%)	40 (7.3)	17 (5.5)	3 (4.3)	1.66 (2)	0.44
	Hormonal agents (sex hormones/modifiers), No. (%)	35 (6.4)	23 (7.4)	4 (5.7)	0.42 (2)	0.81
	Gastrointestinal agents, No. (%)	32 (5.8)	12 (3.8)	4 (5.7)	1.63 (2)	0.44
	Genitourinary agents, No. (%)	9 (1.6)	10 (3.2)	2 (2.8)	2.35 (2)	0.31

J&J, Johnson & Johnson; OTC, over the counter.
*Refer Supplementary Table 1 for definitions for categories. †The χ^2 statistic, df, and p-values refer to a Kruskal-Wallis rank sum test for continuous variables and a chi-square test for categorical variables comparing the three vaccine types. The bold values indicate the statistically significant p-values.

TABLE 3 COVID-19 and side effects by vaccine type.

Category*	Demographic	Pfizer ($n = 545$)	Moderna ($n = 309$)	J&J ($n = 69$)	χ^2 statistic† (df)	*P*-value†
Previous COVID infection	Yes, No. (%)	79 (14.4)	45 (14.5)	20 (**28.9**)	**10.14 (2)**	**0.006**
	Symptomatic, No. (%)	58 (73.4)	40 (88.8)	15 (75.0)	4.22 (2)	0.12
	Severe limitations and/or hospitalization, No. (%)	19 (32.7)	12 (30.0)	3 (20.0)	0.92 (2)	0.63
COVID vaccination side effects, first dose/single dose	Yes, No. (%)	174 (31.9)	128 (41.4)	33 (**47.8**)	**11.98 (2)**	**0.003**
	Pain/redness/swelling at injection site, No. (%)	111 (20.3)	95 (**30.7**)	12 (17.3)	**13.37 (2)**	**0.001**
	Fatigue, No. (%)	82 (15.0)	73 (23.6)	23 (**33.3**)	**18.77 (2)**	**<0.001**
	Headache, No. (%)	52 (9.5)	36 (11.6)	13 (18.8)	5.67 (2)	0.06
	Muscle pain, No. (%)	43 (7.8)	43 (13.9)	17 (**24.6**)	**20.88 (2)**	**<0.001**
	Chills, No. (%)	27 (4.9)	29 (9.3)	10 (**14.4**)	**11.88 (2)**	**0.003**
	Fever, No. (%)	19 (3.4)	20 (6.4)	8 (**11.5**)	**10.16 (2)**	**0.006**
	Nausea, No. (%)	8 (1.4)	3 (0.9)	3 (4.3)	4.32 (2)	0.11
	Mild-moderate limitation of activities, No. (%)	14 (2.5)	25 (8.0)	10 (**14.4**)	**24.47 (2)**	**<0.001**
	Severe limitation of activities, No. (%)	2 (0.3)	1 (0.3)	3 (**4.3**)	**15.79 (2)**	**<0.001**
	Other, No. (%)	11 (2.0)	5 (1.6)	1 (1.4)	0.23 (2)	0.89
COVID vaccination side effects, second dose	Yes, No. (%)	257 (47.1)	216 (**69.9**)	NA	**40.37 (1)**	**<0.001**
	Pain/redness/swelling at injection site, No. (%)	126 (23.1)	127 (**41.1**)	NA	**4.11 (1)**	**0.04**
	Fatigue, No. (%)	183 (33.5)	166 (53.7)	NA	1.65 (1)	0.20
	Headache, No. (%)	106 (19.4)	90 (29.1)	NA	0.00 (1)	>.99
	Muscle pain, No. (%)	101 (18.5)	104 (33.6)	NA	3.39 (1)	0.07
	Chills, No. (%)	75 (13.7)	108 (**34.9**)	NA	**20.57 (1)**	**<0.001**
	Fever, No. (%)	57 (10.4)	82 (**26.5**)	NA	**13.34 (1)**	**<0.001**
	Nausea, No. (%)	14 (2.5)	24 (**7.7**)	NA	**4.35 (1)**	**0.04**
	Mild-moderate limitation of activities, No. (%)	46 (8.4)	69 (**22.3**)	NA	**11.83 (1)**	**<0.001**
	Severe limitation of activities, No. (%)	12 (2.2)	18 (5.8)	NA	2.07 (1)	0.15
	Other, No. (%)	16 (2.9)	9 (2.9)	NA	0.62 (1)	0.43
COVID booster	Yes, No. (%)	50 (**9.1**)	13 (4.2)	1 (1.4)	**11.01 (2)**	**0.004**
COVID vaccination side effects, booster[1]	Yes, No. (%)	26 (52.0)	9 (69.2)	0 (0.0)	2.46 (2)	0.29
	Pain/redness/swelling at injection site, No. (%)	17 (65.3)	8 (88.8)	NA	0.84 (1)	0.36
	Fatigue, No. (%)	13 (50.0)	5 (55.5)	NA	0.00 (1)	>.99
	Headache, No. (%)	9 (34.6)	4 (44.4)	NA	0.01 (1)	0.90
	Muscle pain, No. (%)	8 (30.7)	3 (33.3)	NA	0.00 (1)	>.99
	Chills, No. (%)	4 (15.3)	4 (44.4)	NA	1.76 (1)	0.18
	Fever, No. (%)	6 (23.0)	2 (22.2)	NA	0.00 (1)	>.99
	Nausea, No. (%)	2 (7.6)	2 (22.2)	NA	0.32 (1)	0.57
	Mild-moderate limitation of activities, No. (%)	6 (23.0)	3 (33.3)	NA	0.02 (1)	0.87
	Severe limitation of activities, No. (%)	0 (0.0)	2 (22.2)	NA	2.69 (1)	0.10
	Other, No. (%)	3 (11.5)	0 (0.0)	NA	0.14 (1)	0.71
Post vaccination exposure1	Yes, No. (%)	87 (15.9)	44 (14.2)	7 (10.1)	1.81 (2)	0.40
	Tested Positive, No. (%)	18 (20.6)	9 (20.4)	1 (14.2)	0.16 (2)	0.92
	Rapid test (Antigen), No. (%)	2 (11.1)	2 (22.2)	1 (100)	5.75 (6)	0.45
	RT-PCR, No. (%)	7 (38.9)	3 (33.3)	0 (0.0)		
	Antibody, No. (%)	1 (5.6)	0 (0.0)	0 (0.0)		
	Not reported, No. (%)	8 (44.4)	4 (44.4)	0 (0.0)		

J&J, Johnson & Johnson.
*Refer Supplementary Table 1 for definitions for categories. †The χ^2 statistic, df, and p-values refer to chi-square tests for each categorical variable comparing the three vaccine types. The bold values indicate the statistically significant p-values.

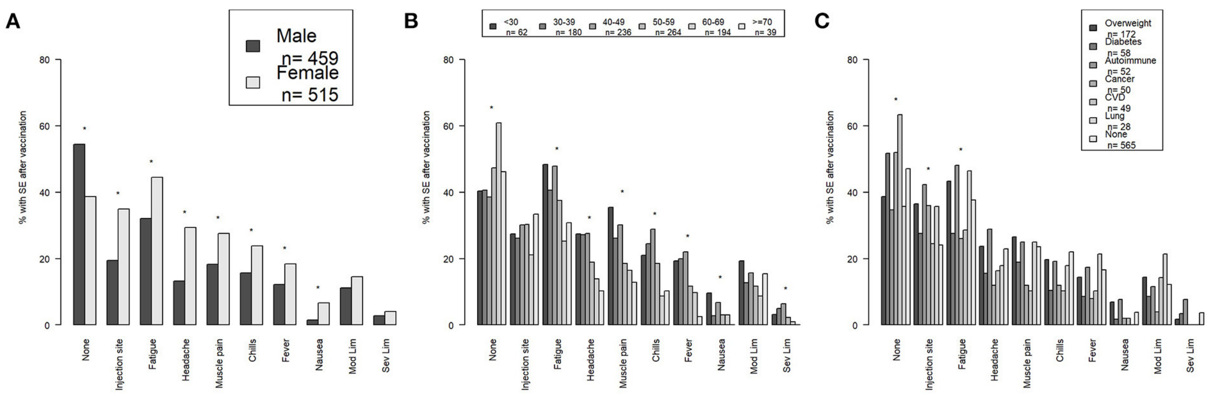

FIGURE 1
The percentage of no side effects and each specific side effect including mild-moderate and severe limitations by **(A)** sex, **(B)** age group, and **(C)** common health conditions are shown for all vaccinated participants. Side effects after second/single dose are depicted. *Indicates a p-value <0.05. SE, side effects; Mod Lim, mild-moderate limitations; Sev Lim, severe limitations; CVD, cardiovascular disease.

(Supplementary Figure 2). However, there was no longer a significant trend among the age groups for nausea with either Pfizer or Moderna or for severe limitations for Pfizer. There was a significant downward trend in moderate limitations with increasing age for participants who received Moderna ($p = 0.009$).

African-American/Black participants were less likely to report muscle pain compared to Caucasians and Asians ($p = 0.04$) (Supplementary Figure 3a). There were no other significant differences among the different races. Results were similar when Pfizer and Moderna were analyzed separately (data not shown). However, there was no longer a significant difference between races for muscle pain for participants who received either Moderna or Pfizer. Further, African-American/Black participants who received Pfizer were more likely to report severe limitations ($p = 0.008$).

Non-Hispanic/Non-Latino participants were significantly more likely to report fatigue ($p = 0.001$) and chills ($p = 0.03$) (Supplementary Figure 3b). There were no other significant differences among the different ethnicities. Results were similar when Pfizer and Moderna were analyzed separately (data not shown). However, only fatigue in participants that received Pfizer remained significant ($p = 0.02$).

Participants who reported having diabetes, cancer, and/or cardiovascular disease or no reported health conditions were more likely to have no side effects ($p = 0.01$) (Figure 1C). Participants who reportedly had obesity, autoimmune disease, and cancer and/or lung disease were more likely to report an injection site reaction ($p < 0.001$), while participants who had obesity, autoimmune disease, and/or lung disease or no health conditions were more likely to report fatigue ($p = 0.003$). There were no significant differences in other side effects in participants with the most common health conditions. When Moderna and Pfizer were analyzed separately none of the differences remained significant (Supplementary Figure 4).

Participants taking cardiovascular agents or no medications were significantly less likely to report an injection site reaction ($p < 0.001$), whereas those taking antidepressants, sex hormones/modifiers, and/or respiratory tract agents were more likely to report nausea ($p < 0.001$) (Supplementary Figure 3c). These differences were no longer significant when Pfizer and Moderna were analyzed separately; except for nausea which remained significant for patients taking the medications above who received Moderna ($p < 0.001$) (data not shown). Further, results were similar when participants taking statins were analyzed separately from those taking any cardiovascular agent. There were no significant differences in side effects by smoking status, exercise, exercise duration, and healthy per report (Supplementary Figures 3d–g). Results were similar when Pfizer and Moderna were analyzed separately (data not shown). However, current smokers who received Pfizer were more likely to report chills ($p < 0.001$) and severe limitations ($p < 0.001$).

Regression models to predict COVID-19 side effects

In a multivariate logistic regression analysis, participants receiving the second dose of Moderna had a significantly higher odds ratio of injection site reactions (OR = 1.22), fatigue (OR = 1.24), headache (OR = 1.13), muscle pain (OR = 1.18), chills (OR = 1.25), fever (OR = 1.19), nausea (OR = 1.06), moderate limitations (OR = 1.15), and severe limitations (OR = 1.03), and lower risk of no side effects (OR = 0.33) when compared to the second dose of Pfizer (Table 4). Similarly,

TABLE 4 Multivariate logistic regression models to predict side effects.

Side effects	Moderna vs. Pfizer	J&J vs. Pfizer	Moderna vs. J&J	Significant covariates
None	0.33 (0.24, 0.45) $p < 0.001$	0.97 (0.59, 1.69)	0.33 (0.19, 0.58) $p < 0.001$	Age, sex, vitamins/OTC
Injection site	1.22 (1.15, 1.30) $p < 0.001$	0.95 (0.85, 1.06)	1.28 (1.15, 1.44) $p < 0.001$	Sex, vitamins/OTC, previous positive COVID-19
Fatigue	1.24 (1.16, 1.32) $p < 0.001$	1.00 (0.88, 1.12)	1.24 (1.09, 1.41) $p < 0.001$	Age, sex, ethnicity
Headache	1.13 (1.07, 1.20) $p < 0.001$	0.99 (0.89, 1.09)	1.15 (1.03, 1.28) $p = 0.01$	Age, sex, lung disease, previous positive COVID-19
Muscle pain	1.18 (1.11, 1.26) $p < 0.001$	1.07 (0.96, 1.19)	1.11 (0.99, 1.24)	Age, sex
Chills	1.25 (1.18, 1.32) $p < 0.001$	1.01 (0.91, 1.11)	1.24 (1.12, 1.38) $p < 0.001$	Age, sex
Fever	1.19 (1.13, 1.25) $p < 0.001$	1.01 (0.92, 1.11)	1.17 (1.06, 1.29) $p = 0.001$	Age, sex
Nausea	1.06 (1.03, 1.09) $p < 0.001$	1.02 (0.97, 1.07)	1.04 (0.98, 1.10)	Sex, lung disease, antidepressants, sex hormones
Moderate limitation of activities	1.15 (1.10., 1.21) $p < 0.001$	1.05 (0.97, 1.15)	1.10 (1.00, 1.20) $p = 0.04$	Age, previous positive COVID-19
Severe limitation of activities	1.03 (1.00, 1.06) $p = 0.02$	1.02 (0.97, 1.06)	1.02 (0.97, 1.07)	Age, antidepressants

OTC, over the counter; J&J, Johnson & Johnson.
Multivariate model adjusts for age, sex, race, ethnicity, health conditions, medications and previous positive COVID-19 testing. Significant p-values are shown. Values are adjusted odds ratios with 95% confidence intervals and p-values are for the respective odds ratio.

the risk of injection site reactions (OR = 1.28), fatigue (OR = 1.24), headache (OR = 1.15), chills (OR = 1.24), fever (OR = 1.17), and moderate limitations (OR = 1.1) was higher with Moderna than J&J, while the risk of no side effects was lower (OR = 0.33). There were no significant differences in side effects between Pfizer and J&J. Interaction models showed similar findings (Supplementary Tables 3, 4). However, males were more likely to have severe limitations with Moderna as compared to Pfizer.

Discussion

Our survey participants were primarily healthy, middle-aged, non-Hispanic/non-Latino Caucasians from the United States. According to the 2020 census, the United States is 57.8% Caucasian, 12.4% Black, 6% Asian, and 18.7% Hispanic, notably different than our survey participants (22). Approximately 40% of participants reported a health condition, most commonly obesity. Cardiovascular and antidepressant medications represented the majority of prescription medications. However, the health conditions and prescription medications taken by our participants were comparable to the United States population (23). The high rate of antidepressant prescriptions may be explained by the increase in depression, anxiety, and stress in HCP during the pandemic (24–28), though no pre-pandemic data is available for comparison in this particular population.

There was a relatively low number of suspected or confirmed cases of COVID-19 in our participants. However, almost 90% had at least one SARS-CoV-2 test performed. Less than 10% of participants reported multiple positive SARS-CoV-2 results. However, the positive results were either within a short time window or inclusive of a positive PCR test followed by positive antibody results. This suggests the participants were not infected more than once with a different SARS-CoV-2 variant.

A majority (56%) of survey participants received the Pfizer vaccine. This is similar to that seen in the United States (29). Most participants had not received a booster at the time of completing the survey, likely because the booster had not been recommended for healthy adults. Those that received a booster most commonly received Pfizer. Those that received a Moderna booster had higher rates of side effects but the differences were not significant due to the low numbers. Reports from additional participants may provide insights on the impact of COVID-19 boosters and risk of side effects. Post-vaccination exposure was relatively low (15%) suggesting participants may have responded yes only if they met CDC criteria for a close contact (30).

Similar to CDC reports (31–33), injection site reactions, fatigue, headache, and muscle pain were the most common side effects. When comparing the incidence of side effects in the first/single dose group, J&J had a higher rate than Moderna and Pfizer for most side effects including mild to moderate and severe limitations. However, Moderna had a higher rate of injection site reactions after the first dose. The higher incidence of side effects with J&J may be because it is a viral vector, J&J recipients were significantly less healthy per report, and/or J&J recipients had significantly higher rates of previous COVID-19.

Given that the highest rates of side effects were seen after the second/single dose, which is consistent with reports from the CDC and other studies (31–34), we analyzed side effects by demographics and health conditions by grouping second/single dose responses together. Younger and female survey participants had the highest incidence of most side effects regardless of the vaccine administered. Similarly, the CDC (31–33) and Camacho et al. (34) demonstrated higher rates of side effects in younger adults (defined as 18–55 years by CDC and <50 years by Camacho) and both Ahsan et al. (13) and Camacho et al. (34) reported that females had more side effects. In addition to sex and age, we did not find any other demographics and/or health conditions that had a significant impact on side effects.

In multivariate analysis, the risk of side effects was significantly higher after the second dose of Moderna than after the second dose of Pfizer or a single dose of J&J. These findings were similar to a study by Camacho et al. (34). Although Moderna led to more side effects, Moderna contains a higher concentration of mRNA compared to Pfizer (35) and previous studies suggest that Moderna confers additional protective immunity and leads to fewer breakthrough infections (36–39).

Our study had several limitations. First, our participant population is not representative of the U.S. population, particularly in terms of race, ethnicity, vaccination rates, and co-morbidities. Only 30 states were represented. Second, AACC required vaccination and proof of negative SARS-CoV-2 testing (PCR or antigen) prior to attending the meeting. Therefore, most participants were fully vaccinated. Third, our findings are based on self-reported historical data and are subject to response bias or misinterpretation of questions. Fourth, we were unable to determine, due to the design of the survey, whether patients were positive for SARS-CoV-2 before or after vaccination.

Younger people, females, and those receiving the second dose of Moderna had more COVID-19 vaccine side effects that may have led to moderate to severe limitations. This observation may be explained by higher mRNA concentrations (35). However, as shown in other studies, the increase in side effects may be associated with additional protective immunity and fewer breakthrough infections (36–39).

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author/s.

Ethics statement

The studies involving human participants were reviewed and approved by University of Maryland Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

Author contributions

SM designed the study, reviewed the data, drafted the paper, and critically reviewed the manuscript. ZZ, AK, QM, AW, FA, CO, KS, JW, DK, RC, and YZ designed the study, reviewed the data, and critically reviewed the manuscript. TL performed the data analysis and critically reviewed the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

Author YZ is a consultant for Thermo Fisher. Author JW is Co-PI on a US and International patent. Specificity enhancing reagents for COVID-19 Antibody Testing. Author ZZ has sponsored research supported by Novartis, Waters, Siemens, Polymedco, Waters, Roche and ET Healthcare and has received consulting/speaker fee from Siemens, Roche and ET Healthcare.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.975781/full#supplementary-material

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Trends in willingness to receive COVID-19 vaccines among healthcare workers in India: Findings from repeated cross-sectional national surveys

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Background: COVID-19 vaccination of the healthcare workers (HCWs) is a key priority in the fight against the SARS-CoV-2 pandemic. India launched its COVID-19 vaccination program in January 2021. We aimed to understand the trends in willingness to receive COVID-19 vaccines and its associated factors among HCWs in India.

Methods: Using a repeated cross-sectional survey design, we collected information from HCWs in three critical time points: before ($n = 937$, October 2020), during ($n = 1346$, January 2021); and after ($n = 812$, May 2021) the introduction of COVID-19 vaccines in India. The third survey coincided with the peak of the second wave of COVID-19 pandemic in India.

Findings: Of the study participants, 43.7, 60.2, and 73.2% were willing to receive COVID-19 vaccines during the first, second and third rounds of surveys, respectively. In multivariable logistic regression analysis, participants who trusted the health care system were more likely to report willingness to receive a COVID-19 vaccine; medical trust emerged as a significant factor in all the three rounds of surveys (First survey—aOR: 2.24, 95% CI: 1.67–2.99; Second survey—aOR: 3.38, 95% CI: 2.64-4.33; Third survey—aOR: 2.54, 95% CI: 1.65–3.91). Having confidence in domestic vaccines (Second survey—aOR: 2.21, 95% CI: 1.61–3.02; Third survey—aOR: 2.05, 95% CI: 1.24–3.37); and high perceived risk of contracting COVID-19 (Second survey—aOR: 1.48, 95% CI: 1.13–1.93; Third survey—aOR: 2.02, 95% CI: 1.31–3.13) were found to be associated with willingness to receive vaccines. Among socio-demographic characteristics, being married (aOR: 1.71, 95% CI: 1.08–2.71) and having high socio-economic status (aOR: 3.01, 95% CI: 1.65–5.51) emerged as significant factors associated with willingness to receive COVID-19 vaccines in the third round of the surveys.

Interpretation: Willingness to receive COVID-19 vaccine increased with time, as the severity of the pandemic increased. To increase COVID-19 acceptance and coverage among HCWs, it is important to instill confidence in domestic vaccines and assist in accurate assessment of risk toward contracting COVID-19 infection.

KEYWORDS

vaccine acceptance, intention, hesitancy, domestic vaccine, trust

Introduction

Globally, severe acute respiratory syndrome (SARS-CoV-2) has affected 170 million people and caused 3.5 million deaths (1). Almost all the countries have suffered a major blow to their health systems and economies. India is among the top three countries reporting the highest number of COVID-19 cases in the world, with 247,968,227 confirmed cases including 5,020,204 deaths till November 4, 2021 (2). Under such gloomy circumstances, the COVID-19 vaccines have emerged as a ray of hope for halting the pandemic (3, 4). As the scientific world raced toward developing a vaccine, many vaccine candidates appeared on the horizon. The clinical trials of vaccine candidates from Pfizer/BioNtech, Moderna, Oxford/AstraZeneca, and Johnson & Johnson's Janssen Pharmaceuticals demonstrated their immunogenicity, safety, and efficacy (5–8). As the pandemic worsened, some vaccines were authorized for emergency use (9–12). India launched its COVID-19 vaccination drive with two vaccines, namely CoviShield (Serum Institute of India) and Covaxin (Bharat Biotech), on January 16, 2021 (13). In the first phase, the healthcare workers (HCWs) and frontline workers were vaccinated. Although HCWs can serve as ambassadors of COVID-19 vaccine acceptance, surveys have found low acceptance levels among HCWs; and many people remain skeptical about the safety and efficacy (14, 15).

The availability of vaccines does not guarantee uptake. In the 2009 influenza-A pandemic, less than one-fourth of the Americans were vaccinated during the first year (16). Low uptake of influenza vaccine was reported among HCWs (25%) in China (17). During the H1N1 Influenza pandemic, the intention of people to get vaccinated mirrored the severity of the pandemic and its decline, ultimately leading to a reduction in vaccine intent from 50 to 16% within 10 months (18). Despite the USA reporting the highest number of confirmed cases of COVID-19 in 2020, only half of the medical students expressed willingness to participate in a vaccine trial and 23% were unwilling to get vaccinated (19). After the first wave of the pandemic in India, vaccine hesitancy was 10.6% among medical students (20). The success of the COVID-19 vaccination program will depend on the HCWs' intention to receive vaccines.

Globally, vaccination rates have stagnated for the past few years (21). Recently, outbreaks of vaccine-preventable diseases such as measles and mumps in the USA were attributed to vaccine hesitancy and refusal (22). The World Health Organization has declared vaccine hesitancy among one of the top 10 threats to global health (23). The COVID-19 vaccine intent may also decline in the post-pandemic period due to a reduction in stress related to working conditions (24). Although few cross-sectional studies have reported the intention of COVID-19 vaccines among HCWs in India during the first wave, until now there is no information on the effect of the second wave of COVID-19 pandemic on vaccine acceptance. Moreover, the determinants of vaccine hesitancy may change with time as the COVID-19 pandemic advances. Accordingly, in this paper we report the trends in willingness to receive COVID-19 vaccine and its associated factors among healthcare workers during the first and second waves of COVID-19 pandemic in India.

Abbreviations: COVID-19, Coronavirus disease-2019; WHO, World Health organization.

Methods

Study design and participants

Three repeated cross-sectional surveys were conducted on the acceptability of COVID-19 vaccines among HCWs in India. The first survey was conducted in October 2020; the second survey in January 2021, and the third in May 2021. The first survey period corresponded with the period of the first wave of pandemic, before the launch of COVID-19 vaccination drive in India. The second survey period corresponded with the end of the first wave and the launch of COVID-19 vaccines in India. The third round of survey corresponded with the peak of the second wave of COVID-19 pandemic (25). We recruited 937, 1346 and 812 participants for the first, second and third rounds of surveys, respectively. As there was no prior data available at the time of design of the study on COVID-19 vaccine acceptance among healthcare workers, we relied on the standard parametric approach for a choice probability to approximate the minimum sample size. To be conservative, we calculated the minimum sample size ($N = 768$) on the assumption that COVID-19 vaccine acceptance level will be 50% ($p = 50\%$); with absolute precision of 5 and 95% confidence interval. We considered a design effect of 2.0 given the non-random nature of suervey sampling. The OpenEpi 3.01 was used for calculating the sample size. The survey instruments were developed by a literature review of similar studies, and has been described elsewhere (26, 27). Study participants were recruited through convenience and snowball sampling. Study participants were invited through email and social media such as Twitter, Facebook, and the WhatsApp. Key healthcare forums were also targeted to recruit study participants. Efforts were made to recruit participants across major geographic regions including northern, southern, eastern, western, central and north-eastern India. The survey was administered in English language.

Measures

Outcomes

The key outcome measure was participant's intention or willingness to receive COVID-19 vaccines. The responses were recorded on a three-point Likert scale (accept, refuse, and undecided).

Co-variables

We collected sociodemographic characteristics such as age, gender, marital status, education level, place of residency, occupation sector (government vs. private), and social status. Information about history of exposures to COVID-19; perceived risk of infection; trust in the healthcare system; and perception on domestic vaccines were captured.

Statistical analyses

Descriptive statistical analysis was performed by cross-tabulating demographic characteristics with the primary outcome variable. Chi-square tests were performed for bivariate analysis (cross-tabulation) between the outcome variable (willingness to vaccinate) with all potential explanatory variables. Willingness to receive COVID-19 vaccines was measured as participants who reported to accept the vaccine at the time of survey. We performed multivariable logistic regression analysis to compute adjusted odds ratio (aOR) and 95% confidence interval (CI). We included only significant variables from the bivariate analysis in the multivariable model. An association was considered to be statistically significant if the two-tailed *p*-values was <0.05. Stata 15.0 software (StataCorp LP, Texas, USA) was used for all statistical analyses.

Ethical considerations

The study protocol was reviewed and approved by the Institutional Research Ethics Committee of Post-Graduate Institute of Medical Education & Research (PGIMER), Chandigarh, India, and electronic informed consent was obtained from all participants. De-identified data were used for analysis, interpretation, and reporting.

Results

Between October 2020 and May 2021, a total of 3,095 HCWs responded to the three surveys. The sociodemographic characteristics of the participants showed that about half of them were aged 18–29 years in the first (43.0%), second (47.2%) and third surveys (53.0%), with a relatively higher proportion of females (59.6, 60.4, and 53.0%), married persons (55.6, 53.3, and 60.1%), and those with a postgraduate medical degree (40.4, 42.2, and 61.9%). Most participants (70.1, 75.2, and 56.6%) belonged to middle socio-economic status with 45.5, 47.3, and 43.8% reporting a family income of more than 50,000 rupees in the three rounds of the survey. Of the 937, 1,346 and 812 HCWs, 40.4, 33.1, and 45.0% worked in government sector, and 53.9, 48.0, and 41.2% were from rural areas in the first, second and third rounds of surveys, respectively (Table 1).

Table 2 presents the changes in willingness to accept COVID-19 vaccines, contact history with COVID-19 patients, risk perception, and vaccine preferences. We observed a steady increase in the intention to receive COVID-19 vaccines during the period of three surveys (43.7, 61.1, and 73.2%), with a 30% increase in willingness to receive vaccines between the first and third surveys. Between the first and third surveys, there was a significant increase in risk perception (67.5 vs. 81.1%), exposure to a confirmed COVID-19 patient (29.9 vs. 55.4%), and increased knowledge of COVID-19 (93.3 vs. 99.1%) and development of vaccines (86.7 vs. 92.6%). However, trust in the healthcare system (62.9 vs. 30.7%) was found to be lower between the first and third surveys ($p < 0.001$). Confidence in domestic vaccines was found to be unchanged (23.8, 25.3, and 25.8%) in the three surveys.

TABLE 1 Socio-demographic characteristics of the study participants.

Variables	First survey ($n = 937$)	Second survey ($n = 1,346$)	Third survey ($n = 812$)
Age (in years)			
18–29	403 (43.01%)	636 (47.25%)	431 (53.08%)
30–49	362 (38.63%)	634 (47.10%)	361 (44.46%)
Above 50	172 (18.36%)	76 (5.65%)	20 (2.46%)
Gender			
Man	378 (40.34%)	532 (39.52%)	381 (46.92%)
Woman	559 (59.66%)	814 (60.48%)	431 (53.08%)
Highest level of education			
Primary school or below	49 (5.23%)	25 (1.86%)	75 (9.24%)
High school/diploma	361 (38.53%)	303 (22.51%)	41 (5.05%)
Undergraduate	148 (15.80%)	449 (33.36%)	190 (23.40%)
Postgraduate	379 (40.45%)	569 (42.27%)	503 (61.95%)
Marital status			
Single	521 (55.60%)	718 (53.34%)	488 (60.10%)
Married	416 (44.40%)	628 (46.66%)	324 (39.90%)
Family size			
Five and below	689 (73.53%)	1,048 (77.86%)	683 (84.11%)
Six and above	248 (26.47%)	298 (22.14%)	129 (15.89%)
Place of work			
Government sector	379 (40.45%)	858 (65.15%)	366 (45.07%)
Private sector	558 (59.55%)	459 (34.85%)	204 (25.12%)
Family income (INR)			
Below 10,000	146 (15.58%)	168 (12.48%)	185 (22.78%)
11,000–20,000	118 (12.59%)	238 (17.68%)	105 (12.93%)
21,000–50,000	246 (26.25%)	303 (22.51%)	166 (20.44%)
Above 50,000	427 (45.57%)	637 (47.33%)	356 (43.84%)
Social status			
Low	99 (10.57%)	143 (10.62%)	194 (23.89%)
Middle	657 (70.12%)	1,013 (75.26%)	460 (56.65%)
High	181 (19.32%)	190 (14.12%)	158 (19.46%)
Geographical regions			
Eastern	230 (24.55%)	278 (20.65%)	154 (18.97%)
Western	79 (8.43%)	108 (8.02%)	130 (16.01%)
Northern	356 (37.99%)	561 (41.68%)	217 (26.72%)
Southern	112 (11.95%)	204 (15.16%)	205 (25.25%)
Central	88 (9.39%)	103 (7.65%)	59 (7.27%)
North-east	72 (7.68%)	92 (6.84%)	47 (5.79%)
Area of residence			
Urban	432 (46.10%)	699 (51.93%)	477 (58.74%)
Rural	505 (53.90%)	647 (48.07%)	335 (41.26%)

Table 3 shows the findings from multivariable logistic regression analysis of the factors influencing COVID-19 vaccine uptake among HCWs. Trust in the healthcare system was consistently associated with the intention to receive COVID-19 vaccines [(aOR: 2.24, 95% CI: 1.67–2.99); (aOR: 3.38, 95% CI: 2.64–4.33), and (aOR: 2.54, 95% CI: 1.65–3.91)] in all the three surveys. Participants with a higher risk perception were likely to be vaccinated in the second (aOR: 1.48, 95% CI: 1.13–1.93) and third surveys (aOR: 2.02, 95% CI: 1.31–3.13). Confidence in domestic vaccines was found to be a significant factor associated

TABLE 2 Change over time in willingness to accept COVID-19 vaccine among healthcare worker during first and second wave of COVID-19 pandemic.

Variables	First survey (*n* = 937)	Second survey (*n* = 1346)	Third survey (*n* = 812)	*P*-value
Willingness to vaccinate				<0.001
Accept	410 (43.76%)	810 (60.18%)	595 (73.28%)	
Refuse	213 (22.73%)	154 (11.44%)	150 (18.47%)	
Undecided	314 (33.51%)	382 (28.38%)	67 (8.25%)	
Exposed to COVID-19 cases*				<0.001
No	656 (70.01%)	888 (65.97%)	362 (44.58%)	
Yes	281 (29.99%)	458 (34.03%)	450 (55.42%)	
Knowledge about COVID-19				<0.001
No/not sure	62 (6.62%)	77 (5.72%)	7 (0.86%)	
Yes	875 (93.38%)	1,269 (94.28%)	805 (99.14%)	
Knowledge on development of COVID-19 vaccines				
No/not sure	124 (13.23%)	161 (11.96%)	60 (7.39%)	
Yes	813 (86.77%)	1,185 (88.04%)	752 (92.61%)	
History of vaccine hesitancy				<0.001
Yes	135 (14.41%)	219 (16.27%)	279 (34.36%)	
No	802 (85.59%)	1,127 (83.73%)	533 (65.64%)	
Perceived risk of COVID-19 infection				<0.001
Yes	633 (67.56%)	955 (70.95%)	659 (81.16%)	
No	304 (32.44%)	391 (29.05%)	153 (18.84%)	
Trust in the healthcare system				<0.001
No	347 (37.03%)	485 (36.03%)	562 (69.21%)	
Yes	590 (62.97%)	861 (63.97%)	250 (30.79%)	
Confidence in domestic vaccines				<0.001
Better	223 (23.80%)	341 (25.33%)	210 (25.86%)	
Neutral	338 (36.07%)	450 (33.43%)	423 (52.09%)	
Worst	376 (40.13%)	555 (41.23%)	179 (22.04%)	

P-values by Chi^2 test for binary/categorical variables.
*Exposed to the COVID-19 cases: HCW who came in contact with a confirmed COVID-19 cases during treatment, travel and or residence.

with the acceptance of COVID-19 vaccines. Those participants who were married (aOR: 1.71, 95% CI: 1.08–2.71) and who belong to high socio-economic status (aOR: 3.01, 95% CI: 1.65–5.51) were also more likely to report willingness to receive COVID-19 vaccine in all the three surveys. When compared to those aged 49 and below, participants aged 50 and above were found to have lower odds of accepting the vaccine (aOR: 0.21, 95% CI: 0.07–0.61; $p = 0.004$) in the third round of survey.

Discussion

This is probably the first study from India that documented the trends in COVID-19 vaccine acceptance among HCWs and identified significant correlates of acceptance at three critical time points of the COVID-19 pandemic in India. A repeated cross-sectional survey design has advantages over an one-time cross-sectional survey, especially while investigating changes in the health-related behavioral outcomes. Our study reported an increment of 30% (43.7 vs. 73.3%, $p < 0.001$), in the first and third rounds) of acceptance of COVID-19 vaccines before and after the introduction of vaccines in India, which may be as a results of the massive campaigns on the COVID-19 vaccinations after the introduction of the vaccines might influence participants' willingness. There was a significant improvement in the knowledge about COVID-19 and the development of COVID-19 vaccines between the first and third surveys. Trust in the healthcare system, trust in domestic vaccines, and high-risk perception emerged as key predictors of COVID-19 vaccine acceptance among HCWs in India. The other significant predictors during the third round of the survey were higher social status (aOR: 3.01; 95% CI: 1.65–5.52) and being married (aOR: 1.72; 95% CI: 1.09–2.71).

During the first wave of the pandemic, a high rate of intention to receive vaccines was observed in China (83.5%), Malaysia (83.3%), and the USA (78%) (28–30). The vaccine

TABLE 3 Factors influencing COVID-19 vaccine uptake among HCWs: multivariable logistic regression analysis+.

	Willingness to receive COVID-19 vaccines					
	First survey ($N = 937$)		Second survey ($N = 1,346$)		Third survey ($N = 812$)	
	aOR (95% CI)	*p*-value	aOR (95% CI)	*p*-value	aOR (95% CI)	*p*-value
Trust in healthcare system						
No	Ref		Ref		Ref	
Yes	2.24 (1.67, 2.99)	0.000	3.38 (2.64, 4.33)	0.000	2.54 (1.65, 3.91)	<0.001
Exposed to COVID-19 cases						
No	Ref		Ref		Ref	
Yes	0.99 (0.73, 1.34)	0.972	0.78 (0.60, 1.00)	0.053	0.75 (0.52, 1.07)	0.120
History of vaccine hesitancy						
Yes	Ref		Ref		Ref	
No	1.13 (0.76, 1.67)	0.263	0.83 (0.59, 1.15)	0.263	0.78 (0.54, 1.13)	0.196
Confidence in domestic vaccines						
Worst	Ref		Ref		Ref	
Neutral	0.99 (0.69, 1.43)	0.994	1.94 (1.47, 2.55)	0.000	1.62 (1.05, 2.49)	0.028
Better	1.30 (0.95, 1.78)	0.100	2.21 (1.61, 3.02)	0.000	2.05 (1.24, 3.37)	0.005
Perceived risk of COVID-19 infection						
No	Ref		Ref		Ref	
Yes	1.27 (0.942 1.716)	0.100	1.48 (1.13, 1.93)	0.004	2.02 (1.31, 3.13)	0.001
Age (in years)						
18-29	Ref		Ref		Ref	
30-49	0.73 (0.48, 1.11)	0.151	1.21 (0.82,1.78)	0.325	1.57 (0.98, 2.50)	0.058
Above 50	0.41 (0.26, 0.64)	0.000	1.35 (0.72, 2.52)	0.340	0.21 (0.07, 0.61)	0.004
Gender						
Man	Ref		Ref		Ref	
Woman	1.40 (1.04, 1.88)	0.023	1.07 (0.83, 1.37)	0.589	1.46 (0.99, 2.16)	0.054
Marital status						
Single	Ref		Ref		Ref	
Married	1.05 (0.71, 1.56)	0.788	1.05 (0.72, 1.53)	0.772	1.71 (1.08, 2.71)	0.020
Place of residence						
Urban	Ref		Ref		Ref	
Rural	0.88 (0.67, 1.16)	0.373	1.12 (0.88, 1.42)	0.326	1.13 (0.80, 1.58)	0.474
Highest level of education						
Primary school	Ref		Ref		Ref	
Diploma/High School	0.87 (0.45, 1.68)	0.694	0.86 (0.35, 2.14)	0.760	1.29 (0.66, 2.52)	0.448
Undergraduate	1.01 (0.50, 2.04)	0.962	1.53 (0.60, 3.84)	0.365	2.16 (0.86, 5.41)	0.098
Postgraduate	0.81 (0.42, 1.55)	0.530	1.59 (0.63, 4.00)	0.317	1.18 (0.77, 1.81)	0.436
Social status*						
Low	Ref		Ref		Ref	
Middle	0.68 (0.44, 1.04)	0.075	0.68 (0.44, 1.04)	0.075	1.33 (0.85, 2.09)	0.206
High	1.13 (0.66, 1.92)	0.640	1.13 (0.66, 1.92)	0.640	3.01 (1.65, 5.51)	<0.001

*Self-reported information about perceived social status in participants neighborhoods.
+We included only significant variables from the bivariate analysis in the multivariable model.

acceptance rates among HCWs varied between 27.7 and 78.1% for COVID-19 vaccines (31). In the present study, after the first wave of COVID-19 pandemic (2020), about 60.2% reported willingness to receive COVID-19 vaccines while 73.3% were willing during the second wave in 2021. In China, the vaccine acceptance rate was 91.3% in March, 83.5% in May, and 88.6% in June, 2020 (28, 32). Studies reported the vaccine acceptance rate of 79% in April, 83% in May, 64% in July, and 71.7% in the fall of 2020 in the United Kingdom (31). In the present study, the exposure of HCWs to COVID-19 cases significantly increased from 34.3% in the first wave compared to 55.1% in the second wave. This increase in exposure of cases probably contributed to increase in risk perception and in turn to increase in acceptance of COVID-19 vaccines. This hypothesis is supported by findings from other studies that reported that people who perceived themselves at high risk of COVID-19 infection are more likely to get vaccinated (20, 27, 32). In the present study, we found that those HCWs who perceived themselves at high risk had higher odds of COVID-19 vaccine acceptance than those who had lower risk perception (aOR: 1.48 and 95% CI: 1.14–1.93, during the second round, and aOR: 2.03 and 95% CI: 1.31–3.14, during the third round).

During the first round, age, gender, education, marital status, area of residence, socioeconomic status had no influence on COVID-19 vaccine uptake among healthcare workers. In the second round, participants older than 50 years had lower odds of COVID-19 vaccine acceptance when compared to younger participants (aOR: 0.22, 95% CI: 0.08-0.62). It is not clear what could have contributed to this difference. Similar findings were reported in a Malaysian study where vaccine hesitancy among people aged 60 years and above was five times than the young people aged 18–29 years (29). In the present study, participants with higher socioeconomic status were three times more likely to be willing to receive COVID-19 vaccines (aOR: 3.02, 95% CI: 1.65–5.52) than those with lower socioeconomic status, and married participants were 1.7 times more likely to accept COVID-19 vaccines than those who were single. Similar findings were also reported in China and Saudi Arabia that marital status can influence the intention to accept the vaccine (27, 32). It is possible that married people feel that they have a responsibility to protect their family members and more likely to accept COVID-19 vaccines.

Studies have shown that trust in the healthcare system increases the likelihood of acceptability of COVID-19 vaccines (27, 33). In the present study, the trust of healthcare workers in the healthcare system declined (63.9% in the first survey to 30.8% in the third survey, $p < 0.001$). The second wave of the SARS-CoV-2 pandemic strained the healthcare system in India, leading to a shortage of life-saving drugs, medical supplies, oxygen and ultimately resulted in greater mortality than the first wave. This might have contributed to the decrease in trust on the healthcare system. Also, since HCWs were among the first set of people to receive vaccines in India, it is possible that they were concerned about the safety of vaccines, a concern reported in studies from other countries (34). During the first wave of the pandemic, only one-fourth of the HCWs trusted the domestic vaccines while 34.5% were neutral about them. This is in contrast to a study from China that reported 94.8% of the participants had confidence on domestic vaccines (28). After the announcement about COVID-19 vaccines for healthcare workers, the mistrust in the domestic vaccines reduced from 41.2% in the second round to 22.0% in the third round (during the second wave of COVID-19 pandemic). In the present study, HCWs who had confidence on domestic vaccines were two times more likely to get vaccinated than those who did not have confidence on domestic vaccines.

Numerous studies highlighted major barriers in accepting COVID-19 vaccines which include side-effects of vaccine, speed of development of the vaccine, uncertainty about the effectiveness and effective duration of vaccine, and medical mistrust (24, 33, 35). Low income, ethnic minorities, young women, older people (75 years and above), political beliefs, and rural areas were some of the characteristics associated with hesitancy (30, 33, 36).

This study has several limitations. First, convenience and snowball sampling techniques were used to recruit the participants. The questionnaire was distributed *via* e-mail, social media, and WhatsApp which might have hampered its circulation among participants who might not be skilled in using these media or who may not prefer these media or apps leading to selection bias. However, this method of recruitment is pragmatic in the context of COVID-19 pandemic, considering the safety of participants and travel restrictions. Second, the study was not conducted among a cohort to have more robust estimation of change in trends. However, the participants were recruited from similar online spaces using similar sampling strategies, to minimize the potential differences between the participants in the three rounds of the surveys. The results of this study represent only the three points when the data were collected. The healthcare providers' willingness may have changed after the last phase of the study. Thirdly, the study failed to account to dissect the results based on the various categories of HCWs. It would be interesting if the data about the healthcare providers' specialty is also available. Despite these limitations, the repeated cross-sectional survey design was helpful in assessing the trends in willingness to receive COVID-19 vaccines over time. The observed substantial increase in acceptance during the survey periods needs to be further investigated to explore key barriers and facilitators of vaccine uptake.

This is one of the first studies in India to report the changes in willingness to accept COVID-19 vaccines among healthcare workers during the first and second waves of the SARS-CoV-2 pandemic. Willingness to receive COVID-19 vaccines among HCWs increased with time (between the first and third surveys), as the severity of the pandemic increased. To increase COVID-19 vaccine acceptance and coverage among HCWs, it is important to instill confidence in domestic vaccines and assist them to conduct accurate self-assessment of risk toward contracting COVID-19 infection. Perceived risk of infection, trust in the healthcare system and confidence in domestic vaccines were found to be significant predictors of uptake of COVID-19 vaccines. High vaccine acceptance among healthcare workers has the potential to improve acceptance in the general population as well. The study warrants multisectoral intervention for the improvement of vaccine acceptance among healthcare providers.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Institutional Research Ethics Committee of Post-Graduate Institute of Medical Education and Research (PGIMER), Chandigarh, India. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

BPad, MG, and AKA conceptualized the study and designed the tools. BPad, LJ, JV, PS, VC, BPat, SK, RS, SP, SB, NR, VR, TK, KG, BM, LS, MG, and AKA conducted the study at national level and collected the data. All authors reviewed drafts, provided edits, and approved the final submission.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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COVID-19 vaccination hesitancy and willingness among pregnant women in Italy

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Background: Pregnant women, especially those with comorbidities, compared to those non-pregnant, have higher risk of developing a severe form of COVID-19. However, COVID-19 vaccine uptake is very low among them.

Methods: An anonymous questionnaire was administered to randomly selected women 18 years of age that were currently pregnant or had just given birth between September 2021 and May 2022 in the geographic area of Naples. Vaccine hesitancy was assessed using the vaccine hesitancy scale (VHS).

Results: A total of 385 women participated. Women who had not been infected by SARS-CoV-2 and who needed information about vaccination against COVID-19 had a higher perceived risk of being infected with SARS-CoV-2. More than half (54.3%) of the women were very afraid of the potential side effects of the COVID-19 vaccination on the fetus. There was higher concern of the side effects of the vaccine on the fetus among those who did not have a graduate degree, those with high-risk pregnancy, those who had not been infected by SARS-CoV-2, those who were more concerned that they could be infected by SARS-CoV-2, those who did not know that this vaccination was recommended for them, and those trusting mass media/internet/social networks for information. Only 21.3% were vaccinated when pregnant, mostly women with a university degree, those who had been infected by SARS-CoV-2 before pregnancy, those who did not need information, and those who acquired information about the vaccination from gynecologists. Almost three-quarters (71.9%) were willing to receive the vaccination and those more likely were those with a university degree, those who have had at least one relative/cohabitant partner/friend who had been infected by SARS-CoV-2, those who were more concerned that they could be infected by SARS-CoV-2, and those who were not extremely concerned of the side effects of the vaccine on the fetus. A total of 86.4% were highly hesitant. Highly hesitant were respondents who did not get a graduate degree, those less concerned that they could be infected by SARS-CoV-2, and those trusting mass media/internet/social networks for information.

Conclusion: Public health efforts and education campaigns for pregnant women are needed for changing their perception patterns and for supporting gynecologists in promoting the uptake of this vaccination.

KEYWORDS

pregnancy, vaccination, vaccine hesitancy, COVID-19, Italy

Introduction

The pandemic caused by the new strain of coronavirus (SARS-CoV-2) is still affecting more than 200 countries and by August 23, 2022, over 590 million confirmed cases of Coronavirus disease 2019 (COVID-19) and 6.45 million deaths had been reported globally (1). Public health measures in communities remain the foundation to prevent and to reduce the spread of the SARS-CoV-2 infection. It is well-known that these universal measures include hand washing with soap and water, wearing of face masks, social distancing, covering of the mouth and nose when coughing, and avoiding touching the face. Moreover, the availability of efficacious vaccines against SARS-CoV-2 and its variants has raised hope for the control of the pandemic (2).

In Italy, the COVID-19 vaccination program began in December 2020 for priority groups, including healthcare workers, long-term care residents, elderly, and essential workers and in March 2021 for all adults (3). Two m-RNA COVID-19 vaccine shots have been recommended during pregnancy in any trimester (4, 5). Although pregnant women, especially those with comorbidities, compared to non-pregnant with COVID-19, are at increased risk of hospital admission, critical care, and invasive ventilation (6, 7), yet, COVID-19 vaccine uptake is very low among this group (8–10). A few recent studies have identified a number of individual profiles who would either be hesitant to receive the vaccine or refuse it despite the severity of the disease (11–14). However, to date the hesitancy and the intention about vaccination against SARS-CoV-2 of pregnant women is scarcely reported in Italy (15, 16). Taking this into consideration, a cross-sectional survey has been conducted to evaluate primarily the uptake, the hesitancy, and the willingness regarding the vaccination against the SARS-CoV-2 in a large sample of pregnant and postpartum women in Italy. Secondarily, the predictors influencing uptake, hesitancy, and intention to be vaccinated were also examined.

Materials and methods

Setting and population

This work is part of a larger research project toward COVID-19 vaccination among different groups of people living in Southern Italy (17–23). This survey was conducted between September 2021 and May 2022 in two public hospitals selected by simple random sampling from the list of those with a gynecology ward in the geographic area of Naples, Southern part of Italy.

The inclusion criterion consisted of women 18 years of age that were currently pregnant (from all three trimesters of gestation) or had just given birth in the 3 days before the time of the survey. Study participants were randomly approached while waiting for their regularly scheduled clinical appointment at the Gynecology and Obstetrics outpatient clinics or while attending the maternity wards located in the two hospitals.

A minimum target sample size of 380 was estimated based on the assumption that 30% of the subjects in the population were willing to receive the vaccination against COVID-19 during the pregnancy, with a margin of error of 5%, a confidence interval of 95%, and an expected response rate of 85%.

Procedures

This study was approved by the Ethics Committee of the Teaching Hospital of the University of Campania "Luigi Vanvitelli". A letter with the request of collaboration and the explanation of the purpose of the survey was sent to the health directors of the selected hospitals. Experienced trained personnel not involved in the clinical care approached the participants and explained the purpose, contents, and methodology of the research, that the participation was on an anonymous and voluntary basis, that all questions were compulsory, and that they were free to quit at any time. The experienced personnel conducted a face-to-face interview in a setting that was safe for both participants and personnel or a telephone interview. All participants prior to enrollment in the study gave written or verbal informed consent. No gifts or monetary compensation was provided to participants.

Questionnaire

The questionnaire was developed based on the content of instruments that were used in surveys conducted by some of us on the same topic enrolling different populations (17–20, 23). Piloting of the questionnaire was undertaken among 10 non-selected women to evaluate the comprehension of the questions and answers. Those involved in the pre-test were not included in the results.

The questionnaire consisted of 42 questions exploring four domains relating to the respondents: (1) socio-demographic and general characteristics, including age, marital status, education, number of children in home, whether or not they worked in healthcare, having been infected with SARS-CoV-2, and if they know someone who had been infected with SARS-CoV-2; (2) knowledge and attitude toward COVID-19 infection and vaccination with three statements regarding the concern that she could be infected with SARS-CoV-2, the vaccine recommendation for pregnant women, and the concern of potential side effects of the vaccine on the fetus; (3) COVID-19 vaccination receipt was determined and women were considered vaccinated if they reported having received ≥ 1 dose or fully vaccinated before or during pregnancy (independent of the term of pregnancy). If vaccination had or had not been received, the women were asked to select from predefined answers relevant to their decision or to complete an open field question. The intention to be vaccinated against COVID-19 was investigated among those unvaccinated by asking if they were willing to receive it and the reason(s) in favor or against the vaccination. This survey item was designed by using a close-ended multiple-choice question with options, in which respondents could select all that apply. Vaccine hesitancy was assessed using the 10-item Vaccine Hesitancy Scale (VHS) adapted to COVID-19 (24, 25). Each of the 10 items was assessed on a 5-point Likert scale. The wording of the VHS was slightly modified, and the questions were adapted to refer to oneself on COVID-19 vaccination during the pregnancy; and (4) sources of information related to COVID-19 vaccination in pregnancy. Options included gynecologist or other healthcare workers, family, friends, social networks, other internet sites, and mass-media, as well as, other and none. Finally, whether they would like to receive additional information.

Statistical analysis

Descriptive statistics were used to determine the socio-demographic and the general profile of the respondents. To explore the association between each of the independent characteristics and the outcomes of interest, a chi-square test and a Student's *t*-test were carried out for the categorical and for the continuous variables, respectively. The independent characteristics with a $p \leq 0.25$ in the bivariate analyses were incorporated into five multivariate linear and logistic regression models to address their possible role on the following dependent variables: perceived concern that she can be infected by the SARS-CoV-2 (continuous) (Model 1); concern of potential side effects of the COVID-19 vaccine on the fetus (not at all concerned, slightly concerned, uncertain, moderately concerned = 0; extremely concerned = 1) (Model 2); having received $\geq$1 dose of the COVID-19 vaccine during pregnancy (no = 0; yes = 1) (Model 3); willingness to receive the vaccine against COVID-19 (no = 0; yes = 1) (Model 4); and COVID-19 vaccine high hesitancy (no = 0; yes = 1) (Model 5). The following independent variables have been selected because they are potentially related to all dependent variables: age in years, marital status, baccalaureate/graduate degree, working in healthcare, at least one other child, at-risk pregnancy, at least one chronic disease, at least one relative/cohabitant partner/friend who had contracted SARS-CoV-2, and the need for additional information on COVID-19 vaccinations. The following variables were also included in the different models: having been infected by SARS-CoV-2 in Models 1, 2, 4, and 5; having been infected by SARS-CoV-2 before the pregnancy and concern that she can be infected by the SARS-CoV-2 going to the gynecologist in Model 3; perception of their health status during pregnancy in Models 1 to 3; knowing the recommendation of the COVID-19 vaccine for pregnant women in Model 2; having received the influenza vaccination in the past year in Models 3 to 5; having received the COVID-19 vaccine in Model 1; having not received the COVID-19 vaccine because they believed that it was not effective in Model 5; concern that she can be infected by the SARS-CoV-2 in Models 2, 4, and 5; belief that COVID-19 is a serious illness for the fetus if contracted during the pregnancy in Models 2 to 5; concern of the potential side effects of the COVID-19 vaccine on the fetus in Model 4; most trusted source of information related to the COVID-19 vaccination being the gynecologist in Models 3 and 4; and most trusted source of information related to the COVID-19 vaccination being mass media/internet sites/social networks in Models 1, 2, and 5. The variables with $p = 0.2$ and $p = 0.4$ were retained or excluded from the multivariate models by using a stepwise forward selection method, respectively. Results of the logistic regression models were measured using Odds Ratios (ORs) together with their 95% confidence intervals (CIs), whereas results of the linear regression models used standardized regression coefficients (ß). All analyses were based on two-sided *p*-values, with statistical significance defined as $p \leq 0.05$. STATA statistical software version 15.1 was used to analyze the data.

Results

Characteristics of the respondents

A total of 406 pregnant women were approached and 385 agreed to participate in this study giving a response rate of 94.8%. The main characteristics of the study population are summarized in Table 1. The mean age was 32.2 years, the vast majority were married or were living with a partner, less than one-fourth had completed a university degree, the majority had at least one other child at home, 32.5% were in the third trimester of pregnancy, 32.5% had been infected by SARS-CoV-2 and 47.2% of which were infected during their pregnancy, 52.8% reported being previously infected by COVID-19, and 15.3% had one or more comorbidities.

Attitude toward COVID-19

The overall mean value of the respondent's subjective perception of the risk of being infected by SARS-CoV-2, measured with a ten-point Likert scale ranging from 1 representing not at all to 10 representing extremely likely, was 6.7 with 26.5% that responded with a value of 10. Potential predictors of the different outcomes tested in the multivariate linear and logistic regression analysis are shown in Table 2. Women had a significantly higher level of concern of being infected by SARS-CoV-2 if they had not been infected by it and if they needed additional information about vaccination

TABLE 1 Socio-demographic and key characteristics of the study population.

Characteristics	N	%
Age, years	32.2 ± 5.4 (19–46)*	
Marital status		
Married/cohabited with a partner	349	90.7
Unmarried/separated/divorced/widowed	36	9.3
Educational level		
High school degree or less	293	76.1
Baccalaureate/graduate degree	92	23.9
Employment		
Worker in healthcare	12	3.1
Other	373	96.9
Number of children		
0	172	44.7
≥1	213	55.3
Trimester of pregnancy		
First	5	1.3
Second	19	4.9
Third	125	32.5
Given birth	236	61.3
Having been infected by SARS-CoV-2		
No	260	67.5
Yes	125	32.5
During pregnancy	59	47.2
Before pregnancy	66	52.8
Pregnancy at risk		
No	265	68.8
Yes	120	31.2
At least one chronic disease		
No	326	84.7
Yes	59	15.3
At least one relative/cohabitant partner/friend who had been infected by SARS-CoV-2		
No	65	16.9
Yes	320	83.1

*Mean ± Standard deviation (range).

against COVID-19 (Model 1). More than half (54.3%) of the women were very afraid of the potential side effects of the vaccination against COVID-19 on the fetus. The multivariate logistic regression model showed that this concern was higher among women who did not have a graduate degree, in those whose pregnancy was at risk, in those who had not been infected by SARS-CoV-2, in those with higher perceived concern of being infected by SARS-CoV-2, in those who did not know that this vaccination was recommended for pregnant women, and in those trusting mass media, internet sites, and social networks for their information about vaccination against COVID-19 (Model 2 in Table 2).

COVID-19 vaccine behavior and willingness

Of the respondents, 136 (35.3%) had received the vaccine against COVID-19 with only 82 having received the vaccine during the pregnancy for an overall prevalence of 21.3%. Of these 82 women, 32 were fully vaccinated during pregnancy, 42 received the first dose before pregnancy, and 8 received only the first dose during pregnancy. The multivariate logistic regression model performed with having had the COVID-19 vaccine during the pregnancy as an outcome variable showed that four independent predictors were significantly associated. Women with a university degree, those who have been infected by SARS-CoV-2 before the pregnancy, those who did not need additional information about vaccination against COVID-19, and those whose most trusted source of information about vaccination against COVID-19 were gynecologists were more likely to have received this vaccine (Model 3 in Table 2). The main reasons for having received the vaccination were for the protection of themselves (79.4%), of the newborn (64.7%), and of the family members (54.4%). The main reasons for those who did not receive this vaccination during pregnancy included concerns that the vaccine is not safe (58.6%), the gynecologist did not recommend it (36.9%), and a lack of knowledge (24.9%). Among those unvaccinated, almost three-quarters (71.9%) were willing to receive the vaccination. The results of the multivariate logistic regression model revealed that women with a university degree, those who have had at least one relative/cohabitant partner/friend who had been infected by SARS-CoV-2, those with higher perceived concern of being infected by SARS-CoV-2, and those who were not extremely concerned about the potential side effects of the COVID-19 vaccine on the fetus were more likely to be willing to receive the vaccine against COVID-19 (Model 4 in Table 2). Among the respondents who intend to get a COVID-19 vaccine, the main reasons given were for the protection of themselves (82.7%), of the newborn (82.1%), and of the family members (79.3%), whereas among those who did not intend to get this vaccine, leading reasons were concern about side effects (78.5%) and efficacy (37.1%), followed by thinking that it is not safe during the pregnancy (25.7%).

COVID-19 vaccine hesitancy

Among the women who did not receive the vaccination, the vast majority (86.4%) were highly hesitant, with a VHS score ≥25. The distribution of responses for each item on the VHS is presented in Table 3. A total of 80.3% respondents either disagreed or were undecided about whether the COVID-19 vaccines are effective during pregnancy, 85.2% strongly agreed or agreed that they were concerned about serious adverse effects, and more than one-third strongly agreed or agreed

TABLE 2 Determinants of the different outcomes of interest using linear and logistic regression analysis.

Variable	Coeff.	SE	*t*	*p*
Model 1. Perceived concern of being infected by SARS-CoV-2				
F (4, 380) = 6.59, $p < 0.0001$, $R^2 = 6.5\%$, adjusted $R^2 = 5.5\%$				
Need to receive additional information about COVID-19 vaccine during pregnancy	0.98	0.32	3.05	0.002
Not having been infected by SARS-CoV-2	−0.78	0.31	−2.52	0.012
Not having been vaccinated against COVID-19	−0.44	0.31	−1.44	0.151
Older	0.02	0.02	0.85	0.395
	OR	**SE**	**95% CI**	***p***
Model 2. Extremely concerned of the potential side effects of the vaccine against COVID-19 on the fetus				
Log likelihood = −219.58, $\chi^2 = 90.16$ (9 df), $p < 0.0001$				
Trusting mass media, internet sites, and social networks for their information about the COVID-19 vaccine	2.80	0.82	1.57–4.98	<0.001
Not knowing that the COVID-19 vaccine was recommended for pregnant women	0.31	0.09	0.17–0.54	<0.001
Not having baccalaureate/graduate degree	0.39	0.11	0.22–0.69	0.001
Higher perceived concern of being infected by SARS-CoV-2	1.14	0.05	1.04–1.24	0.002
Not having been infected by SARS-CoV-2	0.51	0.13	0.31–0.84	0.008
Pregnancy at risk	1.87	0.51	1.09–3.19	0.022
Need to receive additional information about COVID-19 vaccine during pregnancy	1.52	0.41	0.89–2.61	0.122
Unmarried	0.53	0.22	0.23–1.22	0.139
Lower self-rated health status during pregnancy	0.94	0.06	0.83–1.07	0.392
Model 3. Having received $\geq$ 1 dose of the COVID-19 vaccine during pregnancy				
Log likelihood = −167.63, $\chi^2 = 58.02$ (9 df), $p < 0.0001$				
Having been infected by SARS-CoV-2 before pregnancy	4.33	1.39	2.31–8.12	<0.001
Trusting gynecologists for their information about the COVID-19 vaccine	2.92	0.92	1.58–5.42	0.001
No need to receive additional information about COVID-19 vaccine during pregnancy	0.41	0.14	0.21–0.79	0.009
Having baccalaureate/graduate degree	1.92	0.61	1.03–3.57	0.038
Believing that COVID-19 is a serious disease when contracted during pregnancy	1.48	0.41	0.85–2.57	0.158
Having received the influenza vaccine over the past year	1.85	1.01	0.64–5.36	0.252
Higher self-rated health status during pregnancy	1.10	0.09	0.93–1.29	0.24
Pregnancy not at risk	0.68	0.23	0.35–1.32	0.263
Model 4. Willingness to receive the vaccine against COVID-19				
Log likelihood = −128.33, $\chi^2 = 39.15$ (7 df), $p < 0.0001$				
Higher perceived concern of being infected by SARS-CoV-2	1.19	0.06	1.06–1.32	0.002
Having baccalaureate/graduate degree	5.24	3.39	1.47–18.65	0.01
Not being extremely concerned of the potential side effects of the vaccine against COVID-19 on the fetus	0.46	0.17	0.22–0.94	0.035
Having at least one relative/cohabitant partner/friend who had been infected by SARS-CoV-2	2.06	0.74	1.02–4.18	0.044
Having at least one chronic disease	2.73	1.45	0.96–7.76	0.059
Believing that COVID-19 is a serious disease when contracted during pregnancy	1.35	0.43	0.72–2.53	0.339
Need to receive additional information about COVID-19 vaccine during pregnancy	1.37	0.46	0.70–2.67	0.354
Model 5. COVID-19 vaccine high hesitancy during pregnancy				
Log likelihood = −81.87, $\chi^2 = 34.77$ (4 df), $p < 0.0001$				
Trusting mass media, internet sites, and social networks for their information about the COVID-19 vaccine	6.18	2.81	2.53–15.09	<0.001
Lower perceived concern of being infected by SARS-CoV-2	0.77	0.07	0.64–0.93	0.007
Not having baccalaureate/graduate degree	0.38	0.17	0.15–0.92	0.033
Not having received the vaccine because the vaccine was not effective	2.69	2.09	0.59–12.34	0.201

that these vaccines carried more risks than older vaccines. Less than one-third strongly agreed or agreed that the COVID-19 vaccine is important for their health (27.7%) and that vaccines are a good way to protect their newborn from the disease

(22.9%). Results of the final multivariate logistic regression model revealed that three factors were significantly associated with the high hesitancy toward anti-COVID-19 vaccination. Respondents who did not have a graduate degree, those who were less concerned about the risk of being infected by SARS-CoV-2, and those trusting mass media, internet sites, and social networks for their information about vaccination against COVID-19 were more likely to be highly hesitant (Model 5 in Table 2).

Sources of COVID-19 vaccination-related information

Almost all women reported that they had received information about vaccination against COVID-19 (98.7%). In the multiple-choice question regarding the sources of information, gynecologists (61%), internet (59.2%), and mass media (54.5%) were the most trusted sources. Almost one-third of the respondents needed to receive additional information about vaccination against COVID-19 (29.3%).

Discussion

This survey is among the first to provide an insight on the coverage, hesitancy, and willingness to receive the SARS-CoV-2 vaccination among pregnant women in Italy, as well as to identify factors that were related to an individual's decision.

A striking observation in the results of this study was the very low number of women (21.3%) that claimed that they had received at least one dose of the COVID-19 vaccine during pregnancy. A higher coverage has been observed in developed countries such as Japan with a value of 82.1% (26), Canada with 48.2% (27), New Zealand with 44% (28), whereas lower values of 20.8, 18.1, 10.5, and 1.2% have been found respectively in Israel (29), in Norway and Sweden (30), in the United Kingdom (8) and in Germany (31). Interestingly, very low uptake also of other recommended vaccines among pregnant women have been reported in the literature, including for example results from Italy with none having received tetanus, diphtheria, and acellular pertussis vaccine, and only 1.4% for influenza (32), and from Tunisia, France, United States, and Peru respectively with 4.6% (33), 7.4% (34), 10.3% (35), and 19% (36) for influenza. These findings underline the need to promote education intervention, especially during pregnancy, in order to improve women's knowledge on the benefits of antenatal recommended vaccinations. Not surprisingly, women who did not get the COVID-19 vaccine or did not intend to receive it indicated as major reasons the fears about its side effects and doubts about its efficacy. This fear of adverse events was already observed as a prevalent reason for refusing the COVID-19 vaccination in other studies in Italy (15) and elsewhere (13, 37–41). Among the unvaccinated participants, 71.9% reported their willingness to receive the vaccine. This frequency is lower compared to the values of 84.1% (20) and of 80.7% (19) observed by some of us in the same geographic area among different groups of individuals. However, the proportion was considerably higher than the values reported in several other studies among pregnant women: 13.8% in Germany (31), 16.7% in Ukraine (41), 29.5% in France (38), 29.7% in Switzerland (42),

TABLE 3 Descriptive characteristics of respondents' VHS index about the COVID-19 vaccine.

Item	Participants' response	N	%
Getting vaccinated against COVID-19 during pregnancy is important for my health	Disagree	111	44.6
	Not sure	69	27.7
	Agree	69	27.7
Getting vaccinated against COVID-19 during pregnancy is efficacy	Disagree	106	42.5
	Not sure	94	37.8
	Agree	49	19.7
It is important to get COVID-19 vaccine during pregnancy to protect the newborn	Disagree	124	49.8
	Not sure	68	27.3
	Agree	57	22.9
Being vaccinated against COVID-19 during pregnancy is useful	Disagree	122	49
	Not sure	78	31.3
	Agree	49	19.7
The COVID-19 vaccine is more dangerous than the other vaccines administered during pregnancy (such as diphtheria, tetanus, pertussis, influenzae)	Disagree	78	31.3
	Not sure	62	25
	Agree	109	43.7
The information I receive from the Ministry of Health on the COVID-19 vaccine during pregnancy is reliable	Disagree	113	45.4
	Not sure	76	30.5
	Agree	60	24.1
Getting the COVID-19 vaccine during pregnancy is an effective strategy to protect me from the disease	Disagree	124	49.8
	Not sure	60	24.1
	Agree	65	26.1
I follow my gynecologist's advice about getting the COVID-19 vaccine during pregnancy	Disagree	80	31.3
	Not sure	29	11.7
	Agree	142	57
I am worried about a serious side effect after getting the COVID-19 vaccine during pregnancy	Disagree	27	10.8
	Not sure	10	4
	Agree	212	85.2
I do not need the COVID-19 vaccine during pregnancy	Disagree	85	35.7
	Not sure	55	22.1
	Agree	105	42.2

37% in Turkey (43), 43% in the United States (11), and 60.8% in Thailand (44). Moreover, the observed finding is consistent with those found in Czechia and in China with respectively, 76.6% (45) and 77.4% (46) of pregnant populations willing to receive the vaccine. Nevertheless, it is important to underline that the differences in the access to the vaccination services, in the various periods of time the studies have been conducted, in the methodologies used, and in the characteristics of the samples may hinder comparison between studies.

It is noteworthy to mention that the results of this survey provide important insight into the main sources commonly utilized by pregnant women to obtain information on COVID-19 vaccinations. Gynecologists were identified as the main source thus pinpointing their unique opportunity for the delivery of reliable information on how to prevent the disease and about its vaccine to this population. Indeed, gynecologists are the most familiar physicians with the conditions of pregnant women and, therefore, the information and recommendations they provide can directly affect vaccination decisions. This is confirmed by the finding that the women who had received information from the gynecologist were more likely to be vaccinated. This study contributes to the ample literature showing that communication and recommendations from healthcare providers are powerful factors in addressing vaccine concerns and promoting adherence to immunization schedules (47, 48). However, a large proportion of pregnant women report seeking online sources for information, and this is of concern since vaccine-hesitant groups are very active in the media environment, and most information from this source is anti-vaccination. Such content has had a negative impact on the attitudes toward vaccines and vaccine hesitancy. Indeed, pregnant women who had acquired information on the COVID-19 vaccination from online sources were more likely to perceive that the vaccine is dangerous for the fetus and to be highly hesitant. These results corroborate the findings of previously similar studies conducted elsewhere (12, 49). Moreover, it is disturbing the finding that 23.9% of the sample did not get the COVID-19 vaccine because the gynecologist did not recommend it. Therefore, there is need for further education for the gynecologists on existing guidelines to increase vaccination rates. The need of additional information also has a significant impact. Indeed, pregnant women who would like to get additional information were more likely to be concerned about being infected by SARS-CoV-2, whereas those who did not have this need were more likely to be vaccinated. These associations underlined the importance of the information on immunization in improving the level of knowledge and in changing intentions toward vaccination. The findings have been acknowledged among different populations in several geographic areas (17–19, 23, 50, 51).

The results of the present survey on the factors affecting the different outcomes of interest showed several additional significant associations. Among the socio-demographic characteristics, the level of education was the only significant factor associated with several outcomes. Indeed, pregnant women with a university degree were more likely to be vaccinated and to be willing to receive the vaccination, whereas those without a degree were more likely to be vaccine highly hesitant. These interesting findings highlight the positive impact of education on the vaccine uptake and on the attitudes toward vaccination as also previously found in the literature (39, 42). Moreover, the current study discovered that the evidence of a personal prior infection with SARS-CoV-2 or in a relative/cohabitant partner/friend was linked with several outcomes. Women who have had a prior infection were more likely to have been vaccinated and those who have had such experience in a relative/cohabitant partner/friend were more likely to be willing to receive the vaccination. These findings may be explained by the fact that these women may have had health consequences or have been well-informed about the negative effects of this infection and, therefore, see the vaccination as a positive intervention, whereas those without such experience may be less informed about the consequences. Finally, as expected, women with a lower perceived concern of being infected by SARS-CoV-2 were more likely to be vaccine highly hesitant. This finding underlined the need for educational campaigns and appropriate communication on this group also, because, as already reported, respondents who were vaccine highly hesitant and were worried of the potential side effects of the vaccination on the fetus were those who had acquired information also from the internet.

The potential methodological limitations of this survey should be considered in interpreting the findings. First, this survey was conducted using a cross-sectional design and, therefore, this prevents drawing any conclusion about causality in the associations found between predictors and outcomes of interest. Second, findings of the survey may not be totally generalizable to the Italian population of pregnant women, as it has been conducted in only one geographic area. Third, participants may have answered in a socially desirable manner mainly regarding a positive attitude toward the vaccination. However, participants were assured of complete anonymity in the responses at the beginning of the interview and this may have reduced the influence of desirability bias. As such, the findings are likely to be authentic. Despite these limitations, the survey outlines useful data for policymakers and healthcare workers on this sensitive topic.

In summary, the present survey has generated solid data regarding COVID-19 vaccination uptake, hesitancy, and intention to be vaccinated of pregnant women. The findings clearly indicate a low vaccine uptake and identified a high hesitancy and unwillingness to accept this vaccination irrespective of the pandemic spread of the SARS-CoV-2 that has determined an extraordinarily high number of cases and deaths. Safety of the vaccine and the lack of recommendation by the gynecologist have been identified as the major reasons for those who did not receive this vaccine unless its safety has been widely disseminated together with the recommendation for pregnant women by the scientific and health authorities. Public health efforts and education campaigns regarding the importance of this vaccine during pregnancy are needed for changing their perception patterns and for supporting gynecologists in promoting the uptake of vaccination against COVID-19.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The study involving human participants was reviewed and approved by Ethics Committee of the Teaching Hospital of the University of Campania Luigi Vanvitelli. The patients/participants provided their written or oral informed consent to participate in this study.

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Author contributions

GMdG, FC, and LF participated in the conception and design of the study, contributed to the data collection, data analysis, and interpretation. AN contributed to the data collection, data analysis, and interpretation. IFA designed the study, was responsible for the statistical analysis and interpretation, drafted and wrote the article. All authors have read and approved the final version of the article and agree to be accountable for all aspects of the work.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Association between close interpersonal contact and vaccine hesitancy: Findings from a population-based survey in Canada

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Background: Vaccine hesitancy threatens efforts to bring the coronavirus disease 2019 (COVID-19) pandemic to an end. Given that social or interpersonal contact is an important driver for COVID-19 transmission, understanding the relationship between contact rates and vaccine hesitancy may help identify appropriate targets for strategic intervention. The purpose of this study was to assess the association between interpersonal contact and COVID-19 vaccine hesitancy among a sample of unvaccinated adults in the Canadian province of British Columbia (BC).

Methods: Unvaccinated individuals participating in the BC COVID-19 Population Mixing Patterns Survey (BC-Mix) were asked to indicate their level of agreement to the statement, "*I plan to get the COVID-19 vaccine.*" Multivariable multinomial logistic regression was used to assess the association between self-reported interpersonal contact and vaccine hesitancy, adjusting for age, sex, ethnicity, educational attainment, occupation, household size and region of residence. All analyses incorporated survey sampling weights based on age, sex, geography, and ethnicity.

Results: Results were based on survey responses collected between March 8, 2021 and December 6, 2021, by a total of 4,515 adults aged 18 years and older. Overall, 56.7% of respondents reported that they were willing to get the COVID-19 vaccine, 27.0% were unwilling and 16.3% were undecided. We found a dose-response association between interpersonal contact and vaccine hesitancy. Compared to individuals in the lowest quartile (least contact), those in the fourth quartile (highest contact), third quartile and second quartile groups were more likely to be vaccine hesitant, with adjusted odd ratios (aORs) of 2.85 (95% CI: 2.02, 4.00), 1.91(95% CI: 1.38, 2.64), 1.78 (95% CI: 1.13, 2.82), respectively.

Conclusion: Study findings show that among unvaccinated people in BC, vaccine hesitancy is greater among those who have high contact rates, and hence potentially at higher risk of acquiring and transmitting infection. This may also impact future uptake of booster doses.

KEYWORDS

interpersonal contact, COVID-19, vaccine hesitancy, transmission, Canada

Introduction

The Coronavirus Disease 2019 (COVID-19) pandemic continues to have adverse social, economic and health impact on societies across the globe. As of August 7, 2022, over 580 million confirmed cases of (COVID-19), have been reported globally, with over 6.4 million deaths (1). The availability of approved safe and effective COVID-19 vaccines offered hope and optimism to end the COVID-19 pandemic, and a potential way to return to pre-pandemic normalcy, even though the emergence of new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants presents new challenges. Current data indicates high effectiveness of the COVID-19 vaccines against infection, transmission, severe disease, and death (2–6).

However, the potential population-level reduction in transmission, morbidity, and mortality due to COVID-19 ultimately depends on high vaccine uptake which is in turn threatened by vaccine hesitancy, a complex and context specific behavior defined as "the delay in acceptance or refusal of vaccines despite availability of vaccination services" (7). In fact, due to the recent global resurgence of highly infectious vaccine-preventable diseases such as measles, the World Health Organization (WHO) named vaccine hesitancy as one of the ten greatest threats to global health in 2019 (8). Varying degrees of COVID-19 vaccine hesitancy have been reported across the world. In Bangladesh, two cross sectional studies showed vaccine hesitancy of 32.5% (9) and 27.4% (10). A recent scoping review of COVID-19 vaccine hesitancy in Africa showed vaccine acceptance ranged from 6.9 to 97.9% (11). A systematic review of COVID-19 vaccine hesitancy in the U.S revealed vaccine acceptance rate ranging from 12 to 91.4% (12).

As of July, 2022, the following COVID-19 vaccines had received authorization for use in Canada from Health Canada: Pfizer-BioNTech Cominarty, Moderna Spikevax, AstraZeneca Vaxzevria, Janssen (Johnson & Johnson), Novavax Nuvaxovid and Medicago Covifenz (13, 14). In British Columbia (BC), Pfizer-BioNTech Cominarty and Moderna Spikevax COVID-19 vaccine were the first to receive authorization for use on September 16, 2021, according to the British Columbia Centre for Disease Control (14). A study by Statistics Canada conducted in March/April 2021 indicated that 88% of Canadians aged 12 and older were willing to get vaccinated for COVID-19 when a vaccine is available to them or have already received one dose of the vaccine (15). Ogilvie et al. (16) also reported a 79.8% COVID-19 vaccine acceptance rate among the general population of British Columbia, Canada.

Some factors associated with COVID-19 vaccine hesitancy include age, gender, chronic medical condition, fears about COVID-19, income, employment status, ethnicity, location of residence, religion, marital status, educational level etc., (17). As individuals with high interpersonal or social contacts may have a higher risk of COVID-19 transmission, vaccine uptake among this population is critical to curbing the spread of COVID-19. Although COVID-19 vaccine uptake and interpersonal contact have been investigated independently in light of their association with COVID-19 transmission, we are not aware of any study that has examined the relationship between these two important factors that affect COVID-19 transmission dynamics. Hence, the purpose of this study was to evaluate the association between interpersonal contact rate and COVID-19 vaccine hesitancy.

Methods

This study used data from the BC COVID-19 Population Mixing Patterns Survey (BC-Mix), a repeated online survey developed to assess population mixing patterns in BC during the COVID-19 pandemic. The ongoing survey was launched in September 2020 and is open to all BC residents aged 18 years or older. Anonymous links to the survey are circulated *via* advertisements placed on social media platforms (including Facebook, Instagram, YouTube and Twitter), on flyers distributed at grocery stores, community centers and places of worship, including those frequented by ethnic minority groups. Suspected duplicate responses are removed prior to analyses. Also, survey responses that do not have completion rate of at least 33%, and valid non-missing responses for the sex and age questions are excluded for weighting and further analyses. Using the 2016 Census data (18) as reference, the survey data is weighted with the following auxiliary variables: age, sex, geography, and ethnicity, using the *weighting adjustment technique* (19). As of June 2022, more than 88,000 individuals had participated in the survey. Further details about the survey development, design and domains are described

TABLE 1 Characteristics of study participants (unweighted $N = 4,515$), March 8, 2021-December 6, 2021.

		N	Weighted *N*	Weighted % (95% CI)
Willingness to receive vaccine				
	Hesitant	1,028	1,561	27.0 (24.9, 29.2)
	Willing	2,903	3,273	56.7 (54.3, 59.1)
	Undecided	584	939	16.3 (14.3, 18.2)
Sex				
	Male	1,159	3,590	62.2 (60.1, 64.2)
	Female	3,356	2,183	37.8 (35.8, 39.9)
Age				
	18–34	623	1,728	29.9 (27.4, 32.4)
	35–54	1,542	2,161	37.4 (35.1, 39.8)
	55+	2,350	1,884	32.6 (30.6, 34.7)
Ethnicity				
	Chinese	79	392	6.8 (5.1, 8.5)
	Not a visible minority (White)	3,623	3,443	59.6 (57.1, 62.2)
	South Asian	101	586	10.1 (7.9, 12.4)
	Other ethnicities	458	955	16.5 (14.7, 18.4)
	Missing/Unknown	254	396	6.9 (5.7, 8.1)
Educational attainment				
	Below high school	122	181	3.1 (2.3, 4.0)
	Below bachelor	1,818	2,166	37.5 (35.2, 39.9)
	University degree	1,351	1,701	29.5 (27.2, 31.7)
	Missing/Unknown	1,224	1,725	29.9 (27.7, 32.1)
Employment status				
	Employed full-time (30 h or more/week)	1,100	1,708	29.6 (27.2, 31.9)
	Employed part-time (<30 h/week)	283	392	6.8 (5.4, 8.1)
	Self-employed	352	457	7.9 (6.5, 9.3)
	Unemployed but looking for a job	136	207	3.6 (2.7, 4.4)
	Unemployed and not looking for a job	63	88	1.5 (1.0, 2.1)
	Full-time parent, homemaker	138	128	2.2 (1.7, 2.8)
	Retired	1,051	791	13.7 (12–15)
	Student/Pupil	53	159	2.7 (1.8, 3.7)
	Long-term sick or disabled	128	145	2.5 (1.8, 3.2)
	Prefer not to answer	92	163	2.8 (1.8, 3.8)
	Missing/Unknown	1,119	1,536	26.6 (24.5, 28.7)
Occupation				
	Essential workers	862	1,343	23.3 (21.1, 25.4)
	Non-essential workers	1,137	1,338	23.2 (21.1, 26.3)
	Do not work	941	880	15.2 (13.6, 16.9)
	Other occupations	323	465	8.0 (6.6, 9.5)
	Prefer not to answer	133	212	3.7 (2.7, 4.6)
	Missing/Unknown	1,119	1,536	26.6 (24.5, 28.7)
Household size				
	1	809	849	14.7 (13.2, 16.2)
	2	1,978	2,090	36.2 (34.0, 38.4)
	3	593	883	15.3 (13.4, 17.2)

(Continued)

TABLE 1 (Continued)

		N	Weighted *N*	Weighted % (95% CI)
	4	635	887	15.4 (13.5, 17.2)
	5	181	333	5.8 (4.4, 7.1)
	6+	292	663	11.5 (9.6, 13.3)
	Prefer not to answer	27	68	1.2 (0.5, 1.9)
Health region				
	Interior	753	877	15.2 (13.6, 16.8)
	Fraser	831	1,510	26.2 (23.6, 28.7)
	Vancouver Coastal	681	827	14.3 (12.7, 15.9)
	Vancouver Island	869	673	11.7 (10.4, 12.9)
	Northern	213	275	4.8 (3.8, 5.7)
	Missing/Unknown	1,168	1,611	27.9 (25.8, 30.0)
Material deprivation				
	1 (Privileged)	619	649	11.2 (9.9, 12.6)
	2	580	749	13.0 (11.3, 14.6)
	3	685	724	12.5 (11.0, 14.1)
	4	527	670	11.6 (10.1, 13.2)
	5 (Deprived)	491	775	13.4 (11.4, 15.5)
	Missing/Unknown	1,613	2,205	38.2 (35.9, 40.5)
Social deprivation				
	1 (Privileged)	451	639	11.1 (9.3, 12.8)
	2	458	544	9.4 (8.0, 10.9)
	3	693	826	14.3 (12.5, 16.1)
	4	576	709	12.3 (10.6, 13.9)
	5 (Deprived)	724	850	14.7 (13.2, 16.3)
	Missing/Unknown	1,613	2,205	38.2 (35.9, 40.5)

in detail elsewhere (20–22). We followed the checklist for Reporting Results of Internet E-Surveys (CHERRIES) (23). The domain on vaccine hesitancy was added to the survey on March 8, 2021.

Measures

To assess vaccine hesitancy, participants were asked whether they had received any of the approved COVID-19 vaccines. Individuals who answered that they had not yet received the COVID-19 vaccine at the time of the survey were asked to indicate their level of agreement with the statement, "*I plan to get the COVID-19 vaccine.*" Responses were rated on a five-point scale ranging from 1 to 5, with 1 being "*Strongly disagree*" and 5 being "*Strongly agree.*" For the purposes of analyses, the responses were recoded, with those who responded, "*Strongly Disagree*" or "*Disagree*" coded as "*unwilling to receive COVID-19 vaccine or vaccine hesitant*" and those who responded "*Agree*" and "*Strongly Agree*" coded as "*willing to receive a COVID-19 vaccine.*" Individuals who chose "*Neutral*" were considered "*undecided.*"

Interpersonal contact was assessed by the number of in-person, face-to-face contacts that a participant had within the past 24 h. The number of contacts was categorized by quartiles.

We assessed age, sex, ethnicity, educational attainment, occupation, household size, employment status and health region of participants (24), based on self-reported data from survey questions. The literature guided our choice of these characteristics as confounders in our assessment of the association between interpersonal contact and vaccine hesitancy.

Additional variables such as material and social deprivation index were derived using census and location data (25). Further details (including definitions and response categories) on all the survey questions relevant to this study are provided in Supplementary Table 1 of the Supplementary material.

Analyses

Participant characteristics were summarized using weighted frequencies and percentages and are presented in Table 1. Survey methodology and weighting technique

TABLE 2 Characteristics of study participants by interpersonal contact (unweighted, $N = 4{,}515$), March 8, 2021- December 6, 2021.

		Q1 (lowest)		Q2		Q3		Q4 (highest)	
		Weighted,	*N* % (95% CI)	Weighted,	*N* % (95% CI)	Weighted,	*N* % (95% CI)	Weighted,	*N* % (95% CI)
Sex									
	Male	1,378	38.4 (34.7, 42.1)	420	11.7 (9.4, 14.0)	754	20.9 (18.2, 23.8)	1,037	28.9 (25.7, 32.1)
	Female	875	40.0 (38.0, 42.5)	290	13.3 (11.6, 15.0)	496	22.7 (20.7, 24.7)	523	23.9 (21.8, 26.0)
Age									
	18–34	621	36.0 (30.8, 41.1)	214	12.4 (8.9, 15.8)	351	20.3 (16.0, 24.6)	542	31.4 (26.6, 36.2)
	35–54	792	37.0 (32.5, 40.8)	245	11.3 (8.6, 14.0)	509	23.6 (20.5, 26.7)	614	28.4 (25.0, 31.9)
	55+	839	45.0 (41.2, 47.9)	252	13.4 (11.4, 15.3)	390	20.7 (18.2, 23.2)	403	21.4 (18.7, 24.1)
Ethnicity									
	Chinese	190	48.4 (35.2, 61.6)	55	14.1 (5.4, 22.8)	75	19.2 (9.1, 29.4)	71	18.2 (8.7, 27.8)
	Not a visible minority (White)	1,233	35.8 (33.4, 38.2)	443	12.9 (11.2, 14.5)	834	24.2 (22.1, 26.4)	933	27.1 (24.7, 29.5)
	South Asian	341	58.3 (46.3, 70.2)	69	11.8 (3.4, 20.1)	69	11.9 (4.7, 19.0)	106	18.1 (9.7, 26.6)
	Other ethnicities	366	38.3 (32.4, 44.2)	117	12.2 (8.4, 16.0)	187	19.6 (14.7, 24.4)	286	30.0 (24.6, 35.3)
	Missing/Unknown	123	31.0 (23.3, 38.7)	27	6.8 (2.8, 10.8)	84	21.3 (13.8, 28.7)	162	40.9 (31.7, 50.1)
Educational attainment									
	Below high school	102	56.7 (43.2, 70.2)	32	17.5 (7.9, 27.2)	25	13.9 (6.8, 20.9)	22	11.9 (3.2, 20.6)
	Below bachelor	992	45.8 (41.8, 49.8)	278	12.9 (10.4, 15.4)	498	23.0 (19.9, 26.1)	398	18.4 (15.0, 21.7)
	University degree	822	48.3 (43.7, 53.0)	256	15.1 (11.7, 18.4)	365	21.5 (17.9, 25.0)	257	15.1 (12.1, 18.1)
	Missing/Unknown	336	19.5 (15.7, 23.3)	144	8.3 (6.0, 10.7)	361	21.0 (17.4, 24.5)	883	51.2 (46.9, 55.6)
Employment status									
	Employed full-time (30 h or more/week)	657	38.5 (33.6, 43.4)	226	13.3 (9.9, 16.6)	420	24.6 (20.5, 28.7)	404	23.7 (19.6, 27.7)
	Employed part-time (<30 h/week)	176	44.9 (34.4, 55.4)	70	18.0 (9.6, 26.4)	74	19.0 (12.3, 25.6)	71	18.1 (9.4, 26.8)
	Self-employed	207	45.2 (35.7, 54.9)	73	16.1 (9.7, 22.5)	98	21.5 (15.4, 27.7)	78	17.1 (10.9, 23.3)
	Unemployed but looking for a job	128	61.9 (49.5, 74.2)	15	7.1 (2.8, 11.4)	39	19.1 (10.0, 28.2)	25	12.0 (0.6, 23.3)

(Continued)

TABLE 2 (Continued)

		Q1 (lowest)		Q2		Q3		Q4 (highest)	
		Weighted,	*N* % (95% CI)	Weighted,	*N* % (95% CI)	Weighted,	*N* % (95% CI)	Weighted,	*N* % (95% CI)
	Unemployed and not looking for a job	57	64.1 (46.6, 81.6)	10	10.9 (1.3, 20.5)	14	16.4 (4.5, 28.3)	8	8.6 (0.0, 19.7)
	Full-time parent, homemaker	59	46.1 (33.8, 58.4)	16	12.3 (6.1, 18.5)	45	34.8 (23.5, 46.0)	9	6.8 (2.6, 11.0)
	Retired	473	59.8 (55.1, 64.5)	114	14.4 (11.4, 17.4)	146	18.4 (15.3, 21.6)	58	7.4 (4.8, 10.0)
	Student/Pupil	83	52.5 (34.6, 70.3)	28	17.5 (4.7, 30.3)	30	19.2 (3.8, 34.6)	17	10.8 (0.8, 20.8)
	Long-term sick or disabled	87	59.7 (46.8, 72.6)	20	13.8 (5.9, 21.6)	30	20.7 (10.2, 31.1)	9	5.9 (0.4, 11.4)
	Prefer not to answer	97	59.8 (42.9, 76.6)	12	7.4 (0.0, 16.9)	10	6.2 (1.4, 11.0)	43	26.7 (11.9, 41.4)
	Missing/Unknown	230	14.9 (11.6, 18.3)	127	8.2 (5.8, 10.7)	342	22.3 (18.4, 26.1)	838	54.5 (50.1, 59.0)
Occupation									
	Essential workers	516	38.4 (33.3, 43.6)	178	13.3 (9.4, 17.2)	340	25.3 (20.8, 29.9)	308	23.0 (18.5, 27.4)
	Non-essential workers	638	47.7 (42.5, 52.9)	216	16.2 (12.7, 19.6)	280	21.0 (17.3, 24.6)	203	15.2 (11.8, 18.6)
	Do not work	540	61.4 (56.0, 66.8)	118	13.4 (9.5, 17.2)	161	18.3 (14.4, 22.2)	61	7.0 (4.2, 9.8)
	Others	221	47.5 (37.8, 57.2)	52	11.3 (5.9, 16.6)	91	19.6 (13.5, 25.7)	101	21.6 (12.7, 30.6)
	Prefer not to answer	109	51.5 (37.9, 65.0)	19	9.1 (1.4, 16.9)	35	16.7 (7.2, 26.2)	48	22.7 (11.8, 33.7)
	Missing/Unknown	230	14.9 (11.6, 18.3)	127	8.2 (5.8, 10.7)	342	22.3 (18.4, 26.1)	838	54.5 (50.1, 59.0)
Household size									
	1	429	50.5 (45.0, 56.0)	79	9.4 (5.9, 12.8)	149	17.6 (13.7, 21.4)	192	22.6 (18.0, 27.2)
	2	986	47.2 (43.7, 50.7)	261	12.5 (10.2, 14.8)	363	17.4 (14.9, 19.8)	479	22.9 (20.0, 25.9)
	3	343	38.9 (31.9, 45.8)	122	13.8 (9.8, 17.9)	177	20.1 (15.3, 24.9)	241	27.3 (21.2, 33.3)
	4	253	28.5 (21.8, 35.1)	132	14.9 (11.0, 18.8)	280	31.5 (25.7, 37.4)	223	25.1 (19.8, 30.4)
	5	69	20.9 (9.7, 32.1)	33	10.0 (3.4, 16.5)	105	31.6 (20.6, 42.5)	125	37.6 (26.4, 48.8)
	6+	140	21.1 (13.0, 29.3)	81	12.3 (5.1, 19.4)	170	25.6 (18.4, 32.7)	272	41.0 (32.7, 49.3)
	Prefer not to answer	32	47.5 (15.2, 79.9)	1	1.9 (0.0, 5.9)	6	9.1 (0.0, 19.1)	28	41.5 (11.1, 72.0)
Health region									
	Interior	344	39.2 (33.9, 44.6)	128	14.6 (10.5, 18.7)	202	23.0 (18.4, 27.6)	203	23.2 (18.1, 28.2)
	Fraser	744	49.3 (43.2, 55.3)	186	12.3 (8.5, 16.1)	314	20.8 (16.4, 25.2)	266	17.6 (13.3, 21.9)
	Vancouver Coastal	390	47.1 (41.3, 53.0)	106	12.9 (9.0, 16.7)	156	18.9 (14.5, 23.3)	175	21.1 (16.3, 25.9)
	Vancouver Island	284	42.3 (36.9, 47.6)	107	15.8 (11.9, 19.8)	169	25.1 (20.4, 29.8)	113	16.8 (12.7, 20.9)

(Continued)

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TABLE 2 (Continued)

	Q1 (lowest)		Q2		Q3		Q4 (highest)	
	Weighted,	*N* % (95% CI)	Weighted,	*N* % (95% CI)	Weighted,	*N* % (95% CI)	Weighted,	*N* % (95% CI)
Northern	104	37.8 (27.9, 47.7)	33	12.1 (6.3, 17.9)	55	20.2 (13.7, 26.7)	82	29.9 (19.6, 40.1)
Missing/Unknown	387	24.0 (20.2, 27.8)	150	9.3 (6.8, 11.9)	353	21.9 (18.3, 25.6)	721	44.7 (40.4, 49.1)
Material deprivation								
1 (Privileged)	292	45.0 (39.0, 51.0)	70	10.8 (7.3, 14.3)	173	26.7 (20.9, 32.4)	114	17.6 (12.8, 22.4)
2	342	45.7 (38.9, 52.4)	124	16.5 (11.2, 21.8)	148	19.7 (15.0, 24.4)	136	18.1 (12.8, 23.4)
3	323	44.6 (38.0, 51.2)	116	16.0 (11.8, 20.1)	150	20.7 (15.8, 25.6)	135	18.7 (13.8, 23.6)
4	315	47.0 (39.9, 54.3)	61	9.1 (6.1, 12.1)	157	23.4 (18.1, 28.6)	137	20.5 (15.0, 26.1)
5 (Deprived)	329	42.5 (34.0, 51.0)	135	17.4 (10.9, 23.9)	158	20.3 (14.1, 26.5)	153	19.8 (13.3, 26.3)
Missing/Unknown	652	29.5 (26.0, 33.1)	205	9.3 (7.2, 11.4)	465	21.1 (18.0, 24.2)	884	40.1 (36.4, 43.8)
Social deprivation								
1 (Privileged)	274	43.0 (34.4, 51.5)	113	17.7 (11.3, 24.1)	130	20.4 (14.4, 26.4)	121	18.9 (11.9, 25.9)
2	207	38.1 (30.0, 46.6)	65	12.0 (7.9, 16.1)	121	22.3 (16.5, 28.1)	150	27.7 (20.3, 35.0)
3	344	41.7 (35.0, 48.4)	121	14.6 (10.4, 18.9)	233	28.3 (22.2, 34.4)	127	15.4 (10.9, 19.9)
4	337	47.5 (40.3, 54.7)	98	13.8 (7.9, 19.7)	148	20.9 (15.5, 26.3)	126	17.8 (12.6, 23.0)
5 (Deprived)	438	51.6 (46.0, 57.2)	108	12.8 (9.2, 16.3)	151	17.8 (14.1, 21.5)	151	17.8 (13.7, 22.0)
Missing/Unknown	652	29.5 (26.0, 33.1)	205	9.3 (7.2, 11.4)	465	21.1 (18.0, 24.2)	884	40.1 (36.4, 43.8)

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have been described elsewhere (20). Characteristics of study participants were stratified by contact rate (Table 2) and also by COVID-19 vaccine hesitancy (Table 3).

We investigated the association between interpersonal contact (primary exposure) and COVID-19 vaccine hesitancy (outcome measure) while accounting for demographic and other variables using multivariable multinomial logistic regression (Table 4). In a sensitivity analysis, we repeated this analysis but for the outcome variable, we considered those who had already received the vaccine as willing to receive it (Supplementary Tables 2, 3 of the Supplementary material).

All analyses incorporated survey sampling weights that were estimated based on age, sex, geography (region), and ethnicity distribution as described elsewhere (20). All tests were two-sided significant at the 0.05 level. Analyses were performed in SAS software version 9.4 (26).

Ethics approval

Informed consent was obtained from all participants. Ethical approval for this study was provided by the University of British Columbia Behavioral Research Ethics Board (No: H20-01785).

Results

Participant characteristics (overall)

Out of 15,796 respondents completing the survey between March 8 and December 6, 2021, 11,127 (70.4%) had received COVID-19 vaccine and 154 (1.0%) had missing/non-valid responses, so were ineligible for analysis, leaving 4,515 (28.6%) eligible records for analysis (i.e., people who had not yet been vaccinated and who provided valid responses to the willingness to get vaccinated question). The results presented here are based on weighted survey responses from these 4,515 responses.

The majority of participants were male (62.2%), between 35 and 54 years old (37.4%), identified as White (59.6%), had a full-time employment (29.6%), and lived with one other person in their household (36.2%). The Fraser Health region contributed the largest number of participants (26.2%). Also, 37.5% of respondents had below bachelor's education, while 29.5% had a University degree (Table 1).

Overall, 56.7% of respondents reported that they were willing to get the COVID-19 vaccine, 27.0% were unwilling (vaccine hesitant) and 16.3% were undecided about getting the COVID-19 vaccine (Table 1). However, when people who had already received the vaccine were included with those who said were willing to receive the vaccine, the proportion willing to get the vaccine was 86.5% (Supplementary Table 2 in the Supplementary material).

Participant characteristics by interpersonal contact

Characteristics of study participants by interpersonal contact are summarized in Table 2. Whereas, 28.9% of contacts made by males were in the highest quartile, only 23.9% of contacts made by females were in the highest quartile of interpersonal contacts. Among the 18–34 years age group, 31.4% of contacts were in the highest quartile, compared to 28.4 and 21.4% in the highest quartile among the 35–54 and ≥55 years age groups, respectively. Whereas, 23.0% of contacts made by essential workers were in the highest quartile, only 15.2% of contacts made by non-essential workers were in the highest quartile of interpersonal contacts distribution.

Participant characteristics by vaccine hesitancy

The characteristics of study participants by vaccine hesitancy are presented in Table 3. Among individuals with the least interpersonal contacts, only 17.1% were vaccine hesitant compared to 40.3% among those with the highest interpersonal contact. Whereas, 32.2% of males were vaccine hesitant, only 18.6% of females were deemed vaccine hesitant. Also, 36.5% of essential workers were vaccine hesitant compared to 20.1% of non-essential workers. Vaccine hesitancy was identified in 29.6% of Whites, 13.2% of Chinese, and 11.3% of South Asians. Individuals in large households (≥ 6 household members) were more likely to report vaccine hesitancy, compared to those in smaller households. Also, people in the most privileged quintiles (Q1) of both material and social deprivation indices were more willing to receive the COVID-19 vaccine (67.3 and 65.8 %, respectively) compared to those in the least privileged (correspondingly 53.8 and 58.5%).

Association between interpersonal contact and vaccine hesitancy

Results from the multivariable multinomial logistic regression model assessing the association between interpersonal contact and vaccine hesitancy are shown in Table 4. In the model, we found a dose-response association between interpersonal contact and vaccine hesitancy; compared to individuals in the lowest quartile (least contact), those in the fourth quartile (reporting the highest number of contacts), third quartile and second quartile were more likely to be vaccine hesitant, adjusted odd ratios (aORs) 2.85 (95% CI: 2.02, 4.00), 1.91 (95% CI: 1.38, 2.64) and 1.78 (95% CI: 1.13, 2.82). In the sensitivity analysis where the outcome variable (willingness to vaccinate) included individuals who had already received

TABLE 3 Characteristics of study participants by vaccine hesitancy (unweighted, $N = 4,515$), March 8, 2021-December 6, 2021.

	Willing to get vaccine		Unwilling to get vaccine (hesitant)		Undecided	
	Weighted,	*N* % (95% CI)	Weighted,	*N* % (95% CI)	Weighted,	*N* % (95% CI)
Interpersonal contact						
Q1 (lowest)	1,524	67.7 (63.8, 71.6)	385	17.1 (14.1, 20.0)	344	15.3 (12.1, 18.4)
Q2	406	57.2 (50.3, 64.1)	182	25.6 (19.1, 32.1)	122	17.2 (11.8, 22.6)
Q3	665	53.2 (48.3, 58.1)	367	29.4 (24.9, 33.8)	218	17.4 (13.5, 21.3)
Q4 (highest)	677	43.4 (38.9, 47.9)	628	40.3 (35.9, 44.6)	255	16.3 (12.6, 20.1)
Sex						
Male	1,798	50.1 (46.4, 53.7)	1,155	32.2 (28.9, 35.4)	637	17.7 (14.9, 20.6)
Female	1,475	67.6 (65.3, 69.8)	406	18.6 (16.8, 20.5)	301	13.8 (12.1, 15.5)
Age						
18–34	984	56.9 (51.7, 62.2)	389	22.5 (18.1, 26.9)	356	20.6 (16.2, 25.0)
35–54	1,180	54.6 (50.6, 58.6)	646	29.9 (26.2, 33.5)	335	15.5 (12.8, 18.3)
55+	1,109	58.9 (55.6, 62.2)	527	28.0 (25.1, 30.9)	248	13.1 (10.3, 16.0)
Ethnicity						
Chinese	302	76.9 (65.2, 88.7)	52	13.2 (3.3, 23.2)	39	9.8 (1.9, 17.8)
Not a visible minority (White)	1,960	56.9 (54.3, 59.5)	1,021	29.6 (27.2, 32.1)	463	13.4 (11.6, 15.3)
South Asian	387	66.1 (54.3, 77.9)	66	11.3 (3.0, 19.6)	132	22.6 (12.4, 32.8)
Other ethnicities	469	49.1 (43.1, 55.1)	283	29.6 (24.2, 35.0)	203	21.3 (16.0, 26.5)
Missing/Unknown	155	39.2 (30.3, 48.1)	139	35.2 (26.7, 43.6)	102	25.7 (17.6, 33.7)
Educational attainment						
Below high school	91	50.5 (36.3, 64.8)	53	29.6 (17.0, 42.2)	36	19.9 (6.6, 33.2)
Below bachelor	1,140	52.6 (48.6, 56.6)	604	27.9 (24.4, 31.3)	422	19.5 (16.0, 23.0)
University degree	1,203	70.8 (66.4, 75.1)	333	19.6 (15.7, 23.4)	165	9.7 (6.9, 12.4)
Missing/Unknown	838	48.6 (44.2, 52.9)	571	33.1 (29.1, 37.1)	316	18.3 (14.9, 21.7)
Employment status						
Employed full-time (30 h or more/week)	964	56.5 (51.5, 61.4)	454	26.6 (22.2, 31.0)	289	16.9 (12.9, 21.0)
Employed part-time (<30 h/week)	265	67.6 (57.9, 77.3)	53	13.5 (7.1, 20.0)	74	18.9 (10.4, 27.4)
Self-employed	245	53.7 (44.6, 62.8)	153	33.6 (25.6, 41.5)	58	12.7 (7.1, 18.4)
Unemployed but looking for a job	123	59.5 (47.5, 71.5)	51	24.7 (15.1, 34.3)	33	15.7 (5.8, 25.7)
Unemployed and not looking for a job	54	60.9 (43.2, 78.6)	28	31.8 (15.7, 47.9)	6	7.3 (0.0, 15.7)
Full-time parent, homemaker	57	44.7 (33.1, 56.4)	36	28.1 (15.9, 40.3)	35	27.2 (16.3, 38.1)
Retired	553	69.9 (64.7, 75.1)	153	19.4 (15.2, 23.6)	85	10.7 (6.4, 15.0)
Student/Pupil	119	75.1 (59.9, 90.4)	19	11.8 (0.0, 24.4)	21	13.1 (2.5, 23.7)
Long-term sick or disabled	85	58.4 (45.2, 71.6)	34	23.7 (12.5, 34.9)	26	17.9 (8.3, 27.4)
Prefer not to answer	61	37.6 (19.9, 55.4)	71	43.5 (25.7, 61.2)	31	18.9 (5.9, 31.8)
Missing/Unknown	747	48.6 (44.1, 53.1)	508	33.1 (29.0, 37.2)	281	18.3 (14.8, 21.8)
Occupation						
Essential workers	601	44.8 (39.5, 50.0)	490	36.5 (31.3, 41.7)	251	18.7 (14.5, 23.0)
Non-essential workers	930	69.5 (64.7, 74.3)	269	20.1 (16.1, 24.1)	139	10.4 (6.8, 14.0)

(Continued)

TABLE 3 (Continued)

	Willing to get vaccine		Unwilling to get vaccine (hesitant)		Undecided	
	Weighted,	*N* % (95% CI)	Weighted,	*N* % (95% CI)	Weighted,	*N* % (95% CI)
Do not work	626	71.1 (65.9, 76.4)	132	15.1 (11.8, 18.3)	122	13.8 (9.1, 18.6)
Others	297	64.0 (55.0, 73.0)	76	16.3 (10.9, 21.6)	92	19.7 (11.4, 28.0)
Prefer not to answer	71	33.7 (21.6, 45.9)	87	40.9 (27.0, 54.8)	54	25.4 (13.9, 36.8)
Missing/Unknown	747	48.6 (44.1, 53.1)	508	33.1 (29.0, 37.2)	281	18.3 (14.58, 21.8)
Household size						
1	473	55.7 (50.2, 61.3)	234	27.5 (22.8, 32.3)	142	16.7 (11.9, 21.6)
2	1,351	64.6 (61.3, 68.0)	472	22.6 (19.8, 25.3)	268	12.8 (10.1, 15.5)
3	463	52.4 (45.6, 59.3)	258	29.3 (23.3, 35.3)	161	18.3 (12.2, 24.3)
4	513	57.8 (51.5, 64.1)	208	23.5 (18.4, 28.5)	166	18.7 (13.8, 23.7)
5	198	59.6 (48.5, 70.6)	69	20.7 (12.9, 28.6)	66	19.7 (10.9, 28.5)
6+	262	39.5 (30.7, 48.2)	276	41.7 (33.0, 50.4)	125	18.9 (12.5, 25.2)
Prefer not to answer	13	19.6 (0.0, 45.1)	44	65.0 (36.2, 93.7)	10	15.4 (0.0, 32.5)
Health region						
Interior	415	47.3 (41.8, 52.8)	315	35.9 (30.5, 41.3)	147	16.8 (12.3, 21.3)
Fraser	945	62.6 (56.7, 68.4)	283	18.7 (14.2, 23.3)	282	18.7 (13.7, 23.6)
Vancouver Coastal	536	64.8 (59.1, 70.4)	217	26.3 (21.0, 31.5)	74	9.0 (5.7, 12.2)
Vancouver Island	475	70.5 (65.3, 75.7)	126	18.7 (14.3, 23.1)	73	10.8 (7.0, 14.6)
Northern	92	33.5 (24.0, 43.0)	116	42.1 (32.0, 52.3)	67	24.4 (16.2, 32.6)
Missing/Unknown	811	50.3 (46.0, 54.7)	505	31.3 (27.4, 35.2)	295	18.3 (14.9, 21.8)
Material deprivation						
Q1 (Privileged)	437	67.3 (61.4, 73.2)	141	21.7 (16.5, 26.9)	71	11.0 (6.9, 15.2)
Q2	425	56.7 (50.0, 63.4)	180	24.1 (18.2, 30.0)	144	19.2 (13.9, 24.5)
Q3	473	65.4 (59.1, 71.6)	177	24.4 (19.3, 29.6)	74	10.2 (5.2, 15.2)
Q4	380	56.7 (49.6, 63.8)	189	28.3 (21.9, 34.6)	101	15.0 (9.5, 20.5)
Q5 (Deprived)	417	53.8 (45.4, 62.2)	208	26.9 (19.5, 34.3)	150	19.4 (12.7, 26.0)
Missing/Unknown	1,141	51.7 (47.9, 55.5)	666	30.2 (26.9, 33.5)	399	18.1 (15.0, 21.2)
Social deprivation						
1 (Privileged)	420	65.8 (57.7, 73.9)	111	17.4 (11.7, 23.1)	107	16.8 (9.7, 23.9)
2	321	59.0 (50.8, 67.2)	153	28.2 (20.6, 35.8)	70	12.8 (7.3, 18.3)
3	488	59.1 (52.5, 65.7)	218	26.4 (20.8, 32.0)	119	14.5 (9.2, 19.7)
4	406	57.2 (49.8, 64.6)	192	27.1 (20.1, 34.2)	111	15.7 (10.0, 21.3)
5 (Deprived)	497	58.5 (53.0, 64.0)	220	25.9 (21.1, 30.8)	132	15.6 (11.7, 19.5)
Missing/Unknown	1,141	51.7 (47.9, 55.5)	666	30.2 (26.9, 33.5)	399	18.1 (15.0, 21.2)

the vaccine, we also found that compared to individuals in the lowest quartile (least contact), those in the fourth quartile (highest contact) were more likely to be vaccine hesitant, aOR =1.65 (95% CI: 1.26, 2.16) (Supplementary Table 3 of the Supplementary File).

Discussion

To our knowledge, this is the first study to investigate the association between vaccine hesitancy and interpersonal contacts, a major risk factor for COVID-19 transmission. Overall, we found that 56.7% of our study population was willing to receive COVID-19 vaccines. This compares to the 79.8% vaccine acceptance reported in a study (16) conducted in the same province (BC), almost a year prior to our study. Although differences in the time periods in which the two studies were conducted could account for the variability in these rates, some of differences may be related to the differences in sample characteristics. Specifically, whereas our study drew a sample of BC residents from social media, the previous study sampled from research cohorts who had consented to be contacted for future research and therefore participants in that study would be more likely to be health conscious and thus less likely to

TABLE 4 Multivariable multinomial logistic regression model for association between interpersonal contact and vaccine hesitancy, March 8, 2021-December 6, 2021.

		Undecided	Unwilling to get vaccine
		Adjusted OR (95% CI)	Adjusted OR (95% CI)
Interpersonal contact			
	Q1	Reference	Reference
	Q2	1.41 (0.88, 2.25)	**1.78 (1.13, 2.82)**
	Q3	1.38 (0.94, 2.03)	**1.91 (1.38, 2.64)**
	Q4	1.28 (0.80, 2.04)	**2.85 (2.02, 4.00)**
Sex			
	Male	Reference	Reference
	Female	**0.63 (0.48, 0.83)**	**0.49 (0.40, 0.61)**
Age			
	18–34	Reference	Reference
	35–54	0.87 (0.59, 1.29)	**1.47 (1.04, 2.08)**
	55+	0.81 (0.53, 1.25)	**1.75 (1.24, 2.48)**
Ethnicity			
	Not a visible minority (White)	Reference	Reference
	Chinese	0.77 (0.31, 1.96)	0.48 (0.20, 1.13)
	South Asian	1.44 (0.73, 2.84)	**0.41 (0.20, 0.86)**
	Other	**1.72 (1.15, 2.55)**	1.22 (0.87, 1.71)
	Missing/Unknown	**2.40 (1.37, 4.19)**	1.38 (0.82, 2.34)
Educational attainment			
	Below high school	Reference	Reference
	Below bachelor	1.06 (0.41, 2.73)	0.74 (0.37, 1.50)
	University degree	0.43 (0.16, 1.14)	**0.46 (0.22, 0.96)**
	Missing/Unknown	0.61 (0.17, 2.12)	0.56 (0.19, 1.70)
Occupation			
	Essential workers	Reference	Reference
	Non-essential workers	**0.53 (0.32, 0.89)**	**0.52 (0.35, 0.75)**
	Do not work	**0.56 (0.33, 0.95)**	**0.33 (0.22, 0.49)**
	Other occupations	0.84 (0.45, 1.54)	**0.36 (0.22, 0.60)**
	Prefer not to answer	1.82 (0.82, 4.07)	1.48 (0.74, 2.94)
	Missing/Unknown	1.07 (0.37, 3.10)	0.62 (0.24, 1.65)
Household size			
	1	Reference	Reference
	2	**0.57 (0.36, 0.88)**	**0.63 (0.46, 0.87)**
	3	0.90 (0.52, 1.56)	1.05 (0.67, 1.64)
	4	0.80 (0.47, 1.36)	0.78 (0.51, 1.19)
	5	0.68 (0.32, 1.47)	0.58 (0.31, 1.06)
	6+	1.04 (0.55, 1.99)	**1.74 (1.06, 2.84)**
	Prefer not to answer	0.88 (0.10, 7.72)	5.74 (0.86, 38.59)
Health region			
	Interior	Reference	Reference
	Fraser	0.87 (0.54, 1.39)	**0.47 (0.31, 0.70)**
	Vancouver Coastal	**0.47 (0.28, 0.79)**	0.77 (0.52, 1.14)
	Vancouver Island	**0.45 (0.27, 0.73)**	**0.39 (0.26, 0.58)**
	Northern	1.96 (1.00, 3.84)	1.43 (0.80, 2.57)
	Missing/Unknown	0.90 (0.53, 1.53)	0.83 (0.54, 1.27)

"Willing to get vaccine" was the reference group in the multinomial logistic regression model. In bold are results whose confidence intervals do not include 1.

be vaccine hesitant. Also, because we surveyed at a time when a larger proportion of the population had already received vaccines, the sample population remaining to receive the vaccine was more likely to be composed of people with anti-vaccination sentiments. In our sensitivity analyses, where individuals who had received the vaccine were included with those who indicated they were willing to be vaccinated, vaccine acceptance was 86.5%, slightly higher than the previous study (16).

We found that individuals with high interpersonal contact were more likely to be vaccine hesitant compared to those with low contacts. Specifically, we found a dose-response association between interpersonal contact and vaccine hesitancy; compared to individuals in the lowest quartile (least contact), those in the fourth quartile (i.e., those with the highest contact), third quartile and second quartile groups had 185, 91, and 78% increased odds of vaccine hesitancy, respectively. Consistently, in the sensitivity analyses where individuals who had already received were assumed to be willing to receive the vaccine, we also found that, compared to individuals in the lowest quartile, those in the fourth quartile of interpersonal contact had a 65% increased odds of vaccine hesitancy. These findings are concerning, given that COVID-19 transmission is driven by interpersonal contact. Therefore, vaccine hesitancy among people who are more likely to transmit the virus due to their high levels of interpersonal contacts, presents a major threat to the expected gains from current and future vaccination efforts.

The gendered patterns of vaccine hesitancy from the COVID-19 literature were also reflected in our study. Contrary to other findings (16, 27, 28) our investigation showed that the likelihood of getting a COVID-19 vaccine was higher among females than males. This discrepancy may be due to differences in the type of sample [as discussed previously in regard to (16)], and time frame [responses in the study by (27) were collected before vaccines were widely available in the U.S.]. Nonetheless, more research with population-based samples is required to elucidate this matter.

Another concerning finding was that individuals who lived in larger households (six or more people in household) were more likely to be vaccine hesitant. This is alarming given individuals in larger households are more likely to be in cramped spaces with limited ability to properly distance from one another.

Racial and ethnic disparities in vaccination have been highlighted in many studies (17). Paul et al. (29) report that individuals with ethnic minority backgrounds have higher distrustful attitudes toward vaccination. These attitudes, which may be fueled by anti-intellectualism and misinformation and lack of appropriate information in accessible language and formats (30), could lead to lower perceived risk of COVID-19 infection and severity of illness. Ongoing racism, historical contexts related to racism, such as unethical research trials on Black and Indigenous Peoples (31–33) may lead to skepticism, distrust and lower perceived benefits of COVID-19 vaccination among these populations. Vaccine hesitancy among ethnic and racial minorities is concerning given the disproportionate burden of COVID-19 outcomes among these groups (34, 35). Studies, particularly in the U.S and UK, have reported lower vaccine acceptance in racial minority populations (35–39). However, we found that whereas 29.6% of Whites reported vaccine hesitancy, 13.2% of Chinese and 11.3% of South Asians were vaccine hesitant in our analysis. These findings are consistent with a Canadian national survey where vaccine hesitancy was lower among South Asian and Chinese population compared to the White population, although higher among Black population (40). These findings reflect the heterogeneity and diverse experiences of minority groups across the world. The disproportionately higher burden of COVID-19 among racialized or minority groups in Canada particularly prior to vaccine availability (41) potentially highlighted the importance of vaccines in preventing further infections to members of this group; potentially making people more willing to accept vaccines. However, the higher burden of COVID-19 among South Asians population in UK did not affect vaccine hesitancy, highlighting differences in underlying beliefs, perceptions, and trust in the healthcare system. In addition, it has been largely recognized that vaccine hesitancy among minority groups, especially the Black community in the U.S, is fuelled by the deep-rooted and long-standing mistrust in the healthcare system and the government, driven by historical events in medical care and research (42, 43). However, the role of trust in the healthcare system and government in shaping vaccine acceptance among various groups is not very clear. Further investigations are needed to understand the differences in vaccine hesitancy and drivers of vaccine hesitancy among various ethnic groups in Canada.

It was expected that individuals considered as essential workers would be less vaccine hesitant. These are individuals in occupations deemed essential to not only the pandemic response but also maintaining essential services. Essential work includes occupations in the health sector (e.g., medical, social work, psychology), natural resources, agriculture and related production occupations, manufacturing and utilities, sales and service occupations, trades, transport and equipment operators and related occupations. In BC, these groups were prioritized in the roll-out of COVID-19 vaccination. We found that individuals in these occupations had higher odds of vaccine hesitancy and reported greater interpersonal contacts compared to those in non-essential work. Similar findings were uncovered by Ogilvie et al. where essential non-healthcare workers were found to have lower adjusted odds of intending to receive COVID-19 vaccine (16). A disconcerting facet to this is the heightened risk among this population, due to their unavoidably high contact rates with the public.

Implication

Whereas, these are important findings which can inform strategic vaccine-acceptance messaging, it is expected that more routine systems are built to monitor vaccine hesitancy, to inform education and communication needs related to the pandemic control. The findings of this study can be used to inform public health interventions aimed at improving vaccine uptake.

Tackling misinformation about vaccination will be critical to reducing the morbidity and mortality of the disease. COVID-19 vaccine hesitancy has been associated with mistrust of vaccine benefit (29), safety concerns over vaccine development, and side effects (15). Unwillingness to receive the vaccine is also driven by misinformation or distrust of government and healthcare systems (44–47). Therefore, health communication strategies aimed at building trust between at-risk communities may be needed to address this issue (34). To make COVID-19 vaccination communication more effective, we can create targeted approaches to change behaviors and promote vaccination among vaccine hesitant individuals.

Motivational interviewing, which aims to support decision making by eliciting and strengthening a person's motivation to change their behavior based on their own arguments for change has been shown to be effective in increasing vaccine uptake (48). Additionally, medical reminders (49) and provider recommendations (48) are also effective strategies in promoting vaccinations. Among communities of color, where issues of misinformation and mistrust of the medical system appear to be a significant factor for vaccine hesitancy, a multipronged approach based on partnerships with trusted community resources such as faith-based leaders, community organizers, and community mentors can be a helpful tool in tackling low rates of vaccine uptake in these communities (50). Furthermore, it has been noted that the misinformation that drive vaccine hesitancy attitudes are propagated *via* social media (11). These same platforms could be used for such targeted campaigns, given their effective knowledge dissemination potential.

Findings from this investigation can also be useful to optimize predictive transmission models by including the impact of vaccine hesitancy on transmission risk.

Limitations and strengths

Like all surveys, our findings are subject to social desirability bias. Although our online-based study minimizes the role of social desirability bias, it cannot be ruled out entirely as exerting some influence. In addition, although vaccine willingness or hesitancy has been highly volatile and changing depending on evolving information, our survey only captured respondent's attitudes at one period in time (March 2021 to December 2021). Further studies should examine changing trends of vaccine hesitancy. Despite these limitations, a major novelty to this study is our ability to account for each individual's contact behaviors. Furthermore, our study investigated the characteristics and factors associated with vaccine hesitancy among people who remain unvaccinated in the province, as this population may differ from the population who were ready to receive the vaccine as soon as it became available to them. Future vaccination strategies may need to be staggered, to target different aspects related to vaccination acceptance among hesitant subgroups.

Conclusion

Despite public campaigns urging people to get vaccinated, vaccine hesitancy remains a challenge in pandemic response. We found vaccine hesitancy to be greater among individuals with higher interpersonal contacts, suggesting the need for targeted interventions to increase vaccine acceptance among this population.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by University of British Columbia Behavioral Research Ethics Board (No: H20-01785). The patients/participants provided their written informed consent to participate in this study.

Author contributions

NJ and PA conceptualized the study. All authors reviewed and agreed on the final submission.

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Conflict of interest

Author NJ has advised and spoken for AbbVie, not related to this project or COVID-19.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.971333/full#supplementary-material

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COVID-19 vaccine acceptance and hesitancy in patients with Parkinson's disease

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Background: As coronavirus disease 2019 (COVID-19) vaccination campaign underway, little is known about the vaccination coverage and the underlying barriers of the vaccination campaign in patients with Parkinson's disease (PD).

Objective: To investigate the vaccination status and reasons for COVID-19 vaccine acceptance and hesitancy among PD patients.

Methods: In concordance with the CHERRIES guideline, a web-based, single-center survey was promoted to patients with PD *via* an online platform from April 2022 and May 2022. Logistic regression models were used to identify factors related to COVID-19 vaccine hesitancy.

Results: A total of 187 PD cases participated in this online survey (response rate of 23%). COVID-19 vaccination rate was 54.0%. Most participants had a fear of COVID-19 (77.5%) and trusted the efficacy (82.9%) and safety (66.8%) of COVID-19 vaccine. Trust in government (70.3%) and concerns about the impact of vaccine on their disease (67.4%) were the most common reasons for COVID-19 vaccine acceptance and hesitancy, respectively. COVID-19 vaccine hesitancy was independently associated with the history of flu vaccination (OR: 0.09, $p < 0.05$), trust in vaccine efficacy (OR: 0.15, $p < 0.01$), male gender (OR: 0.47, $p < 0.05$), disease duration of PD (OR: 1.08, $p < 0.05$), and geographic factor (living in Shanghai or not) (OR: 2.87, $p < 0.01$).

Conclusions: The COVID-19 vaccination rate remained low in PD patients, however, most individuals understood benefits of vaccination. COVID-19 vaccine hesitancy was affected by multiple factors such as geographic factor, history of flu vaccination, disease duration and trust in efficacy of vaccine. These findings could help government and public health authorities to overcome the barrier to COVID-19 vaccination and improve vaccine roll-out in PD patients.

KEYWORDS

COVID-19, vaccination, vaccine hesitancy, Parkinson's disease, SARS-CoV-2

Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). As of June 2, 2022, there have been over 500 million confirmed cases of COVID-19 and 6.3 million deaths worldwide (https://covid19.who.int/). Emerging evidence has demonstrated that the elderly population is particularly vulnerable to SARS-CoV-2 infection (1). It has been shown that the risk for hospitalization, intensive care unit (ICU) and death due to COVID-19 continuously increases with age among people older than 40 years (2–4).

Parkinson's disease (PD) is now one of the fastest growing neurological diseases affecting ~6.1 million individuals worldwide in 2016 (5). The overwhelming majority of patients with PD are aged over 60 years. According to a recent nationwide report, the prevalence of PD in China was 1.37% in people older than 60 years, corresponding to a total estimated number of 3.6 million PD cases (6). The current COVID-19 pandemic has raised extensive concerns among neurologists, some of whom have warned that the world healthcare systems should be ready for the third wave of parkinsonism as influenza has long been considered as a potential driver in PD pathogenesis (7, 8). It has been suggested that influenza (e.g., the Spanish Flu) is associated with an increased risk of PD (9, 10). In addition, the COVID-19 mortality rate is found to be higher in PD patients as compared to the general elderly population (11, 12). Moreover, patients with PD are more likely to experience worsening motor and non-motor symptoms in the setting of SARS-CoV-2 infection (13). Consistent with clinical observations, basic research also provided intriguing insights into the association between COVID-19 and PD pathogenesis (14–16). The α-synuclein (α-syn) aggregation is the most critical driver in PD development. Recent vitro studies reported that SARS-CoV-2 protein can directly interact with α-syn and accelerate the formation of α-syn aggregation (14, 16). The short- and long-term impact of COVID-19 on PD was demonstrated in rodent models, in which the neuronal loss and microglia activation was more severe in PD mice infected and recovered from SARS-CoV-2 infection (15). In order to protect PD patients from COVID-19, the International Parkinson's and Movement Disorder Society (IPMDS) strongly recommends COVID-19 vaccination for PD patients unless they have a specific contraindication (17).

With COVID-19 vaccine roll-out underway, the vaccination coverage in China has reached 91.22% nationwide and 86.23% in people over 60 years of age. However, little is known about the COVID-19 vaccination status among patients with PD in China. Given the low flu vaccination willingness reported in PD patients, it is reasonable to assume that there may exist a barrier that prohibits patients from accepting and receiving the COVID-19 vaccine (18). In addition, several case studies has observed the occurrence of functional psychogenic-neurological disorders (FNDs) in healthy recipients and worsening motor symptoms in PD patients following COVID-19 vaccination, which may further create a negative impression on COVID-19 vaccine among the public (19, 20).

Widespread public acceptance and population coverage are foundations for the success of COVID-19 vaccination campaign. It is worth mentioning that though the Chinese government has encouraged the elderly to receive vaccination for a year, the vaccination coverage rate in people older than 60 years remain relatively low in Shanghai (21). The present study aimed to investigate the COVID-19 vaccination status, reasons for vaccine acceptance/hesitancy and factors related to vaccine hesitancy in PD patients. To explore whether PD patients in Shanghai was similarly at risk of vaccine hesitant compared to those living in other cities and the reasons underlying Shanghai's low vaccination willingness, participants was divided into patients in Shanghai and those in other cities. This study may help public health agencies develop strategies to improve vaccination coverage and protect patients' health.

Methods

Survey design and study participants

A cross-sectional, web-based online survey was conducted according to the CHERRIES guideline between April 25, 2022 and May 2, 2022. To guarantee honest feedback, a self-reported, anonymous questionnaire entitled "COVID-19 vaccines and Parkinson's disease" was developed and distributed *via* the domestic largest social platform (Wechat, Tencent Co., Ltd., Shenzhen, China). Briefly, the questionnaire was randomly promoted to 813 patients with regular follow-up at the Movement Disorder Clinic of Ruijin Hospital (Shanghai Jiao Tong University School of Medicine, Shanghai, China) and fulfilled the UK Brain Bank criteria. Patients were all informed the purpose of study and were asked to voluntarily answer the questionnaire at their convenience. Participants could review and change their answers before clicking the submit button. A total of 188 patients submitted the questionnaire by the end of study. One respondent was excluded due to the incompleteness of the submitted questionnaire. Therefore, the response rate was 23% (187/813). Each respondent was confirmed to be a unique individual by their IP addresses and telephone numbers. The study was approved by the institutional review board of Ruijin Hospital. Online informed consent was obtained from all participants.

Data collection

The content of the questionnaire included: (1) socio-demographic and clinical data; (2) history of COVID-19;

(3) history of COVID-19 vaccination and flu vaccination; (4) attitudes toward COVID-19 and COVID-19 vaccines; (5) reasons for COVID-19 vaccines acceptance and hesitancy. Sections of 2-5 were queried through multiple-choice. To assess the attitudes toward COVID-19 (Table 2), participants were asked the following questions: "Are you afraid if you/your family get SARS-CoV-2 infection?" and "Do you agree that asymptomatic COVID-19 individuals cannot infect others?" Correct attitude was defined as "a little or very" and "disagree", respectively. Participants were further asked "Do you wear a mask/avoid taking public transport/ avoid going out/maintain social distance from people?". Correct attitude was defined as "yes". The following questions were presented to assess the attitudes toward COVID-19 vaccines: "Do you agree that COVID-19 vaccine is important for health?" and "Do you agree that COVID-19 vaccine is safe?" and the right attitude was defined as "agree".

Since the nucleic acid amplification test is more readily accessible than antigen test in China, the diagnosis of COVID-19 was confirmed based on positive nucleic acid amplification test results. Additionally, sticking with the "dynamic zero" policy, residents in China are asked to take PCR test every 2–3 days. Therefore, a positive PCR result is available in most of the cases. In this study, symptomatic patients with negative laboratory results were not defined as SARS-CoV-2 infection. Patients who had already received or planned to receive COVID-19 vaccination were classified as the vaccine acceptance group. Patients who were reluctant or refused to receive the COVID-19 vaccination despite the availability of vaccination services were defined as vaccine hesitancy group. Their reasons for vaccine acceptance and hesitancy were shown in the Tables 3, 4.

Statistical analysis

Statistical analyses were performed on SPSS version 28.0 (SPSS, Chicago, IL, USA). The chi-square test and Fisher's exact test were used to compare categorical variables and the Student's *t*-test were used for continuous variables. Univariate logistic regression analyses were used to explore potential factors associated with vaccine hesitancy, in addition, variables with $p < 0.05$ were further entered into a multivariate analysis. A two-tailed $p < 0.05$ was defined as statistically significant.

Results

Study participants

Of the 187 participants, 46.0% (86/187) lived in Shanghai (SH-PD group) and 54.0% (101/187) lived in other cities (non-SH-PD group). Socio-demographic and clinical characteristics are listed in Table 1. The mean age was 64.2 years (SD 9.2) in total cohort with a gender ratio (male/female) of 1.79. Co-existing psychiatric issues were reported by five participants. Two participants claimed that they had concurrent depression and two had anxiety disorders. None of these cases was clinically confirmed in the study period. Compared with the non-SH-PD group, the SH-PD group was older in age ($p < 0.0001$) and had a higher education level ($p < 0.01$). No differences were found in gender ratio, PD duration, comorbidity, or cohabitation status between the two groups.

History of COVID-19

Among the participants, four patients (2.1%, 4/187) had a history of SARS-CoV-2 infection, including three in the SH-PD group (3.5%, 3/86) and one in the non-SH-PD group (1.0%, 1/101). In addition, three patients (1.6%, 3/187) in the SH-PD group reported that their family members were victims of COVID-19. No statistical difference in SARS-CoV-2 infection rate was detected between the SH-PD and non-SH-PD groups (Table 2).

History of COVID-19 vaccination and flu vaccination

A total of 101 participants (54.0%, 101/187) had received COVID-19 vaccination and 23 patients (12.3%, 23/187) had received flu vaccination in the past 3 years. Regarding the COVID-19 vaccination regimen, 46.0% (86/187) had not been vaccinated yet, 3.2% (6/187) had been vaccinated once, 19.8% (37/187) had been vaccinated twice and 31.0% (58/187) had received a booster shot.

The COVID-19 vaccination rate and flu vaccination rate were markedly lower in the SH-PD group than that in the non-SH-PD group (38.4 vs. 67.3%, $p < 0.001$; 5.8 vs. 17.8%, $p = 0.01$, respectively). In addition, the percentage of patients who had received a booster COVID-19 vaccination was significantly lower in the SH-PD group (19.8 vs. 40.6%, $p < 0.01$) (Table 2; Figure 1).

Attitude toward COVID-19 and COVID-19 vaccine

The majority of participants feared SARS-CoV-2 infection in themselves (77.5%, 145/187) and in their families (82.4%, 154/187). During the current COVID-19 epidemic, over 90% of patients took the following measures to minimize their risk of infection: wearing a mask (97.3%, 182/187), avoiding public transport (90.9%, 170/187), avoiding going out (97.3%, 182/187), and maintaining social distance from people (95.2%, 178/187).

TABLE 1 Socio-demographic and clinical characteristics of patients with PD.

	Total cohort ($n = 187$)	SH-PD ($n = 86$)	Non-SH-PD ($n = 101$)	P-value
Age, years, mean (SD)	64.2 (9.6)	67.3 (7.2)	61.5 (10.5)	**<0.0001**
Gender ratio (M/F)	1.79	1.96	1.65	0.58
PD duration, *n* (%)				
≤5 years	7 (3.7)	1 (1.2)	6 (5.9)	0.38
5–10 years	52 (27.8)	23 (26.7)	29 (28.7)	
10–20 years	111 (59.3)	53 (61.6)	58 (57.4)	
20–30 years	13 (7.0)	6 (7.0)	7 (6.9)	
≥30 years	4 (2.1)	3 (3.5)	1 (1.0)	
Comorbidity, *n* (%)				
No	80 (42.8)	35 (40.7)	45 (44.6)	0.60
Hypertension/diabetes	50 (26.7)	27 (31.4)	23 (22.8)	0.18
Neurological/psychiatric disorders	17 (9.1)	10 (11.6)	7 (6.9)	0.31
Orthopedic disorders	13 (7.0)	7 (8.1)	6 (5.9)	0.58
Others	45 (24.1)	24 (27.9)	21 (20.8)	0.26
Not acquired	2 (1.1)	1 (1.2)	1 (1.0)	>0.99
Cohabitation status, *n* (%)				
Alone	7 (3.7)	3 (3.5)	4 (4.0)	0.46
With family members	176 (94.1)	81 (94.2)	95 (94.1)	0.60
Nursing home	4 (2.1)	2 (2.3)	2 (2.0)	0.34
Education attainment, *n* (%)				
High school or lower	97 (51.9)	34 (39.5)	63 (62.3)	**<0.01**
College or higher	88 (47.1)	50 (58.1)	38 (37.6)	
Not acquired	2 (1.1)	2 (2.3)	0 (0)	

The bold value indicates the p value <0.05.

Most patients could understand the health benefits of COVID-19 vaccination (82.9%, 155/187) and trusted the safety of the COVID-19 vaccine (66.8%, 125/187).

The percentage of patients who had no fear of SARS-CoV-2 infection in themselves or in their families was markedly higher in the SH-PD group ($p < 0.001$ and $p < 0.001$, respectively). Compared to the non-SH-PD group, the SH-PD group was less likely to trust the safety of COVID-19 vaccines, although the difference did not reach statistical significance (59.3 vs. 73.3%, $p = 0.12$) (Table 2).

Reasons for COVID-19 vaccine acceptance and hesitancy

Thirty-three SH-PD patients (38.4%, 33/86) and 68 non-SH-PD patients (67.3%, 68/101) were classified into the vaccine acceptance group. Fifty-three SH-PD participants (61.6%, 53/86) and 33 non-SH-PD participants (32.7%, 33/101) were classified into the vaccine hesitancy group. The COVID-19 vaccine acceptance rate was significantly higher in the non-SH-PD group ($p < 0.001$).

Reasons for COVID-19 vaccine acceptance and hesitancy are presented in Tables 3, 4. The most common reason for vaccine acceptance was trust in government (70.3%), followed by the intention to protect others (47.5%), trust in the safety of vaccine (38.6%), influence from others who had received the COVID-19 vaccination (30.7%), recommendations by specialists (25.7%), the intention to protect themselves (22.8%), and free of charge (15.8%). The most prevalent reason for COVID-19 vaccine hesitancy was concerns regarding the impact of vaccine on PD and/or other comorbidities, which was followed by suggestions from specialists (18.6%), inconvenience or difficulty in accessing the vaccination (15.1%), lack of trust in the safety of vaccine (11.6%) and old age (10.5%). The majority of patients with COVID-19 vaccine hesitancy stated that they would be willing to receive COVID-19 vaccination following recommendations by specialists (77.9%), the government (58.1%), and their family/friends (55.8%).

The types and prevalence of reasons for COVID-19 vaccine acceptance or hesitancy were similar between the SH-PD and non-SH-PD groups.

Factors associated with COVID-19 vaccine hesitancy

In the univariate analysis, COVID-19 vaccine hesitancy was significantly associated with the history of flu vaccination (OR: 0.10, 95% CI: 0.023–0.443, $p < 0.01$), trust in the efficacy of

TABLE 2 History and attitude of COVID-19 and COVID-19 vaccine.

	Total cohort ($n = 187$)	SH-PD ($n = 86$)	Non-SH-PD ($n = 101$)	P-value
A history of COVID-19, *n* (%)	4 (2.1)	3 (3.5)	1 (1.0)	0.34
Family member with a history of COVID-19, *n* (%)	3 (1.6)	3 (3.5)	0 (0)	0.10
Received flu vaccine in past 3 years, *n* (%)	23 (12.3)	5 (5.8)	18 (17.8)	**0.01**
Received COVID-19 vaccine, *n* (%)	101 (54.0)	33 (38.4)	68 (67.3)	**<0.001**
People around received COVID-19 vaccine, *n* (%)				
Yes	173 (92.5)	78 (90.7)	95 (94.1)	0.69
No	6 (3.2)	3 (3.5)	3 (3.0)	
Uncertain	8 (4.3)	5 (5.8)	3 (3.0)	
Attitude toward COVID-19 and vaccine				
1. **"Are you afraid if you get SARS-CoV-2 infection?", *n* (%)***				
No	42 (22.5)	7 (8.1)	35 (34.7)	**<0.001**
A little	109 (58.3)	59 (68.6)	50 (49.5)	
Very	36 (19.3)	20 (23.2)	16 (15.8)	
2. **"Are you afraid if your family get SARS-CoV-2 infection?", *n* (%)***				
No	33 (17.6)	6 (7.0)	27 (26.7)	**<0.001**
A little	105 (56.1)	51 (59.3)	54 (53.5)	
Very	49 (26.2)	29 (33.7)	20 (19.8)	
3. **"Do you agree that COVID-19 vaccine is important for health?", *n* (%)***				
Agree	155 (82.9)	71 (82.6)	84 (83.2)	0.94
Disagree	3 (1.6)	1 (1.2)	2 (2.0)	
Ucertain	29 (15.5)	14 (16.3)	15 (14.9)	
4. **"Do you agree that COVID-19 vaccine is safe?", *n* (%)***				
Agree	125 (66.8)	51 (59.3)	74 (73.3)	0.12
Disagree	8 (4.3)	5 (5.8)	3 (3.0)	
Uncertain	54 (28.9)	30 (34.9)	24 (23.8)	
5. **"Do you agree that asymptomatic COVID-19 individuals cannot infect others?", *n* (%)***				
Agree	7 (3.7)	3 (3.5)	4 (4.0)	0.67
Disagree	144 (77.0)	64 (74.4)	80 (79.2)	
Uncertain	36 (19.3)	19 (22.1)	17 (16.8)	
6. **"Do you wear a mask when you go out?", *n* (%)***				
Yes	182 (97.3)	84 (97.7)	98 (97.0)	0.51
No	3 (1.6)	2 (2.3)	1 (1.0)	
Unclear	2 (1.1)	0 (0)	2 (2.0)	
7. **"Do you try to avoid taking public transport when you go out?", *n* (%)***				
Yes	170 (90.9)	79 (91.9)	91 (90.1)	>0.99
No	1 (0.5)	0 (0)	1 (1.0)	
Unclear	16 (8.6)	7 (8.1)	9 (8.9)	
8. **"Do you try to avoid going out?", *n* (%)***				
Yes	182 (97.3)	85 (98.8)	97 (96.0)	0.08
No	1 (0.5)	1 (1.2)	0 (0)	
Unclear	4 (2.1)	0 (0)	4 (4.0)	
9. **"Do you try to keep social distance from people?", *n* (%)***				
Yes	178 (95.2)	84 (97.7)	94 (93.1)	0.27
No	3 (1.6)	0 (0)	3 (3.0)	
Unclear	6 (3.2)	2 (2.3)	4 (4.0)	

*All "you" referred to the PD patient in the questionnaire.
The bold value indicates the p value <0.05.

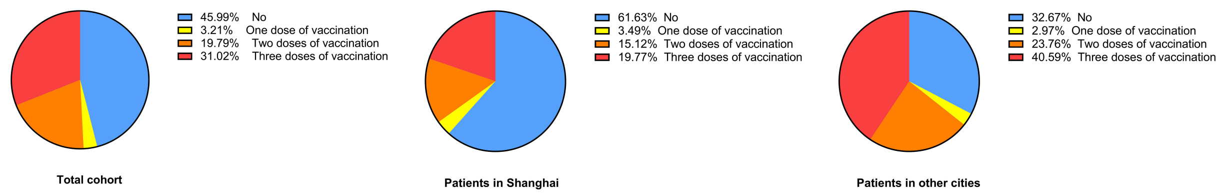

FIGURE 1
COVID-19 vaccination status in patients with PD. The COVID-19 vaccination status in patients with PD is shown with one dose of vaccination in yellow, two doses of vaccination in orange and three doses of vaccination in red. The percentage of patients without vaccination is presented in blue.

TABLE 3 Reasons for vaccine acceptance.

	Total (*n* = 86)	SH-PD (*n* = 53)	Non-SH-PD (*n* = 33)	*P*-value
Trust in the government, *n* (%)	71 (70.3)	19 (57.6)	52 (76.5)	0.06
Willingness for protecting others from COVID-19, *n* (%)	48 (47.5)	13 (39.4)	35 (51.5)	0.29
Trust in the safety of vaccine, *n* (%)	39 (38.6)	9 (27.3)	30 (44.1)	0.13
Willingness of people around to be vaccinated (%)	31 (30.7)	9 (27.3)	22 (32.4)	0.65
Specialist recommandation, *n* (%)	26 (25.7)	5 (15.2)	21 (30.9)	0.14
Willingness for self-protection from COVID-19, *n* (%)	23 (22.8)	11 (33.3)	12 (17.6)	0.13
The vaccine is free of charge, *n* (%)	16 (15.8)	4 (12.1)	12 (17.6)	0.57

TABLE 4 Reasons for vaccine hesitancy.

	Total (*n* = 101)	SH-PD (*n* = 33)	Non-SH-PD (*n* = 68)	*P*-value
Concern about PD and/or comorbidity, *n* (%)	58 (67.4)	38 (71.7)	20 (60.6)	0.35
Suggestions from specialists, *n* (%)	16 (18.6)	10 (18.9)	6 (18.2)	>0.99
Inconvenient accessibility of vaccination (time/distance), *n* (%)	13 (15.1)	10 (18.9)	3 (9.1)	0.35
Lack of trust in safety of vaccine, *n* (%)	10 (11.6)	7 (13.2)	3 (9.1)	0.73
Concern about old age, *n* (%)	9 (10.5)	6 (11.3)	3 (9.1)	>0.99
Suggestions from others other than specialists, *n* (%)	8 (9.3)	4 (7.5)	4 (12.1)	0.48
There is no risk of COVID-19, *n* (%)	7 (8.1)	4 (7.5)	3 (9.1)	>0.99
There is no serious consequence of COVID-19, *n* (%)	2 (2.3)	1 (1.9)	1 (3.0)	>0.99
Other reasons, *n* (%)	6 (7.0)	4 (7.5)	2 (6.1)	>0.99
Lack of trust in efficacy of vaccine, *n* (%)	1 (1.2)	1 (1.9)	0 (0)	>0.99
If the government recommends, are you willing to receive COVID-19 vaccine?				
Yes	50 (58.1)	30 (56.6)	20 (60.6)	0.91
No	15 (17.4)	9 (17.0)	6 (18.2)	
Uncertain	21 (24.4)	14 (26.4)	7 (21.2)	
If specialists recommend, are you willing to receive COVID-19 vaccine? *n* (%)				
Yes	67 (77.9)	42 (79.2)	25 (75.8)	0.93
No	9 (10.5)	5 (9.4)	4 (12.1)	
Uncertain	10 (11.6)	6 (11.3)	4 (12.1)	
If your family and friends recommend, are you willing to receive COVID-19 vaccine? *n* (%)				
Yes	48 (55.8)	27 (50.9)	21 (63.6)	0.50
No	20 (23.3)	13 (24.5)	7 (21.2)	
Uncertain	18 (20.9)	13 (24.5)	5 (15.2)	

TABLE 5 Factors associated with COVID-19 vaccine hesitancy.

	Univariable analysis		Multivariable analysis	
	OR (95%CI)	*P*-value	OR (95%CI)	*P*-value
Received flu vaccination in the past 3 years	0.10 (0.023–0.443)	**<0.01**	0.093 (0.015–0.581)	**0.01**
Trust in safety of vaccine	0.51 (0.267–0.961)	**0.04**	1.086 (0.456–2.584)	0.85
Trust in efficacy of vaccine	0.24 (0.097–0.617)	**<0.01**	0.15 (0.043–0.537)	**<0.01**
Fear of family members being infected with SARS-CoV-2	1.50 (0.668–3.384)	0.33	-	-
Fear of SARS-CoV-2 infection	1.86 (0.88–3.918)	0.10	-	-
Comorbidity	1.27 (0.694–2.319)	0.44	-	-
PD disease duration	1.11 (1.044–1.171)	**<0.001**	1.08 (1.014–1.157)	**0.02**
Age	1.06 (1.021–1.097)	**<0.01**	1.03 (0.989–1.077)	0.15
Gender (male)	0.48 (0.256–0.903)	**0.02**	0.47 (0.22–0.984)	**0.04**
Geographic factor (living in Shanghai)	3.72 (1.979–6.981)	**<0.001**	2.87 (1.369–6.021)	**<0.01**
Education attainment	0.70 (0.385–1.284)	0.25	-	-

The bold value indicates the p value <0.05.

vaccine (OR: 0.24, 95% CI: 0.097–0.617, $p < 0.01$), male gender (OR: 0.48, 95% CI: 0.256–0.903, $p < 0.05$), trust in the safety of vaccine (OR: 0.51, 95% CI: 0.267–0.961, $p < 0.05$), age (OR: 1.06, 95% CI: 1.021–1.097, $p < 0.01$), disease duration of PD (OR: 1.11, 95% CI: 1.044–1.171, $p < 0.001$), and grouping (SH-PD group) (OR: 3.72, 95% CI: 1.979–6.981, $p < 0.001$). The multivariable analyses indicated that vaccine hesitancy was independently associated with the history of flu vaccination (OR: 0.09, 95% CI: 0.015–0.581, $p < 0.05$), trust in vaccine's efficacy (OR: 0.15, 95% CI: 0.043–0.537, $p < 0.01$), male gender (OR: 0.47, 95% CI: 0.22–0.984, $p < 0.05$), disease duration (OR: 1.08, 95% CI: 1.014–1.157, $p < 0.05$) and grouping (SH-PD group) (OR: 2.87, 95% CI: 1.369–6.021, $p < 0.01$) (Table 5).

Discussion

The elderly population, especially those with underlying diseases, presents a high case-mortality rate and poor prognosis in the setting of COVID-19 (2–4). COVID-19 vaccination has proven to be safe and effective in preventing infection and reducing the risks of illness, hospitalization and death. Based on data from real-life and clinical trials, most of the approved COVID-19 vaccines are highly effective (>70%) in people older than 60 years of age. A complete schedule of COVID-19 vaccination has been shown to result in a higher magnitude of neutralizing antibodies and effectiveness than a single vaccination dose. Regarding the safety of COVID-19 vaccines, mild to moderate self-limiting side-effects (e.g., fever) have been documented in the elderly. The incidence of side-effects seems to be lower in older recipients, and severe adverse events are very rare (22–24). To protect older adults from COVID-19, the Chinese government has been devoted to facilitating COVID-19 vaccination coverage for months. According to the National Health Commission (NHC) of China, as of March 17, 2022, the proportion of people who received one dose of COVID-19 vaccination among individuals aged 60–69, 70–79, and over 80 years, was 88.8, 86.1, and 58.8% respectively; the proportion of people with complete course of basic immunization was 86.6, 81.7, and 50.7%, respectively, and the proportion of people with a booster vaccination was 56.4, 48.4, and 19.7%, respectively (http://www.nhc.gov.cn/). Our study indicated that the vaccination coverage was even lower in PD patients as compared to the general elderly population, with only 54.0% of PD cases receiving ≥1 dose of COVID-19 vaccination and 30.0% receiving a booster shot. Although vaccine hesitancy was identified in nearly half of the PD patients, most patients believed that the COVID-19 vaccines available in China were effective and safe. Most patients feared being infected with by SARS-CoV-2. Therefore, they complied with several recommended physical measures to reduce the risk of COVID-19. These findings suggests that most PD patients were fully aware of the dangers of COVID-19 and the importance of COVID-19 vaccination, but were hesitant to be vaccinated.

The two most prevalent reasons for COVID-19 vaccine hesitancy were concerns about the impact of vaccine on their disease and suggestions from specialists. In fact, the Technical Guideline for Vaccination Against SARS-CoV-2, published by the NHC of China, recommends COVID-19 vaccination for people older than 60 years and for patients with chronic diseases. This guideline further states that people with uncontrolled epilepsy and other serious nervous system diseases (such as transverse myelitis, Guillain Barre syndrome, and demyelinating diseases) are not recommended to receive the COVID-19 vaccination. This contradiction notion is ambiguous and, to some extent, leaves patients and even specialists uncertain about whether people with PD or other neurological comorbidities (e.g., stroke) should be vaccinated. In addition, there is a lack of clinical trials assessing the safety and efficacy of COVID-19 vaccines in elderly people with extreme old age, frailty and comorbidity (25–27). Based on sparse case reports, COVID-19 vaccine recipients may experience neurological symptoms classified as functional neurological disorders (19). Moreover, several case studies have reported worsening motor symptoms in PD patients and movement disorders non-PD patients following COVID-19 vaccination (20, 26–29). On the one hand, these observations indicate that side-effects of COVID-19 vaccines are not fully documented and highlight the need for post-injection surveillance and long-term monitoring among vaccine recipients. On the other hand, these reports, if not adequately interpreted, may raise public concerns about the current COVID-19 vaccination campaign and reduce their willingness to be vaccinated.

Taking the COVID-19 vaccination is in essence a trade-off between the benefits of the vaccine and the risks of its side-effects. The current COVID-19 vaccines have proven to be safe for healthy older adults, however, there is a lack of clinical data that specifically evaluates the safety of vaccines on persons with PD. A recent study by Solda et al. recruited 34 PD patients and found that most adverse events of COVID-19 vaccines were mild and, compared with the control group, the incidence of adverse events was significantly lower in the PD group (30). Deteriorated PD symptoms and new-onset movement disorders (e.g., tremor) in non-parkinsonism patients following COVID-19 vaccination have been highlighted in several case reports (26–29). Notably, the neurological side-effects described in these cases were transient and completely resolved with appropriate intervention. However, the mechanisms underlying post-vaccination neurological complications remains unclear. No causal relationship between COVID-19 vaccination and worsening PD symptoms could be established based on current evidence. Whether these side-effects are induced by functional brain network dysfunctions or are elicited by systemic inflammatory responses remains unknown. Taken together, COVID-19 vaccines appear to be safe and tolerable for patients with PD. More clinical data are clearly needed to clarify the safety of COVID-19 vaccines among PD patients in future investigations. Given that the elderly people and PD patients are particularly vulnerable to SARS-CoV-2 infection, the benefits of COVID-19 vaccination seem to outweigh its risks for people with PD (17).

In our study, most patients with vaccine hesitancy were willing to receive the COVID-19 vaccination if specialists, the government, and the people around them recommended it, further supporting the notion that PD patients who are strongly against vaccines compose a tiny minority and that most patients still hold a positive attitude toward COVID-19 vaccination. To build public faith in COVID-19 vaccination, it is necessary for our leading medical organizations, such as the Chinese Medical Doctor Association (CMDA), to release an expert consensus on COVID-19 Vaccination Guidelines for patients with PD and encourage more clinical trials of Chinese COVID-19 vaccines. We believe that PD patients would be more likely to receive the COVID-19 vaccination if they can receive consistent and comprehensive information from specialists, the government, and social media.

It has been reported that the COVID-19 vaccination coverage in general population aged older than 60 years in Shanghai was much lower as compared to the nationwide (62 vs. 86%) (21). Based on these data, we speculated that patients with PD in Shanghai may similarly be at risk of vaccine hesitant. By dividing the total cohort into patients in Shanghai and patients in other cities, our study indicated that the COVID-19 vaccination rate was lower in Shanghai as expected. The multivariate model also indicated that living in Shanghai was an independent risk factor of vaccine hesitancy. The reasons underlying Shanghai's low vaccination coverage are complicated due to its broader socioeconomic status, which involves income, education and international exchanges. According to our results, the percentage of patients who trusted the safety of the COVID-19 vaccines was lower in the SH-PD group, whereas the percentage of patients who were not afraid of SARS-CoV-2 infection was markedly higher in the SH-PD group. We speculated that it might be because Shanghai is an open and modern city with diverse viewpoint and plural information channels. People may misunderstand that the COVID-19 is just a mild flu by neglecting the fact that eased restrictions in Western countries are, at least in part, based on the high vaccination coverage. This situation may be more common in Shanghai since this city is the largest economic, commercial and financial center in China with close exchange with the West. Age is another possible reason for the low vaccination rate in Shanghai. As previously mentioned, the COVID-19 vaccination coverage in China decreases with age among people older than 60 years. In our univariate model, age was a risk factor for vaccine hesitancy. Based on the latest national population census, Shanghai has the second-highest proportion of the aging population across China. Therefore, residents in Shanghai may be more inclined to refuse COVID-19 vaccination because of their older age. To reinforce public confidence in COVID-19 vaccination, local authorities need to strengthen propaganda, correct misconceptions surrounding COVID-19 and vaccines, and highlight the significance of COVID-19 vaccination for individual and community wellbeing.

Factors associated with a decrease odd of COVID-19 vaccine hesitancy included the history of flu vaccination, trust in the efficacy of vaccine, shorter PD disease duration and male gender. Similarly to COVID-19, patients with PD are at an increased risk of hospitalization for influenza. Although vaccination for common respiratory pathogens is recommended for the elderly population, vaccine hesitancy was detected in around one third of patients with PD, suggesting that there might be a general vaccination barrier among individuals with PD (17). It has been reported that compared to men, women are less likely to accept vaccination, which may be attributable to their fear of potential side events (31).

The limitations of this study include small sample size and potential sampling bias by using an online survey. This study may also have selection bias as all participants were from a single center. More large-scale, multi-center studies will be clearly needed to validate the vaccination status among patients with PD in China. In addition, clinical characteristics of PD (e.g., H-Y stage) were not assessed by physicians at the time of the online enrollment. It will be of great value to study the relationship between the severity of PD and vaccine hesitancy as well as the impact of current COVID-19 pandemic on PD progress in our future work.

Despite these limitations, our study provided the first evidence that assessed the COVID-19 vaccination coverage in PD patients and analyzed their reasons for vaccine acceptance/hesitancy. Although the COVID-19 vaccination rate was low in patients with PD, most were convinced that vaccination was beneficial and safe. Based on the available data, the benefits of COVID-19 vaccination seem to outweigh the risks for PD patients. To overcome this barrier to COVID-19 vaccination, the government and healthcare authorities need to establish public confidence in vaccines and detailed COVID-19 vaccination guidelines. On the other hand, caution should be exercised regarding potential neurological side-effects after vaccination. More clinical trials and real-life studies will be helpful to determine the safety and efficacy of COVID-19 vaccines for the PD population, which will in turn build public faith in the current vaccination campaign.

Conclusion

Our data demonstrated that the COVID-19 vaccination coverage in patients with PD was even lower compared to the elderly population. Vaccine hesitancy was observed in around half of PD patients and interprovincial disparities in vaccine hesitation were identified. These issues will impede vaccine uptake and delay the herd immunity. In order to prevent the spread of COVID-19 and protect patients' health, great efforts are needed for health care system to enhance the public faith in vaccine and improve their willingness to vaccination.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Institutional Review Board of Ruijin Hospital. The patients/participants provided their written informed consent to participate in this study.

Author contributions

YW, DL, and CZ designed the study and recruited patients with PD. YZ and ZL drafted the manuscript. XW, JL, JD, and KR assisted in online survey. All authors contributed to the article and approved the submitted version.

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Conflict of interest

Author KR was employed by Gyenno Science Co., LTD.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Effectiveness of the Fiocruz recombinant ChadOx1-nCoV19 against variants of SARS-CoV-2 in the Municipality of Botucatu-SP

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Introduction: As the COVID-19 pandemic progresses, rapidly emerging variants of concern raise fears that currently licensed vaccines may have reduced effectiveness against these new strains. In the municipality of Botucatu, São Paulo State, Brazil, a mass vaccination campaign using ChadOx1-nCoV19 was initiated on 16th of May 2021, targeting people 18–60 years old. Two vaccine doses were offered 12 weeks apart, with the second delivered on 8th of August, 2021. This setting offered a unique opportunity to assess the effectiveness of two ChadOx1-nCoV19 doses in a real-life setting.

Materials and methods: Data on testing, hospitalization, symptoms, demographics, and vaccination were obtained from the Hospital das Clínicas da Faculdade de Medicina de Botucatu. A test-negative study design was employed; whereby the odds of being vaccinated among cases vs controls were calculated to estimate vaccine effectiveness (VE; 1-OR). All individuals aged 18–60 who received a PCR test after the 16th of May and were unvaccinated prior to this date were included in the analysis until the study ended in mid-November 2021.

Results: 77,683 citizens of Botucatu aged 18–60 received the first dose, and 74,051 received a second ChadOx1-nCoV19 dose 12 weeks later for a vaccination coverage of 84.2 and 80.2%, respectively. Of 7.958 eligible PCR tests, 2.109 were positive and 5.849 negative. The VE against any symptomatic infection was estimated at 39.2%, 21 days after dose 1, and 74.5%, 14 days after dose 2. There were no COVID-19-related hospitalizations or deaths among the 74,051 fully vaccinated individuals. The VE against severe disease was estimated at 70.8 and 100% after doses 1 and 2, respectively. 90.5% of all lineages sequenced between doses 1 and 2 (16th of May—7th of August) were of the Gamma variant, while 83.0% were of the Delta variant during the second period after dose 2 (8th of August—18th of November).

Discussion: This observational study found the effectiveness of ChadOx1-nCoV19 to be 74.5% against COVID-19 disease of any severity, comparable to the efficacy observed in clinical trials (81.3% after dose 2), despite the dominance of the Gamma and Delta VoCs. No COVID-19-related hospitalizations or deaths in fully vaccinated individuals were reported.

KEYWORDS

COVID-19, vaccines, ChadOx1, effectiveness, "real world" study, variants of concern

Introduction

In a recent study, the World Health Organization (WHO) estimated that between 13.3 and 16.6 million people worldwide had died in 2020–2021 because of the COVID-19 pandemic, more than 2.5 times the number of reported COVID-19 deaths (1). The excess death rate ranged from as high as 1.031/100 k population in Eastern Europe, to no excess in some smaller countries in various geographies. The excess rate in Brazil is estimated to be 357/100 k—similar to countries like the US or Italy (2). Large scale vaccination was core for containing the pandemic, including deaths and hospitalizations. The most used COVID-19 vaccine globally is the vector construct ChadOx1-C0V19 developed by the University of Oxford.

As the pandemic progresses, variants of concern (VoCs) of SARS-CoV-2 are constantly emerging; and mutations promoting immune escape have raised questions about the effectiveness of currently licensed COVID-19 vaccines against these emerging VoCs. In January 2021, the P.1 variant (also known as the Gamma variant), designated a VoC by the WHO due to its increased transmissibility, was first identified in Japan in travelers arriving from Manaus, Brazil (3). By May 2021, the Gamma variant was the dominant strain circulating in Brazil.

In early 2021 one vaccine against COVID-19—ChadOx1-nCoV19—was licensed in Brazil and the inactivated COVID-19 vaccine Coronavac was approved for emergency use in Brazil. Both vaccines have shown clinical efficacy: Coronavac showed an overall efficacy of 50.7% against symptomatic disease of any severity after two doses (4), while ChadOx1-nCoV19 demonstrated an efficacy of 81.3% against symptomatic infection after two doses given more than 12 weeks apart and of 76.0% 3 weeks after single dose vaccination (5).

At the time of the predominance of Gamma variant circulation in Brazil, there was little evidence of the clinical efficacy or effectiveness of COVID-19 vaccines against this variant (6). In two preclinical studies, sera from ChadOx1-nCoV19 vaccines demonstrated a similar neutralization capacity against the Gamma variant as for Alpha (also known as B.1.17), whereas sera from Coronavac vaccines showed a complete absence of neutralization activity against the Gamma variant (7).

Mass vaccination campaigns offer a unique opportunity to conduct observational studies on the effectiveness and safety of the intervention. With the support from the Brazilian Ministry of Health (MoH), we conducted a test-negative design (TND) observational study on the effectiveness of the recombinant COVID-19 vaccine ChadOx1-nCoV19 from Oxford/Fiocruz as part of a large-scale vaccination campaign in Botucatu, Brazil. Botucatu is a city in inner São Paulo State with a population of 1,42,092 inhabitants, according to the São Paulo Demographic and Statistical Foundation (www.seade.gov.br). The city harbors a university hospital that provides tertiary care for surrounding municipalities, an area comprising half a million people. The municipal health department adheres to the family health program within Brazil's socialized Unified Health System (SUS); and historically has had high adherence to previous vaccination campaigns.

This setting thus offered a unique opportunity to assess the overall effectiveness of 1 and 2 doses of ChadOx1-nCoV19, and specifically against new variants, in a real-life setting.

Materials and methods

Study population and design

The Brazilian MoH launched a mass vaccination campaign using ChadOx1-nCoV19 starting on the 16th of May 2021, in the municipality of Botucatu, Brazil, targeting the population between 18 and 60 years of age. At the time of the study, vaccination in the 18–60-years-old population was not yet implemented in Brazil, except for health care workers (HCWs) and high risk citizens. All citizens in this age group (N = 92,349) were eligible for inclusion in the campaign if not yet vaccinated, including those with underlying conditions. Vaccination was offered by qualified HCWs in four school courts and, importantly, in 45 election-voting locations with which the vaccinees were familiar, to facilitate campaign adherence. A second dose was planned to be administered 12 weeks after the first dose. Whilst there was no lockdown during the entire study period, mask use was mandatory throughout the study period.

Objectives and outcomes

The main objective of the study was to determine the vaccine effectiveness (VE) of ChadOx1-nCoV19 against any COVID-19 disease, by dose, and VoC. The VE against severe COVID-19 disease (defined as hospitalization or death) was a secondary objective.

All individuals fitting the clinical criteria for COVID-19 as established by the municipal secretary of health according to globally accepted standards received one of three types of tests: a PCR test, a rapid antigen test, or a serology test. PCR positive samples were sequenced upon consent from the participant. All participants who received a positive or negative PCR test result after the 16th of May, 2021, and were unvaccinated prior to the same date, were included in the analysis.

Study design

In order to measure VE, a TND was applied, whereby the odds of being vaccinated were compared among cases (testing positive for SARS-CoV-2) and controls (not testing positive). Logistic regression was used to obtain the odds ratio and the VE ($1 - OR$). The VE was calculated from 21 days after dose 1 and 14 days after dose 2, as efficacy has been reported to occur after this interval (5).

Data sources

Records containing information on COVID-19 testing and vaccination status were entered into case report forms (CRFs). Individual information was derived from four de-identified databases for the period from the 17th of May to the 18th of November 2021: (1) E-SUS, used for routine influenza-like-illness (ILI) surveillance, adapted for the COVID-19 pandemic and containing information on symptomatic and asymptomatic cases, (2) SIVEP, containing information on severe, hospitalized ILI cases; (3) VACIVIDA, containing vaccination information on all vaccinated individuals, and (4) a database containing information on testing and sequencing results. Databases were linked using a randomly generated de-identified ID.

Statistical analysis

The analysis was restricted to those that received an RT-PCR test within 10 days of symptom onset, to account for the reduced sensitivity of the PCR test after this time (8). Analysis was based on illness episodes. Multiple tests taken on 1 day were counted as one test, with the positive result counting toward the analysis if one was present. Any tests taken within 21 days of each other were counted as one illness episode. Individuals who received more than two vaccine doses were excluded from the analysis. Individuals who received a positive test result prior to being vaccinated were counted as unvaccinated. We adjusted for sex, week of symptom onset, age group (by 10-year brackets, i.e., 18–30 years, 31–40 years, 41–50 years, and 51–60 years), and comorbidities as per protocol. As a sensitivity analysis, VE was also estimated from an intent-to-treat (ITT) perspective, measured from the first day after each dose.

Ethics approval

The research was approved by the Ethical Committee of Botucatu Medical School/São Paulo State University (FMB/UNESP) and by the Comissao Nacional De Etica em Pesquisa CONEP. Only participants who consented to having their information collected were enrolled in the study. During the statistical analysis phases, only de-identified data were received for analysis.

Results

A total of 65,450 citizens aged 18–60 years received a first dose of ChadOx1-nCoV19 on the first day of the campaign (Sunday, 16th of May), and 12,233 in the following 4 weeks, for a total of 77,683 vaccines (84.2% coverage). Of these, 60,333 citizens received their second ChadOx1-nCoV19 dose 12 weeks later, on Sunday, 8th of August, with an additional 13,718 citizens over the next 4 weeks, for a total of 74,051 fully vaccinated persons (80.2% coverage).

A total of 10,218 PCR tests were available and successfully linked to vaccination data. After various exclusion criteria were applied, 7,958 PCR results were available for analysis, of which 2,109 positive PCRs were recorded in people 18–60 years old (Figure 1).

Table 1 shows the baseline characteristics of the study population. The mean age was 35.7 years for the controls and 37.9 for the confirmed COVID-19 cases. Gender was approximately equally distributed in both groups. The positivity

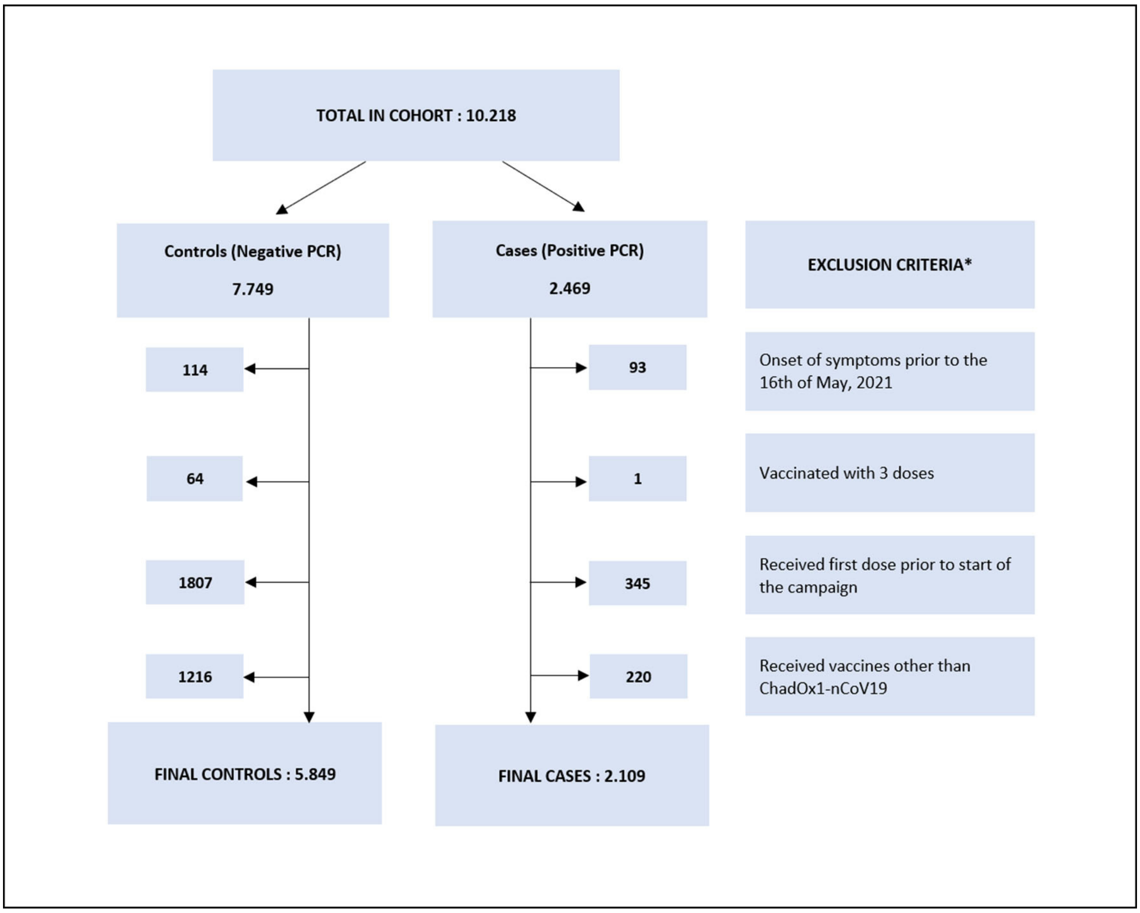

FIGURE 1
Exclusion criteria applied to overall cohort. *Exclusion criteria may overlap.

rate of the PCR was highest (48.2%) in the week immediately following the first campaign, and rapidly declined to below 20% following the second campaign and finally below 10% in October.

Sequencing results

Of the 452 strains with sequencing results, 70.4% were Gamma VoC. The remaining strains were either Delta VoC (27.8%, including B.1.617 or AY variants), or Alpha VoC (1.8%). There was, however, an important shift from Gamma VoC dominance to Delta VoC dominance during the study. Table 2 shows the VoC distribution by time period.

Overall VE

Overall VE against any illness was estimated at 39.2% (95% CI 23.7–51.5) as of 3 weeks after dose 1, and 74.5% (95% CI 23.7–51.5) as of 14 days after dose 2 (Table 3).

A total of 73 patients with PCR-confirmed COVID-19 infections had severe COVID-19 disease: 64 hospitalizations and nine deaths. None of the 74,051 citizens who were fully vaccinated with ChadOx1-nCoV2 was hospitalized or died during the 3 months of observation. Ten hospitalizations and two deaths occurred in one-dose recipients, of which eight occurred within the first 3 weeks after the first dose. The remaining 61 severe disease events occurred all in non-vaccines. The VE against severe COVID-19 disease was thus estimated at 70.8% after dose 1 (95% CI 9.6–90.6%) and 100% (95% CI 44.3–100%) after dose 2.

Vaccine effectiveness against Gamma was estimated at 51.0% (95% CI 21.6–68.6%) following dose 1, and VE against Delta was 76.0 (95% CI 49.5–87.8) following dose 2. We were not able to estimate effectiveness against the Alpha variant, as only a total of eight events occurred. We could also not determine the precise VE against Gamma after two doses nor against Delta after one dose due to the shift in epidemiology with insufficient events and statistical power for those respective periods (Table 2).

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TABLE 1 Baseline characteristics of persons 18–60 years old tested for COVID-19.

	Controls	%	Cases	%
*N**	5,849	73.5%	2,109	26.5%
Age mean (sd)	35.7 (11.3)		38.0 (11.5)	
Age median	34.7		37.9	
Gender				
Female	3,240	55.4%	1,096	52.0%
Age group				
18–30 years	2,147	36.7%	640	30.4%
31–40 years	1,618	27.7%	536	25.4%
41–50 years	1,277	21.8%	537	25.5%
51–60 years	807	13.8%	396	18.8%
Calendar week of test*				
17–23 May 2021	325	51.8%	303	48.2%
24–30 May 2021	479	58.6%	339	41.4%
31 May—6 June 2021	492	55.2%	400	44.8%
7–13 June 2021	482	65.0%	259	35.0%
14–20 June 2021	386	76.6%	118	23.4%
21–27 June 2021	308	78.6%	84	21.4%
28 June—4 July 2021	246	80.9%	58	19.1%
5–11 July 2021	196	79.0%	52	21.0%
12–18 July 2021	232	85.9%	38	14.1%
19–25 July 2021	198	78.9%	53	21.1%
26 July-1 Aug 2021	167	79.5%	43	20.5%
2–8 Aug 2021	239	77.3%	70	22.7%
9–15 Aug 2021	231	78.8%	62	21.2%
16–22 Aug 2021	197	82.8%	41	17.2%
23–29 Aug 2021	175	82.9%	36	17.1%
30 Aug—5 Sep 2021	172	87.8%	24	12.2%
6–12 Sep 2021	114	75.0%	38	25.0%
13–19 Sep 2021	172	85.1%	30	14.9%
20–26 Sep 2021	191	86.4%	30	13.6%
27 Sep—3 Oct 2021	157	93.5%	11	6.5%
4–10 Oct 2021	142	96.6%	5	3.4%
11–17 Oct 2021	104	97.2%	3	2.8%
18–24 Oct 2021	123	98.4%	2	1.6%
25–31 Oct 2021	118	98.3%	2	1.7%
1–7 Nov 2021	78	97.5%	2	2.5%
8–14 Nov 2021	94	97.9%	2	2.1%
15–21 Nov 2021	31	88.6%	4	11.4%
Comorbidities				
Yes	624	11.0%	235	11.5%

*Percentage in relation to the number tested in the same week.

The ITT analysis whereby VE was measured as of the day of vaccination showed an overall VE after the first dose of 30.7% (95% CI 18.9–40.8) and after the second dose of 70.2% (95% CI 53.0–80.8).

TABLE 2 VoC distribution by time period.

VoC	Period	
	Dose 1 (16th of May—7th of Aug) *N* (%)	Dose 2 (8th of Aug—18th of Nov) *N* (%)
Alpha	8 (2.4)	0 (0)
Delta	23 (7.0)	103 (83.0)
Gamma	297 (90.5)	21 (16.9)

We had defined severe disease in this observational study as hospitalization or death. In the absence of sufficient hospitalizations or deaths among the much smaller cohort of control, we could not estimate with reasonable precision the VE against severe disease. A total of 73 patients with PCR-confirmed COVID-19 infections had severe COVID-19 disease: 64 hospitalizations and nine deaths. None of the 74,051 citizens who were fully vaccinated with ChadOx1-nCoV2 was hospitalized or died during the 3 months of observation. Two deaths and 10 hospitalizations occurred in one-dose recipients, all other severe disease events in non-vaccinees.

Discussion

This study aimed to estimate the effectiveness of ChadOx1-nCoV19 following a mass vaccination campaign in Botucatu, Brazil, during which 84.2% of the eligible population of 18–60-year-old citizens received at least one dose and 80.2% received a second dose 3 months later. The vast majority of the latter received their first and second dose on single Sundays in May and August in a set-up where the 45 voting stations for elections of the city were transformed into vaccination centers. The vaccine showed an overall effectiveness of 39.2% from week 3 after dose 1, which increased to 74.5% 2 weeks after dose 2, against any COVID-19 illness in individuals 18–60 years old.

This study adds to the body of evidence of VE during active circulation of emerging VoCs, such as Gamma and Delta which were predominant during the study period. In randomized control trials, the clinical efficacy of ChadOx1-nCoV19 showed a 76.0% reduction in symptomatic illness in the 3 weeks after dose 1, and of 81.3% 14 days after dose 2 (9). This, however, occurred in a controlled setting, and with the ancestor strain Wuhan as the predominant strain, prior to the emergence of the Gamma and Delta VoCs.

The effectiveness of ChadOx1-nCoV19 against variants, including Delta, has been reported elsewhere. Sritipsukho et al. (10) reported a real-life VE against Delta to be <50% after dose 1 and 83% after dose 2 of ChadOx1-nCoV19. Besides, a recent systematic review and meta-analysis described that

TABLE 3 Vaccine effectiveness against any COVID-19 illness, overall and by strain, multivariate analysis only.

Vaccination status, dose	Test-negative status		Vaccine effectiveness (95% CI)		
	Controls	Cases	Overall	Delta variant	Gamma variant
Unvaccinated	381	185		Reference	
Dose 1	2,171	609	39.2 (23.7–51.5)	35.9 (−45.3 to 70.4)	51.0 (21.6–68.6)
Unvaccinated	70	24		Reference	
Dose 2	1,359	122	74.5 (23.7–51.5)	76.0 (49.5–87.8)	81.3 (−298.0 to 97.9)

a non-replicating vector vaccine could achieve a VE of 65% against Delta and 63% against Gamma VoCs (11). However, studies relating to the effectiveness of ChadOx1-nCoV19 against Gamma in real-life settings remain sparse. We were therefore specifically interested in estimating VE against Gamma. The VE against Gamma following dose 1 was estimated at 51.0%. We were not able to precisely estimate the VE against this VoC following dose 2 given the epidemiological shift to Delta in that observation period. Hitchings et al. estimated a VE of 33.4% against symptomatic infection 28 days after the first dose of ChadOx1-nCoV19, and of 77.9% 14 days after the second dose, in adults aged over 60 years of age. This study was conducted in the context of Gamma circulation in São Paulo, Brazil; however, no individual sequencing data were available for analysis (6). We found slightly higher VE estimates against any COVID-19 disease and Gamma following the first dose, with slightly longer follow-up time.

Bernal et al. (12) noted a reduced effectiveness against Delta when compared with the Alpha strain with an estimated effectiveness of ChadOx1-nCoV19 for Delta after dose 1 at 30.0% (vs 48.7% for Alpha) and 67.0% (vs 74.5% for Alpha) after dose 2. Our results suggest a slightly higher VE of 76.0% against Delta, comparable to the originally estimated VE against the Alpha strain.

We also calculated VE from the ITT perspective, whereby VE was estimated from the date of vaccination, which produced slightly lower results. VE was not estimated against severe COVID-19 using the TND case control approach as the recorded number of patients within the respective observation periods was very limited. However, none of the 74,051 citizens who had received a full priming was hospitalized or died.

We restricted the analysis to those that had symptom onset 2 weeks after each of the mass vaccination campaign dates, to avoid that an increase in testing following COVID-like side effects of the vaccine may bias the VE estimates. This finding is supported by an observed increase in Emergency Room attendance and hospitalizations in the 1 week following each campaign, which was noted in our safety results reported elsewhere (13).

Our study is subject to some limitations, both inherent to the study setting, and to the study design. The high vaccination coverage achieved in Botucatu (estimated at 84.2% and 80.2% for the first and second doses, respectively, for the population between 18 and 60 years old) may bias the estimation of VE to the null, as the unvaccinated may also have been protected through herd immunity.

Our analyses were limited to a follow-up period of 14 weeks (104 days) after dose 2. Studies of other COVID-19 vaccines have shown significant waning of VE after about 7 months after the second dose (14–16). On the other hand, estimates of effectiveness have also been shown to be positively correlated with time since vaccination up until a certain point (10). Although it is evident that despite antibody waning, the efficacy of most COVID-19 vaccines against severe disease caused by the Delta VoC is largely maintained, a decline in efficacy is recently noticed against infection and milder disease (17). This study would have benefited from a longer follow-up period to detect any of these effects.

We attempted to reduce any selection biases; however, as this was an observational study residual bias is still possible. The use of the TND attempted to control for any selection bias in health-seeking behavior among study participants. Only people who received a PCR test within 10 days of symptom onset were included in the analysis; however, misclassification of cases/controls due to low sensitivity/specificity of the PCR test, which may affect one variant more than another, is still possible. Given that 70.3% of all sequenced sequences were of the Gamma variant, this reduces the possibility of the latter.

Conclusion

Vaccine effectiveness against any COVID-19 disease was estimated at 39.2% in the 3 weeks after dose 1, and 74.5% 2 weeks after dose 2 of ChadOx1-nCoV19 following a mass vaccination campaign in Botucatu, Brazil, with no hospitalizations or deaths in fully vaccinated individuals. These results suggest that the ChadOx1-nCoV19 was also highly effective in preventing COVID-19 disease in a real-life setting with various circulating variants, not studied in the original efficacy studies. Combined with the reassuring results on the safety of the same vaccine studied in the same campaign, these effectiveness results show the highly beneficial effect that has been achieved through this mass campaign in Botucatu.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The study was reviewed and approved by Ethical Committee of Botucatu Medical School/São Paulo State University (FMB/UNESP) and by the Comissao Nacional De Etica em Pesquisa CONEP. The patients/participants provided their written informed consent to participate in this study.

Author contributions

SC, CF, and RC conceptualized the study. SC and RC provided supervision. CF, KT, RG, JJ, AS, and JAS curated the data. MC, TV, and RC did the statistical analysis. SC, CF, and AS acquired funding. MC wrote the original draft. SC, RC, RS, CF, and TV wrote, reviewed, and edited. All authors critically reviewed and approved the final version. All authors confirm that they had full access to all the data in the study and accept responsibility to submit for publication.

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Conflict of interest

Author CF received funding from the Brazilian Council for Scientific and Technological Development. Authors MC and TV were employed by P95 Epidemiology & Pharmacovigilance. Author RS was employed by Intrials. Author JJ was employed by Vaxtrials.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Analyses of reported severe adverse events after immunization with SARS-CoV-2 vaccines in the United States: One year on

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Objective: To analyze rates of reported severe adverse events after immunization (sAEFI) attributed to SARS-CoV-2 vaccines in the United States (US) using safety surveillance data.

Methods: Observational study of sAEFI reported to the vaccine adverse events reporting system (VAERS) between December 13, 2020, to December 13, 2021, and attributed to SARS-CoV-2 vaccination programs across all US states and territories. All sAEFI in conjunction with mRNA (BNT-162b2 or mRNA-1273) or adenovector (Ad26.COV2.S) vaccines were included. The 28-day crude cumulative rates for reported emergency department (ED) visits and sAEFI viz. hospitalizations, life-threatening events and deaths following SARS-CoV-2 vaccination were calculated. Incidence rate ratios (IRRs) of reported sAEFI were compared between mRNA and adenovector vaccines using generalized Poisson regression models.

Results: During the study period, 485 million SARS-CoV-2 vaccines doses were administered nationwide, and 88,626 sAEFI reported in VAERS. The 28-day crude cumulative reporting rates per 100,000 doses were 14.97 (95% confidence interval, 14.86–18.38) for ED visits, 5.32 (5.26–5.39) for hospitalizations, 1.72 (1.68–1.76) for life-threatening events, and 1.08 (1.05–1.11) for deaths. Females had two-fold rates for any reported AEFI compared to males, but lower adjusted IRRs for sAEFI. Cumulative rates per dose for reported sAEFI attributed to adenovector vaccine were 2–3-fold higher, and adjusted IRRs 1.5-fold higher than mRNA vaccines.

Conclusions: Overall cumulative rates for reported sAEFI following SARS-CoV-2 vaccination in the US over 1 year were very low; single-dose adenovector vaccine had 1.5-fold higher adjusted rates for reported sAEFI, which may however equate with multiple-doses mRNA vaccine regimens. These data indicate absence of high risks of sAEFI following SARS-CoV-2 vaccines and support safety equipoise between mRNA and adenovector vaccines. Public health messaging of these data is critical to overcome heuristic biases. Furthermore, these data may support ongoing adenovector vaccine use, especially in low- and middle-income countries due to affordability, logistical and cold chain challenges.

KEYWORDS

COVID-19 vaccination adenovector, mRNA, severe adverse events following immunization, BNT-162b2 vaccine, mRNA-1273 vaccine, Ad26.COV2.S

Introduction

Coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome novel coronavirus-2 (SARS-CoV-2) was declared a pandemic by the World Health Organization (WHO) in March 2020. Rapid scientific advancements in the management of COVID-19 have been spearheaded by collaborative global efforts, especially in vaccine development utilizing several different platforms, including the mRNA [BNT-162b2 (Pfizer/BioNTech) and mRNA-1273 (Moderna)] and adenovector [ChAdOx1 (AstraZeneca) and AD26.COV2.S (Janssen)] technologies. As of December 13, 2021, 8.5 billion vaccine doses had been administered worldwide, including 485 million in the United States (US) and 1 billion in Europe, though fully vaccinated population proportions remained low at 61% in the US, 59% in Europe, and 46% worldwide (1).

Access remains a key hurdle in low- and middle-income countries (LMICs), whereas vaccine hesitancy is the top reason for low vaccination rates in high-income countries (HICs) (2, 3), even though vaccine safety has been addressed early and methodically in clinical trials (4). However, legitimate concerns of severe adverse events after immunization (sAEFI) (2, 5–8) pose heuristic challenges *via* media narrative, and legitimize vaccine skepticism with incomplete information.

Several severe and life-threatening adverse events, such as thrombosis with thrombocytopenia syndrome (TTS) and cerebral venous sinus thrombosis (CVST) (6, 9), arterial thrombotic events (10), acute demyelinating inflammatory polyneuropathy (Guillain-Barré syndrome, GBS) (7), and myocarditis (11, 12) have been reported as potential SARS-CoV-2 vaccine-related adverse events. Even though causal relationships remain unascertained (13), these occurrences have fueled vaccine skepticism, mistrust and hesitancy (14), affecting specific demographics and minorities (15, 16), who are more likely to suffer severe consequences of COVID-19 (17).

To facilitate the success of vaccine programs and vaccine equity, examining post-clinical trial "real world" surveillance vaccine safety data is necessary to detect possible safety signals which may be too rare to detect even in large clinical trials. This information can empower global health agencies such as the WHO and other policy decision-makers, in the continued planning and implementation of vaccine programs worldwide, as the majorities of global populations remain unvaccinated, while supplies of existing vaccine stocks remain unused in HICs.

In this study, we aimed to identify if composite rates of various vaccine-related illnesses are associated with significant reported rates of hospitalization, life-threatening events and deaths, which are classified as severe adverse events following immunization (sAEFI), using data from the vaccine adverse events reporting system (VAERS) (18).

VAERS is a vaccine safety surveillance registry. Data from it is not meant to provide estimates of true incidence rates of adverse events. Within the spectra of adverse events, there is a wide range of accuracy in reporting (28–72%) (19). However, it has also been demonstrated physicians in hospitals who see severe adverse events are more likely to report them compared to physicians in community practices who see milder adverse events (19). We have therefore selected sAEFI which occur in hospitals, and given the gravity such as hospitalizations, life-threatening events and death, are more likely to be diagnosed and reported. Here we calculate the rates of reported sAEFI from the surveillance system which are not to be conflated with absolute incidence rates. The decisions to define acceptable risks are essentially a task for epidemiologists and taken in relation to risks posed by disease vs. those of prevention and treatments of the disease, not only to individual but also to health systems, and society, keeping in mind that even risks and outcomes of disease themselves may equally be under-reported as has been demonstrated recently with respect to global deaths (20).

Furthermore, risk identification and quantification of vaccine-related adverse events such as myocarditis, GBS or CVST, do not present to society an overall risk of vaccines but rather an arbitrary risk which is not easy for individuals to understand in the larger context of a pandemic, and has resulted in significant anxiety. In such circumstances, composite all-cause risks of sAEFI may present a clearer picture, even if it be an estimate and not an absolute risk.

Materials and methods

Study design and population

In this observational study, we analyzed data on reported sAEFI viz. hospitalizations, life-threatening events, and deaths following vaccination with each of the three SARS-CoV-2 vaccines (BNT-162b2, mRNA-1273 and Ad26.COV2.S) licensed for emergency use in the US, from the VAERS database between December 13, 2020, and December 13, 2021. All events that occurred up to 28 days after vaccination were included (21).

VAERS is a voluntary adverse event reporting system for all vaccines administered to children or adults, established by the Centers for Disease Control and Prevention (CDC) (22). Healthcare providers are required to report any listed adverse event from the VAERS "Table of Reportable Events", such as hospitalization, life-threatening event, death, permanent disability, congenital anomaly, or birth defect that occurs following vaccination within a pre-specified time-period, or any similar adverse event listed as a contraindication to further doses of the vaccine. The VAERS registry includes data on demographics, geographical location, date(s) of vaccination, date(s) of adverse event report, symptoms, recovery, disability, and if there is a report that any healthcare was sought; all entries are anonymized, and data is publicly accessible. Unlike absolute risks, sAEFI rates in VAERS are subject to biases. As stated above, whilst reporting rates of all AEFI range widely (28–72%), sAEFI are more accurately recorded by physicians and reported in hospitals, compared to minor AEFIs seen in primary care (19).

Exposure

The primary exposures of interest were SARS-CoV-2 vaccines, categorized as mRNA (combining BNT-162b2 and mRNA-1273 vaccines) and adenovector (Ad26.COV2.S vaccine). Analyses were also repeated for each mRNA vaccine brand separately (BNT-162b2 and mRNA-1273 vaccines).

Outcomes

We focused on sAEFI viz. hospitalizations, life-threatening events, and deaths attributed to the SARS-CoV-2 vaccines due to population level implications. In addition, we included emergency department (ED) visits to determine whether increased visits to ED were related to sAEFI, for non-severe events or rather due to WHO categorized immunization-anxiety related reaction related to publications of rare but severe illnesses. These four healthcare outcomes are also less likely to be underreported; adverse events severe enough to warrant a hospital visit are mandated to be reported to VAERS (18).

Statistical analysis

The VAERS dataset for all AEFI attributed to SARS-CoV-2 vaccines was downloaded, reformatted, and restricted to vaccines administered between December 13, 2020, and December 13, 2021. Duplicate entries and entries with missing vaccination date or manufacturer information were excluded. Data on numbers of 1st, 2nd, and booster vaccine doses administered were available, but the adverse events are not reported by dose number; therefore, it was not possible to calculate reported event rates per persons or dose sequence, but rather per total doses administered. National vaccine administration demographics and vaccine manufacturer data were obtained from the CDC public access portal (23, 24).

Determination of cumulative reporting rates

Cumulative reporting rates of each reported outcome were calculated for each vaccine and vaccine type. Rates were calculated as cumulative reported sAEFI per 100,000 administered doses for the 366 days for each vaccine, and 95% confidence intervals (CI) were generated. Additional descriptive analyses included the generation of graphical outputs of temporal trajectories of moving 7-days averages of sAEFI for the three vaccines to visualize timelines of reporting rates.

Comparing relative rates for sAEFI reporting between vaccines

A generalized Poisson regression model was used to calculate reporting incidence rate ratios (IRRs) for the adenovector (Ad26.COV2.S) vaccine compared to mRNA vaccines (BNT-162b2 and mRNA-1273) for each of the four outcomes (i.e., ED visits, hospitalizations, life-threatening events, and death) with 95% CIs. The model was adjusted for age [grouped as <17, 18–24, 25–39, 40–49, 50–64, >75 years (referent category)] and sex [males and females (referent category)]. Further, interactions between age, sex and types of vaccine were investigated. These results were decomposed using contrasts to reveal the actual effect for

TABLE 1 Descriptive characteristics.

	All SARS-CoV-2 *n* (%)	BNT-162b2 *n* (%)	mRNA-1273 *n* (%)	Ad26.COV2.S *n* (%)
Age (years) median (IQR)	48 (34–63)	45 (31–60)	52 (37–66)	43 (31–56)
Age category (years)				
≤17	28,876 (5.12)	21,891 (8.52)	5,986 (2.25)	999 (2.44)
18–24	33,283 (5.90)	15,948 (6.20)	12,767 (4.80)	4,568 (11.16)
25–39	129,544 (22.96)	61,570 (23.95)	55,875 (21.00)	12,099 (29.55)
40–49	93,145 (16.51)	44,083 (17.15)	41,317 (15.53)	7,745 (18.91)
50–64	139,130 (24.66)	61,777 (24.03)	65,940 (24.78)	11,413 (27.87)
65–74	76,983 (13.65)	28,753 (11.18)	45,400 (17.06)	2,830 (6.91)
≥75	43,756 (7.76)	16,085 (6.26)	26,579 (9.99)	1,092 (2.67)
Missing	19,391 (3.44)	6,967 (2.71)	12,223 (4.59)	201 (0.49)
Sex				
Female	394,620 (69.95)	177,642 (69.10)	191,669 (72.03)	25,309 (61.81)
Male	161,802 (28.68)	76,616 (29.80)	69,781 (26.22)	15,405 (37.62)
Missing	7,686 (1.36)	2,816 (1.10)	4,637 (1.74)	233 (0.57)
Any adverse events (%)	564,108	257,074 (45.57)	266,087 (47.17)	40,947 (7.26)
Doses administered (%)	485,359,746	282,267,391 (58.15)	185,388,911 (38.19)	17,206,942 (3.54)

Characteristics of patients with any reported AEFI within 28 days of receiving SARS-CoV-2 vaccination between December 13, 2020, and December 13, 2021, inclusive. (Data was obtained from the vaccine adverse events reporting system (VAERS) registry in the United States). (BNT-162b2, Pfizer-Biontech; mRNA-1273, Moderna; Ad26.COV2.S, Janssen).

all possible pairs. We report the joint effects for male and vaccine-types with the female category treated as the reference group; and the joint-effects for the age groups and vaccine-types with the >75 years category as the reference group. All data management and formatting were carried out in Stata 17 (StataCorp, College Station, TX, United States). All statistical analyses were performed in RStudio (1.4.1717).

We further compared the published rates of serious adverse events that have led to restrictions on the use of different vaccine types, to all-cause rates of reported sAEFI in VAERS. The 3 main events we compared were TTS (6, 9) and GBS (7, 25) following adenovector virus vaccine (Ad26.COV2.S),and myocarditis with mRNA vaccines (BNT-162b2 and mRNA-1273) (8, 11, 12).

Results

During the study period, 485,359,746 SARS-CoV-2 vaccine doses were administered in the US; 564,108 unique AEFI and 88,626 sAEFI attributed to SARS-CoV-2 vaccinations were reported within 28 days of vaccination (Supplementary Figure 1). Timeline of cumulative doses of each vaccine, vaccine type, and dose sequences, along with cumulative total sAEFI during study period are shown in Supplementary Figure 2.

Median age (interquartile range, IQR) of recipients with any AEFI was 48 (34–63) years; 45 (31–60) years for BNT-162b2, 52 (37–66) years for mRNA1273, and 43 (31–56) years for Ad26.COV2.S groups (Table 1). Females comprised 69.9% of those who reported any AEFI; 69.1% in the BNT-162b2 group, 72.0% in the mRNA1273 group, and 61.8% in the Ad26.COV2.S group.

The overall crude cumulative rate for any reported sAEFI after SARS-CoV-2 vaccination per 100,000 doses was 18.25 (95% CI, 18.13–18.38), 14.97 (14.86–15.08) for ED visits, 5.32 (5.26–5.39) for hospitalizations, 1.72 (1.68–1.76) for life-threatening events, and 1.08 (1.05–1.11) for deaths (Table 2). The averaged reported sAEFI (per 100,000 doses) decreased over the study period (Figure 1). The crude unadjusted rates for sAEFI after adenovector Ad26.COV2.S vaccine were higher than those for mRNA vaccines for each outcome.

In the multivariable generalized Poisson regression model adjusted for age, sex and vaccine type, IRRs for reported ED, hospitalization and life-threatening events increased with decreasing age, whereas deaths decreased with decreasing age; males had higher IRRs than females for all reported sAEFI (Table 3). Ad26.COV2.S vaccine was associated with higher IRRs for reported ED visits [1.27 (1.24–1.30)], hospitalizations

TABLE 2 Crude cumulative reporting rates for severe adverse events.

	Total reported events *n* (%)	Crude cumulative 28-day reporting rate (95% CI)
Any reported adverse event	**564,108**	
mRNA-1273	266,087 (47.16)	143.52 (142.98–144.07)
BNT-162b2	257,074 (45.57)	91.07 (90.72–91.42)
Ad26.COV2.S	40,947 (7.25)	237.90 (235.66–240.27)
Any reported severe adverse event	**88,626 (15.71)**	**18.25 (18.13–18.38)**
mRNA-1273	34,512 (38.94)	18.61 (18.42–18.81)
BNT-162b2	45,990 (51.89)	16.29 (16.14–16.44)
Ad26.COV2.S	8,124 (9.16)	47.21 (46.18–48.24)
ED visit	**72,676 (12.88)**	**14.97 (14.86–15.08)**
mRNA-1273	27,455 (37.77)	14.80 (14.63–14.98)
BNT-162b2	38,571 (53.07)	13.66 (13.52–13.80)
Ad26.COV2.S	6,650 (9.15)	38.64 (37.71–39.57)
Hospitalization	**25,846 (4.58)**	**5.32 (5.26–5.39)**
mRNA-1273	10,382 (40.16)	5.60 (5.49–5.70)
BNT-162b2	13,132 (50.80)	4.65 (4.57–4.73)
Ad26.COV2.S	2,332 (9.02)	13.55 (13.00–14.10)
Life-threatening event	**8,370 (1.48)**	**1.72 (1.68–1.76)**
mRNA-1273	3,268 (39.04)	1.76 (1.70–1.82)
BNT-162b2	4,155 (49.64)	1.47 (1.42–1.51)
Ad26.COV2.S	947 (11.31)	5.50 (5.15–5.85)
Death	**5,262 (0.93)**	**1.08 (1.05–1.11)**
mRNA-1273	2,553 (48.51)	1.37 (1.32–1.43)
BNT-162b2	2,272 (43.17)	0.80 (0.77–0.83)
Ad26.COV2.S	437 (8.30)	2.54 (2.30–2.77)

Crude cumulative 28-day reporting rate of severe adverse events occurring within 28 days after SARS-CoV-2 vaccination, that were reported to VAERS between December 13, 2020, and December 13, 2021, inclusive. Reporting rate is expressed per 100,000 doses. (BNT-162b2, Pfizer-Biontech; mRNA-1273, Moderna; Ad26.COV2.S, Janssen). CI, confidence intervals; ED, emergency department. Bold value means total of the subgroups as per row and column labels.

[1.36 (1.30–1.42)], life-threatening events [1.60 (1.49–1.71)], and death [1.51 (1.36–1.66)] compared to mRNA vaccines.

In sex-specific interaction, males had higher reporting IRRs for ED visits, hospitalizations and life-threatening events compared to females with both vaccine-types except for Ad26.COV2.S associated ED visits which were similar (Table 4).

When compared to vaccinees older than 75 years, reporting IRRs for ED visits increased with decreasing age in both vaccine groups, while hospitalization and life-threatening events carried a lower reporting IRR in all age groups under 75 years except in the <17 years age group who received mRNA vaccines. Sex adjusted IRRs amongst Ad26.COV2.S group were higher in the 24–49-year group for reported ED visits, but lower for hospitalizations in <18-year-olds and lower for life-threatening across all ages compared to mRNA vaccines.

Discussion

Our study examines sAEFI reported and attributed to vaccination with SARS-CoV-2 and provides data on the absence of significant risk of such events from a vaccine safety surveillance database and is therefore of great public health importance. The data demonstrate that reports of sAEFI rates are very low compared to the corresponding risks from COVID-19 as well as historic data.

The cumulative rates of reported hospitalizations, life-threatening events, and deaths attributed to SARS-CoV-2 vaccines and occurring within 28 days of vaccination were 5.3, 1.7, and 1.1 per 100,000 doses, respectively (the latter two risks are lower than the risk of dying in 100,000 h of flying). While these are not absolute incidence rates and should not be so conflated, surveillance data from VAERS indicates an overall absence of significant rates of sAEFI which would alert regulators of serious safety concerns. These results are comparable to those published by the European Medicines Agency (EMA) from the EudraVigilance database as of August 29, 2022, with a risk of death from BNT-162b2 reported to be 1.23/100,000 doses, for mRNA-1,272 at 0.71/100,000 doses, and Ad26.COV2.S at 1.71/100,000 doses (26).

Crude reporting rates per 100,000 doses for the adenovector Ad26.COV2.S vaccine seem higher than those for mRNA vaccines; however, it is important to note that Ad26.COV2.S is a single dose regimen for initial immunization, whereas the mRNA vaccine regimen would expose vaccinees to this risk twice, making the overall risks similar. These are further borne out in the interactions in Table 4 wherein the reporting rates while higher for ED visits in younger age groups, do not appear to translate into higher rates of hospitalizations or life-threatening events and may reflect increased anxiety associated with reported adverse events in these groups prompting more ED visits (immunization anxiety related disorder). Meanwhile, the lower relative rate of sAEFI attributed to SARS-CoV-2 vaccination for females compared to males may be due to a higher baseline age-specific mortality rates in males for every adult age stratum (numerator) (27), or because of the lower total number of reported adverse events among males (denominator): the latter of which is

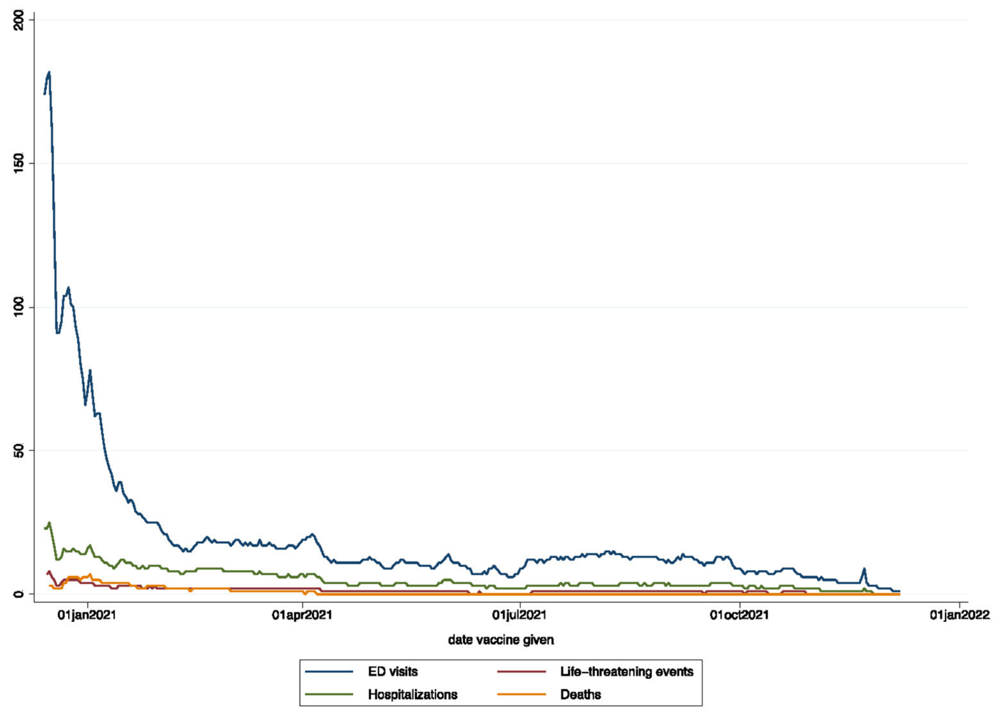

FIGURE 1
Temporal reporting rates for outcomes (7-day moving average per 100,000 doses).

supported by evidence of sociocultural barriers that prevent males from seeking medical services (28). However, this requires further investigation.

The overall risks of sAEFI (hospitalization, life-threatening illness, death) for new vaccines are reported to be up to 7% in the literature, with clear early over-reporting (18). In our findings, the reporting rates are much lower than this threshold, and the initial high reporting rates mirror the expected reporting pattern. However, initial high reporting rates of sAEFI may also be linked to the populations selected to be vaccinated earlier: older, nursing home populations who are more vulnerable. Additionally, the outcomes rates may also include unrelated background population event rates; approximately 723 deaths per 100,000 people occur annually in the US, as well as those related to COVID-19 disease in those experiencing these events in the 14 days after vaccination; therefore, some deaths may have occurred unrelated to the vaccine (27). Similarly, all AEFIs related to vaccines may not be reported completely, though sAEFI occur in hospitals and carry greater reporting accuracy (18, 19).

Clearly recognized illnesses that appear to be related to the vaccines are GBS, TTS and myocarditis. The unadjusted incidence rate of GBS attributed to Ad26.COV2.S in the first 21 days following vaccination was 32.4 (95% CI: 14.8–61.5) per 100,000 person-years, compared to 1.3 (95% CI: 0.7–2.4) per 100,000 person-years attributed to mRNA vaccines, and a between vaccine type groups adjusted relative risk of 20.56 (95% CI: 6.94–64.66) (25). However, the calculated rates are based on 11 confirmed cases from 483,503 recipients of Ad26.COV2.S. of which 8 met Brighton diagnostic criteria level 1 or 2. Similarly, no increase in arterial thrombosis was seen following Ad26.COV2.S, but a nearly two-fold increase in venous thromboembolism with an excess of 29 instances per 100,000 vaccinations, and an excess of 2.5 instances of CVST per 100,000 vaccinations; however, there were 29 fewer deaths than expected (background rate and not reduction from COVID mortality) per 100,000 vaccinations (10). Meanwhile, 1,626 cases of myocarditis were reported in relation to 354 million mRNA vaccine doses, 98% of whom had troponin elevation, 96% were hospitalized and 98% discharged home, in addition to having a shorter course of illness compared to viral myocarditis (8). It would appear that while there is a several fold increase in these illnesses following SARS-CoV-2 vaccinations, the background rate is very low and make the absolute increase in incidence not alarming. If at all rates should be compared it should be between disease-related morbidity vs. protection and risk.

With new variants emerging and a gradual rise in R0 value of the virus, it would appear unsafe to assume some population subgroups such as young children may be not vulnerable to COVID-19, and the risk assessment remains dynamic (29). Furthermore, vaccines not only mitigate risks of disease but also "long-COVID" syndrome (30). Therefore,

TABLE 3 Incidence rate ratios for reported outcomes.

	ED visit	Hospitalization	Life-threatening events	Death
	IRR (95% CI)	IRR (95% CI)	IRR (95% CI)	IRR (95% CI)
Age group (years)				
>75 (referent)	1	1	1	1
65–74	0.85 (0.83–0.88)	0.59 (0.57–0.61)	0.81 (0.75–0.88)	0.31 (0.29–0.34)
50–64	1.20 (1.16–1.23)	0.50 (0.49–0.52)	0.82 (0.77–0.88)	0.18 (0.16–0.19)
40–49	1.45 (1.41–1.50)	0.40 (0.38–0.42)	0.77 (0.71–0.83)	0.07 (0.06–0.08)
25–39	1.66 (1.61–1.71)	0.38 (0.37–0.40)	0.61 (0.57–0.66)	0.05 (0.05–0.06)
18–24	2.68 (2.58–2.78)	0.72 (0.68–0.77)	0.91 (0.81–1.02)	0.06 (0.04–0.08)
≤17	2.62 (2.51–2.73)	1.15 (1.08–1.22)	1.02 (0.89–1.17)	0.05 (0.03–0.07)
Missing	0.40 (0.37–0.43)	0.32 (0.30–0.35)	0.25 (0.20–0.30)	0.11 (0.09–0.14)
Sex				
Female (referent)	1	1	1	1
Male	1.09 (1.07–1.10)	1.97 (1.92–2.02)	1.90 (1.82–1.99)	2.57 (2.43–2.72)
Missing	0.87 (0.77–0.97)	0.84 (0.68–1.02)	1.08(0.77–1.48)	1.97 (1.41–2.66)
Vaccine type				
mRNA (referent)	1	1	1	1
Adenovector	1.27 (1.24–1.3)	1.36 (1.3–1.42)	1.60 (1.49–1.71)	1.51 (1.36–1.66)

Multivariable generalized poisson regression model exploring association between the vaccine type and outcomes, adjusted for age and sex. (December 13, 2020, to December 13, 2021, inclusive). (BNT-162b2, Pfizer-Biontech; mRNA-1273, Moderna; Ad26.COV2.S, Janssen). IRR, Incidence Rate Ratio; CI, confidence intervals; ED, emergency department.

immunization of the population remains central to the control of the SARS-CoV-2 pandemic. Modeling data suggest that every 1% increase between 40–50% vaccination coverage in 270 days (70% vaccine efficacy) can avert 1.5 million cases, 56,240 hospitalizations, 6,660 deaths, gain 77,590 QALYs, save $602.8 million in direct medical costs, and $1.3 billion in productivity losses (31). Expediting to 180 days could save an additional 5.8 million cases, 215,790 hospitalizations, 26,370 deaths, 206,520 QALYs, $3.5 billion in direct medical costs, and $4.3 billion in productivity losses.

Adverse effects to the SARS-CoV-2 vaccines reported to VAERS in the US have been described by diagnoses as minor and severe AEFIs as well as their distribution frequencies within all AEFIs as well as reporting odds ratios (32). While this is very useful information for scientists and public health professionals, the consumers (the public) are likely to benefit from the estimates of reporting sAEFIs, which we endeavor to provide such that the lay public may be able to have an idea of how rare a severe AEFI may be compared to some daily activities, which can be key in overcoming vaccine hesitancy.

Estimates comparing the overall relative risk of vaccine types are important for international decision making and vaccine confidence. Globally, the death toll of COVID-19 is estimated to be 18 million, yet the production of Ad26.COV2.S has ceased and the US Food and Drug Administration (FDA) has restricted the authorization of AD26.COV2.S only to adults for whom other approved vaccines are not accessible or clinically appropriate (33). Vaccine needs remain immense, especially in low- and middle-income countries, where adenovector vaccines are likely to be most utilized due to low-cost and cold-chain logistics. Policy decisions to restrict adenovirus vaccination in countries with a choice of vaccine types may be feasible in HICs but affects vaccine confidence globally.

The reporting rates of sAEFI highlighted in this analysis is in context to the first 2 and possibly 3 doses of vaccines. Given however that the risk of disease with new variants and immune escape is dynamic, it is difficult to estimate a static risk/benefit of these vaccines.

No perfectly safe vaccine exists; disease control efforts consider risks of treatment or prevention of diseases vs. risks of disease to individual health, health systems and society. There is no clearcut threshold as to what an acceptable risk is, but in view of the mortality of 18 million globally, health system collapses, lockdowns, and harm to economies from COVID-19, the threshold of all-cause acceptable risks must be crystallized as much as possible by epidemiologists, health organizations and governments. For this purpose, these data provide crucial risk information to address existing heuristic biases. Furthermore, clear public health messaging of these risks-benefits of vaccines are imperative.

TABLE 4 Interactions for outcomes by demographic characteristics.

	ED visit		Hospitalization		Life-threatening event	
	mRNA	Adenovector	mRNA	Adenovector	mRNA	Adenovector
Age groups (years)						
>75 (referent)	1	1	1	1	1	1
65–74	0.85†	1.01	0.59†	0.59‡	0.82‡	0.69†
50–64	1.21‡	1.19*	0.51‡	0.45‡	0.85‡	0.57‡
40–49	1.45‡	1.64‡	0.40‡	0.36‡	0.80‡	0.50‡
25–39	1.64‡	2.05‡	0.39‡	0.34‡	0.64‡	0.41‡
18–24	2.57‡	4.04‡	0.76‡	0.42‡	0.99	0.39‡
≤17	2.62‡	0.88	1.16‡	0.12†	1.06	0.18
Sex						
Female (referent)	1	1	1	1	1	1
Male	1.1‡	0.98	2.04‡	1.43‡	1.94‡	1.63‡

Post-hoc analysis and decomposition of the interaction terms derived from the generalized multivariable Poisson regression model for vaccine-type with sex and age groups. Interaction model for death failed to converge due to very low sample points. (‡ $p<0.001$; † $0.001<p<0.01$; * $0.01<p<0.05$). mRNA vaccine type, mRNA-1273 and BNT-162b2 vaccines, Adenovector vaccine type, Ad26.COV2.S. (BNT-162b2, Pfizer-Biontech; mRNA-1273, Moderna; Ad26.COV2.S, Janssen). ED, emergency department.

Limitations

While VAERS is a well-established reporting system with mandatory reporting of sAEFI for healthcare providers, with the largest dataset of vaccine adverse events in the world, it is a voluntary and passive reporting system and may not capture every sAEFI, nor can every sAEFI be determined to be vaccine related. VAERS collects data on all adverse events in the time following vaccination: adverse events such as death may be coincidental, unrelated, and even possibly related to COVID-19 in those who were incompletely vaccinated or contracted disease within 14 days of immunization, rather than vaccine-related, and therefore causality cannot be inferred, and reporting rates not conflated with true incidence rates. Diagnostic confirmation of entries in large surveillance databases is infeasible, hence actual association with vaccination cannot be certain, nor can this population-level data be used to identify individual risks. Reports of adverse events in VAERS are also unverified and may contain information that is incomplete or inaccurate. Under-reporting may also result in under-estimation of the adverse events in this study. However, in such a large dataset, under-reporting is unlikely to vary significantly by vaccine type, therefore while overall reported rates may be different from true incidence rates, the comparison between vaccines is less likely to be susceptible to these biases. Lastly, the data on sAEFI in this manuscript are reported as per dose as in VAERS the AEs are not reported by dose number. However, it has by now been established that the risks for sAEFI may vary by dose number, thus this remains a limitation in this analysis, as the sAEFI estimates are aggregated across different dose numbers and combination types. Nor are other individual characteristics that may predispose one to be administered a particular vaccine type or be susceptible to sAEFI included in the database.

Conclusions

Overall rates of reported hospitalizations, life-threatening events and deaths occurring within 28 days of vaccination and attributed to SARS-CoV-2 vaccines in the United States are very low. While adenovector Ad26.COV2.S vaccine appears to carry greater rates for these outcomes; when estimated per individual, the required multiple doses of mRNA vaccines would appear to equate the risks. These results provide population level safety data and equipoise, and support continued use of adenovector vaccine especially in resource-constrained health systems due to low cost and cold-chain requirements. These results provide absence of concerning risks of SARS-CoV-2 vaccines at a population level and appear reassuring for continued vaccination rollout to control COVID-19 related disease. Public health messaging and media dissemination of such data is crucial to maintain public enthusiasm, confidence for vaccine uptake and diminish vaccine hesitancy.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: https://data.cdc.gov/Vaccinations/

COVID-19-Vaccination-Demographics-in-the-United-St/km4m-vcsb/data.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

Conceptualization: HM, AS, SL, and PK. Data acquisition: HM. Data analysis: AM, HM, and PK. Data interpretation: HM, AM, AS, AB, and PK. Writing manuscript: HM, AM, AS, BM, SL, PK, and AB. Reviewing final manuscript: all authors. All authors contributed to the article and approved the submitted version.

Conflict of interest

Author AB was employed by the company Transmissible BV.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.972464/full#supplementary-material

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Student COVID-19 vaccination preferences in China: A discrete choice experiment

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Objective: This study uses a discrete choice experiment (DCE) questionnaire to investigate student vaccination preferences for both intrinsic and extrinsic attributes.

Methods: A two-part DCE questionnaire was distributed to 1,138 students through face-to-face interviews at vaccination centers in Qingdao, China. Conditional logit models were used to understand student preference trade-offs. Mixed logit models (MLM) and sub-group analysis were conducted to understanding student preference heterogeneity.

Results: We found that students preferred vaccines with fewer side effects (β = 0.845; 95% CI, 0.779–0.911), administered through third level health facilities (β = 0.170; 95% CI, 0.110–0.230), and had at least 1 year duration of protection (β = 0.396; 95% CI, 0.332–0.461. Higher perception of COVID-19 risks (β = 0.492; 95% CI, 0.432–0.552) increased the likelihood of student vaccination uptake. Surprisingly, vaccine effectiveness (60%) and percentages of acquaintances vaccinated (60%) reduced vaccination utility, which points to free-rider problems. In addition, we find that student study majors did not contribute to preference heterogeneity, and the main disparities in preferences were attributed to student risk tolerances.

Conclusion: Both intrinsic and extrinsic attributes were influential factors shaping student preferences for COVID-19 vaccines. Our results inform universities and local governments across China on targeting their vaccination programs.

KEYWORDS
student vaccination, COVID-19 vaccination, vaccination preference, DCE, vaccination utility

Introduction

Between January and June of 2022, China experienced local COVID-19 outbreaks across Xian, Changchun, Beijing, Qingdao, Shanghai and other cities, resulting in partial or full regional-wide lockdowns. For example, one of the hardest hit cities, Shanghai recorded over 20 thousand daily infections and over 50 daily deaths during the peak of its outbreak (1). To control regional Covid outbreaks, the government implemented prevention and control measures, including lockdowns, school and university closures, routine testing and mandatory face masks in public (2). Vaccinations, as part of the government's COVID-19 measures (2), play a key role in preventing and controlling the spread of the Omicron variant. In December 2020, the Chinese government decreed a two-dose free and voluntary vaccination program for all eligible citizens (3). Inactivated vaccines account for the majority market share for general usage, with vaccine efficacy of 72.8% (3), and an acceptable safety record (4). While much of the current vaccination efforts are targeting the low vaccination rates among the elderly, young people are increasingly becoming the primary risk drivers of COVID-19 transmissions (5), with college students being a particularly high-risk cohort. Colleges have the same free and voluntary vaccination policy, but have relatively higher vaccination uptake than the general population due to targeted educational campaigns and herd behaviors. However, universities are still prone to outbreaks, for example, Jilin's 2-month provincial-wide lockdown was triggered by an initial college outbreak in Changchun, Jilin's provincial capital. As universities resume on-campus teaching, the need to understand the preferences and barriers to student vaccination is an increasingly important public health issue.

Previous studies have used various methods to investigate the vaccine acceptance, vaccine willingness and vaccine hesitancy of the general public (6–9). Misinformation, lack of trust, vaccination costs, perceptions of vaccine benefits and risks, concerns for vaccine efficacy and safety, and socio-demographic characteristics were reported as contributors to the public's COVID-19 vaccine uptake (10–14).

Discrete choice experiments (DCEs) are a quantitative method to examine stated preferences over hypothetical alternative scenarios (15). Widely used to reveal the preference trade-offs for vaccine related-characteristics, social characteristics and cognition both before and after the implementation of China's 2021 COVID-19 vaccination program (16–18), the theoretical basis of the discrete choice model is the theory of consumer demand choice, where consumers fully understand their preferences, and random utility theory, where consumers can consistently order rank their choices based on their preferences (19). In DCEs, respondents are asked to select from different scenarios comprising hypothetical alternatives to maximize their utility. Each scenario has a number of attributes (vaccine effectiveness, side-effects, vaccination sites, protection duration, acquaintances vaccinated and risk factors) and each attribute has different levels, as shown in Table 1. DCEs quantify the change in utility for alternative attribute levels, providing a superior framework for understanding preference trade-offs (20). In contrast, most mainland Chinese students' COVID-19 vaccination studies, encompassing vaccination acceptance, willingness and hesitancy, mainly used non-DCE online surveys (21–25), reporting similar vaccine hesitancy factors (21–25). In terms of student vaccine heterogeneity, the existing literature suggests that student majors do not contribute to differing vaccination preferences (26), except for medical or nursing students who exhibit overall higher vaccination willingness (27, 28). Two DCE studies identified efficacy, safety, number of doses, origin of vaccine and costs in student vaccination preferences, but for students in Hong Kong (29, 30).

Our understanding of the vaccination preferences of Chinese university students remains contested. To address this lacuna, we conducted a face-to-face DCE investigation to assess the preference trade-offs for COVID-19 vaccinations of university students in Qingdao, a major economic, transport and education hub in coastal Shandong province, and home to over 360 thousand undergraduate students across more than 13 universities (31). Importantly, Qingdao was one of the first regions to roll out the COVID-19 vaccines, and one of the first to experience the 2022 COVID-19 outbreaks (32, 33). Importantly, our DCE model, extends many existing DCE frameworks of vaccine intrinsic attributes (effectiveness, vaccine-related side effects, protection duration and vaccination sites) by including extrinsic social relationship attributes (measured by the percentage of acquaintances vaccinated) and cognition factors (measured by the perception of risk) (17, 18). We also innovatively conducted sub-group analysis to investigate preference heterogeneity based on student majors and risk tolerance. We compare our results against previous DCE non-student and general public DCE studies to gain insight into any different barriers and motivations between student vaccination and general public preferences (16–18). The results of our study will inform universities and local governments on targeted vaccination policies for Chinese college students.

Materials and methods

Identification of attributes and levels

We adopted the well-developed framework from previous DCE COVID-19 studies as the basis for attribute and level setting (17, 18). As shown in Table 1, we identified six key attributes, comprising four vaccine intrinsic attributes (vaccine effectiveness, vaccine-related side effects, vaccination sties and duration of protection), and two vaccine extrinsic attributes, social relationships (percentage of acquaintances vaccinated)

TABLE 1 Attributes and levels used in the discrete choice experiment.

Attributes	Levels	Descriptions
Vaccine effectiveness	40%	Protects 40% of vaccinated
	60%	Protects 60% of vaccinated
	85%	Protects 85% of vaccinated
Self-assessed vaccine-related side effects	50/100,000	50 out of 100,000 risk of severe side effects
	10/100,000	10 out of 100,000 risk of severe side effects
	1/100,000	1 out of 100,000 risk of severe side effects
Vaccination sites	Level 1	Village clinic or community health station
	Level 2	Township or community health center
	Level 3	County hospital and above
Duration of vaccine protection	6 months	Six months of vaccine protection
	1 year	1 year of vaccine protection
	More than 2 years	More than 2 years
Acquaintances vaccinated	30%	30% of your family, friends and acquaintances already vaccinated
	60%	60% of your family, friends and acquaintances already vaccinated
	90%	90% of your family, friends and acquaintances already vaccinated
Risk perception (probability yourself and acquaintances being infected with COVID-19)	100/100,000	100 out of 100,000 contracting COVID-19
	6/100,000	6 out of 100,000 contracting COVID-19
	1/100,000	1 out of 100,000 contracting COVID-19

and cognition (risk perception) (17, 18). Vaccine effectiveness included 3 levels, 40, 60, and 85% and vaccine related side-effects consisted of 1/100,000, 10/100,000 and 50/100,000. Vaccination sites are set as three levels: village community health station (level 1), township community health station (level 2) and county hospitals (level 3). Duration of protection was divided into 6 months protection, 1 year protection and more than 2 years protection. Percentage of acquaintances vaccinated had three levels: 30% of your family, friends and acquaintances already vaccinated, 60% of your family, friends and acquaintances already vaccinated and 90% of your family, friends and acquaintances already vaccinated. Risk perception included 1/100000 chance of contacting COVID-19, 6/100,000 probability of contacting COVID-19 and 100/100,000 probability of contacting COVID-19. Details of attribute levels are shown in Table 1. In addition, other individual-specific characteristics, such as age, sex, urban-rural location and household income, trust in government and risk tolerance, were collected to investigate preference heterogeneity. Our DCE framework is consistent with the DCE COVID-19, seasonal influenza, H1N1 and Hepatitis B vaccine literature (17).

Experimental design

A proven two-part questionnaire (18) was used to collect the data. Part one of the questionnaire obtained background characteristics, including sex (male, female), location (urban or rural based on household registration), family relationships (living with the elderly and children), academic major (humanities/social sciences or non-humanities/social sciences), risk tolerance (risk adverse, risk neutral and risk tolerant), and trust toward government (trust, unknown and mistrust). Part one also included a five-point Likert scale, where six questions surveyed each student's COVID-19 vaccination motives. Part two of the survey investigated student COVID-19 vaccination preference trade-offs. Consistent with Wang et al. (18) and Leng et al. (17), a D-efficient partial profile design was implemented for the main attributes and levels. Twenty-four hypothetical choice tasks were created and divided into three versions, each containing eight binary choice tasks. An additional choice task was added to each version, and later redacted from the analysis, to control for potential survey bias. An example of the choice task is given in Table 2.

Survey

During May 2021, the survey was conducted at vaccination sites in Qingdao, Shandong to everyone over the age of 18 and without cognitive impairment. Trained research students from Shandong University carried out the face-to-face interviews. The effective rate of survey completion was 95%. According to Orme (34), the minimum student sample size was 94, with our 1138 student observations surpassing the DCE minimum number. The survey was approved by Nanjing Medical University Ethics

TABLE 2 Choice set.

Q1	Vaccine A	Vaccine B
Vaccine effectiveness	40%	60%
Vaccine-related side effects	10/100,000	50/100,000
Vaccination sites	Level 1	Level 2
Duration of vaccine protection	1 year	6 months
Acquaintances vaccinated	30%	60%
The probability of infection with COVID-19	100/100,000	6/100,000
Which vaccine do you prefer?		

Committee and participants were informed about the purpose of the survey, that the data were for research purposes only and participants could withdraw from the survey at any stage of the interview.

Data analysis

Our study deployed commonly used statistical models to measure utility trade-offs and preference heterogeneity. Conditional Logit Models (CLM) was used to measure individual vaccination preferences:

$$\begin{aligned} U_{ijs} = {} & \beta_1 \mathrm{effect}(60)_{\mathrm{ijs}} + \beta_2 \mathrm{effect}(85)_{\mathrm{ijs}} + \beta_3 \mathrm{sideeffect}(10)_{\mathrm{ijs}} \\ & + \beta_4 \mathrm{sideeffect}(1)_{\mathrm{ijs}} + \beta_5 \mathrm{site}(\mathrm{secondlevel})_{\mathrm{ijs}} \\ & + \beta_6 \mathrm{site}(\mathrm{thirdlevel})_{\mathrm{ijs}} + \beta_7 \mathrm{protection}(1\mathrm{yr})_{\mathrm{ijs}} \\ & + \beta_8 \mathrm{protection}(2\mathrm{yr})_{\mathrm{ijs}} + \beta_9 \mathrm{acquaintances}(60)_{\mathrm{ijs}} \\ & + \beta_{10} \mathrm{acquaintances}(90)_{\mathrm{ijs}} + \beta_{11} \mathrm{probinfected}(6)_{\mathrm{ijs}} \\ & + \beta_{12} \mathrm{probinfected}(100)_{\mathrm{ijs}} + \varepsilon_{\mathrm{ijs}} \end{aligned}$$

Where U_{ijs} is the utility for individual I for scenario j (j = 1, 2) in the choice set s (s = 1, 2, 3). β are a fixed vector of parameters for each attribute level.

In addition, mixed logit model (MLM) was used to capture preference heterogeneity. Compared to the standard logit model, MLM allows for randomness across individuals by assuming that β follows a random distribution $\beta \sim f(\beta|\theta)$. The MLM is specified as:

$$\begin{aligned} U_{ijs} = {} & \beta_1 \mathrm{effect}(60)_{\mathrm{ijs}} + \beta_2 \mathrm{effect}(85)_{\mathrm{ijs}} + \beta_3 \mathrm{sideeffect}(10)_{\mathrm{ijs}} \\ & + \beta_4 \mathrm{sideeffect}(1)_{\mathrm{ijs}} + \beta_5 \mathrm{site}(\mathrm{secondlevel})_{\mathrm{ijs}} \\ & + \beta_6 \mathrm{site}(\mathrm{thirdlevel})_{\mathrm{ijs}} + \beta_7 \mathrm{protection}(1\mathrm{yr})_{\mathrm{ijs}} \\ & + \beta_8 \mathrm{protection}(2\mathrm{yr})_{\mathrm{ijs}} + \beta_9 \mathrm{acquaintances}(60)_{\mathrm{ijs}} \\ & + \beta_{10} \mathrm{acquaintances}(90)_{\mathrm{ijs}} + \beta_{11} \mathrm{probinfected}(6)_{\mathrm{ijs}} \\ & + \beta_{12} \mathrm{probinfected}(100)_{\mathrm{ijs}} + \varepsilon_{\mathrm{ijs}} \end{aligned}$$

Where U_{ijs} is the utility for individual i for scenario j (j = 1, 2) in the choice set s (s = 1, 2, 3) and β are a vector of random parameters for each individual and attribute level. We estimated the distribution of β for attribute levels to determine the existence of preference heterogeneity. To test model complexity and measure the goodness of fit of the CLM and MLM models, Akaike information criterion (AIC) and Bayesian information criterion (BIC) were calculated. While AIC has better predictive performance than BIC and is suitable for selecting the optimal model for predicting future observations, BIC is more efficient for choosing a correct model (35).

To better understand the underlying preference heterogeneity amongst students, sub-group analysis was performed by dividing the population into sub-groups based on shared characteristics such as risk tolerance and academic major. CLM was performed on each subgroup, and the results were compared cross sub-group to further analyse preference heterogeneity. Sub-group CLM specifications were estimated using the equations:

$$\begin{aligned} U_{\mathrm{ijrs}} = {} & \beta_{1\mathrm{r}} \mathrm{effect}(60)_{\mathrm{ijrs}} + \beta_{2\mathrm{r}} \mathrm{effect}(85)_{\mathrm{ijrs}} + \beta_{3\mathrm{r}} \mathrm{sideeffect}(10)_{\mathrm{ijrs}} \\ & + \beta_{4\mathrm{r}} \mathrm{sideeffect}(1)_{\mathrm{ijrs}} + \beta_{5\mathrm{r}} \mathrm{site}(\mathrm{secondlevel})_{\mathrm{ijrs}} \\ & + \beta_{6r} \mathrm{site}(\mathrm{thirdlevel})_{\mathrm{ijrs}} + \beta_{7r} protection(1yr)_{\mathrm{ijrs}} \\ & + \beta_{8\mathrm{r}} \mathrm{protection}(2\mathrm{yr})_{\mathrm{ijrs}} + \beta_{9\mathrm{r}} \mathrm{acquaintances}(60)_{\mathrm{ijrs}} \\ & + \beta_{10\mathrm{r}} \mathrm{acquaintances}(90)_{\mathrm{ijrs}} + \beta_{11\mathrm{r}} \mathrm{probinfected}(6)_{\mathrm{ijrs}} \\ & + \beta_{12r} \mathrm{probinfected}(100)_{\mathrm{ijrs}} + \varepsilon_{\mathrm{ijrs}} \end{aligned}$$

Where U_{ijrs} is the utility for individual i for scenario j (j = 1, 2) in the choice set s (s = 1, 2, 3) and sub-group r (r = 1, 2). β are a fixed vector of parameters for each attribute level.

Results

Sample characteristics

Of the 1,138 students sampled, 515 (45.3%) were male; 814 (71.5%) were from urban regions; 478 (42%) students studied humanities/social sciences and 660 (58%) students majored in other fields (science, engineering, agriculture and medicine). For risk tolerances, 872 (76.6%) students reported as being risk adverse, 132 (11.6%) were unsure and 134 (11.8%) were risk tolerant; 16 (1.4%) reported low trust in government, 45 (4%) students were unsure, and 1,054 (92.6%) viewed the government as being trustworthy. Other characteristics such as age, family household income and marital status were also collected, and the detailed characteristics of the student sample are shown in Table 3.

Estimation of parameters

Table 4 presents the results of the CLM. When compared to the reference levels, vaccine effectiveness (60%), vaccine related side-effects, vaccination sites, duration of protection, percentage

TABLE 3 Characteristics of the student sample ($n = 1{,}138$).

Characteristics	*n*	%
Sex		
Male	515	45.3
Female	623	54.7
Marital status		
Married	18	1.6
Unmarried/widowed/divorced	1,120	98.4
Residence		
Urban area	814	71.5
Rural area	324	28.5
Household yearly income		
Low income level	174	15.3
Medium income level	819	72.0
High income level	145	12.7
Major		
Humanities/social science	478	42.0
Non-humanities/social science	660	58.0
Trust in government		
Mistrust	16	1.4
Unsure	45	4.0
Trust	1,054	92.6
Risk preference		
Risk adverse	872	76.6
Unsure	132	11.6
Risk tolerant	134	11.8

of acquaintances vaccinated and the probability of infection were all statistically significant. Vaccine effectiveness (85%) was not statistically significant at the 5% level. Our results show that students preferred vaccines with fewer side-effects, administered through third level county hospitals and with at least 1 year duration of protection. In addition, students were more inclined to vaccinate when they perceive a higher risk of infection for themselves or their acquaintances. AIC and BIC results are also reported and model comparisons were conducted based on these goodness-of-fit statistics. Notably, student's vaccination utility decreased when the percentage of acquaintances vaccinated increases from the 30% level to the 60% level. This suggests that student vaccination preferences are dependent upon vaccination choices of acquaintances around them. Overall high vaccination rates entice free riding issues, where students are demotivated to vaccinate because they can enjoy the vaccination benefits of others (36). Surprisingly, this phenomenon is not evident for the 90% acquaintances vaccinated level, perhaps due to higher social conformity pressures.

The results of the mixed logit model are presented in Table 5. Similar to the fixed effects model, we observe that all attributes, except for the 85% vaccine effectiveness level, were statistically significant at the 5% level. Individual preferences under the MLM are in line with our CLM results. In particular, vaccine side-effects were the predominant attribute affecting student decision making, followed by duration of protection and perception of risk. Vaccination sites, vaccine effectiveness and percentage of acquaintances vaccinated were less important attributes. More importantly, when assuming that β follows a random distribution $\beta \sim f(\beta|\theta)$ under the MLM, we observe preference heterogeneity amongst students for vaccine side-effects, vaccination sites and duration of protection (2 years).

To better understand the underlying preference heterogeneities, we performed subgroup analysis by dividing our cohort according to different student characteristics. We sub-divided our student population based on the following two key characteristics: student's major (humanities/social sciences or non-humanities/social sciences) and risk tolerance (risk adverse or risk tolerant). Based on our defined sub-groups, we performed CLM for each subgroup and compared the cross-group results to further investigate existing preference heterogeneity. Sub-group analysis by student major in Table 6 shows that there are no observable preference heterogeneities. Similar to the whole student sample, both humanities/social science majors and non-humanities/social science majors preferred vaccines which were safer, administered in third level county hospitals and had 1 year of protection. As shown in Table 7 for the sub-group analysis based on student's risk tolerance, the likelihood of vaccination increased with an increase in perception of risk, and vaccination utility decreased when percentage of acquaintances increased from 30 to 60%, revealing a free rider problem where individual vaccination preferences are affected by the vaccination decisions of acquaintances around them. In particular, high percentages of acquaintances vaccinated may demotivate students to vaccinate, resulting in low vaccination utility, as they can benefit from herd immunity while avoiding the cost of vaccination themselves (36). In addition, when compared to the baseline, vaccine effectiveness at the 60% level surprisingly reduced both cohort's utility, and the 85% effective level was not statistically significant for both cohorts.

We also observed preference heterogeneity for vaccine effectiveness, vaccination sites, duration of protection and acquaintances vaccinated when dividing our student population by risk tolerance. Risk tolerant students preferred township community health station sites over higher level three county hospital vaccination sites, and exhibited no significant preference between vaccines with 6 months protection or 2 years of protection. By contrast, students who were risk adverse preferred to be administered vaccines at third level county hospitals and had clear preferences for vaccines with longer duration of protection compared to the baseline 6 month of protection. Having high percentages (90%) of acquaintances vaccinated did not statistically

TABLE 4 Conditional logit model of respondent preferences.

Attribute	β	SE	p-Values	95% CI
Vaccine effectiveness (reference = 40%)				
60%	0.423	0.036	0.000	0.351, 0.494
85%	0.806	0.041	0.000	0.727, 0.886
Vaccine-related side effects (reference = 50/100,000)				
10/100,000	0.251	0.035	0.000	0.182, 0.320
1/100,000	0.432	0.037	0.000	0.358, 0.507
Vaccination sites (reference = Level 1)				
Level 2	0.141	0.037	0.000	0.067, 0.214
Level 3	−0.067	0.036	0.063	−0.138, 0.004
Duration of vaccine protection (reference = 6 months)				
1 year	0.245	0.037	0.000	0.173, 0.316
More than 2 years	0.350	0.036	0.000	0.279, 0.421
Acquaintances vaccinated (reference = 30%)				
60%	0.031	0.037	0.409	−0.042, 0.103
90%	0.093	0.037	0.011	0.021, 0.165
The probability of respondents/acquaintances infected (reference = 1/100,000)				
6/100,000	0.221	0.037	0.000	0.148, 0.293
100/100,000	0.346	0.036	0.000	0.274, 0.417
Model fit				

Prob > chi^2 = 0.000, Pseudo R^2 = 0.1024, LR $chi^2(13)$ = 1,292.28, AIC = 1,1352.54, BIC = 1,1446.26.

effect risk tolerant students' vaccination preferences, but did have a positive effect on risk adverse students' vaccination uptake.

Discussion

Comprising both intrinsic and extrinsic attributes, our study is the first DCE study to investigate mainland Chinese university student vaccination preferences. We found that students preferred vaccines which had fewer side-effects, had longer duration of protection and administered through second or third level health facilities. In addition, the perception of higher risks of infection generally lead to higher vaccine uptake. These results are broadly consistent with previous DCE studies on the general public (16–18). Notably, students exhibited vaccination free riding issues at the 60% level, which had not been reported by any other DCE studies, and free riders were a significant problem for the risk adverse student subgroup. From the β coefficients of the CLM, we observe that safety, duration of protection and perception of risk were the three most influential attributes. When compared against studies conducted on the general public before the implementation of China's 2021 vaccination program, we observe that duration of protection has become more influential relative to intrinsic vaccine attributes such as safety and effectiveness (17). This is consistent with findings of studies conducted on the general public after China's 2021 vaccination program (18). However, the Hong Kong based student surveys reported that duration of protection was the least influential attribute (29, 30), perhaps due to the different vaccination contextual backgrounds, such as low trust in government (37) and varying policy settings, which makes inferring the Hong Kong results to mainland Chinese vaccination policies potentially misleading.

Mixed logit models demonstrated clear preference heterogeneity for vaccine intrinsic attributes among students. To better analyze the underlying preference disparities, we conducted sub-group analysis based on student majors (humanities/social science or non-humanities/social science) and risk tolerance (risk tolerant or risk adverse). Our results support previous online survey studies which reported that there are no statistically significant relationships between student majors and vaccine preferences (26). Given our academic major data are social science and non-social science, our results do not contribute to the prior findings that medical and nursing students had higher vaccine willingness than other students due to higher knowledge levels and better perception of vaccines (28, 38). When stratifying the population by risk tolerance, we observed that risk tolerant students exhibited preferences distinct to the risk adverse cohort. In particular, risk tolerant students showed no trade-off in utility between 6 months and 2 years of vaccine protection. In contrast to the whole student population, and consistent

TABLE 5 Mixed logistic regression models of student preferences.

Variables	Coefficients	SE	*p*-Values	95% CI
Mean				
Vaccine effectiveness (reference = 40%)				
60%	−0.240	0.041	0.000	−0.320, −0.160
85%	−0.082	0.0481	0.087	−0.177, 0.012
Vaccine-related side effects (reference = 50/100,000)				
10/100,000	0.695	0.042	0.000	0.612, 0.778
1/100,000	1.027	0.050	0.000	0.928, 1.126
Vaccination sites (reference = level 1)				
Level 2	0.131	0.042	0.002	0.048, 0.214
Level 3	0.166	0.045	0.000	0.078, 0.255
Duration of vaccine protection (reference = 6 months)				
One year	0.488	0.042	0.000	0.405, 0.570
More than 2 years	0.311	0.042	0.000	0.228, 0.393
Acquaintances vaccinated (reference = 30%)				
60%	−0.381	0.041	0.000	−0.461, −0.300
90%	0.167	0.042	0.000	0.085, 0.249
The probability of respondents/acquaintances infected (reference = 1/100,000)				
6/100,000	0.318	0.042	0.000	0.236, 0.400
100/100,000	0.590	0.043	0.000	0.505, 0.675
SE				
Vaccine effectiveness (reference = 40%)				
60%	0.012	0.108	0.914	−0.201 0.224
85%	0.412	0.090	0.000	0.234, 0.589
Vaccine related side-effects (reference = 50/100,000)				
10/100,000	0.417	0.083	0.000	0.254, 0.580
1/100000	0.015	0.324	0.963	−0.620, 0.650
Vaccination sites (reference = level 1 village community health station)				
Level 2	0.510	0.078	0.000	0.357, 0.663
Level 3	0.827	0.071	0.000	0.687, 0.966
Duration of vaccine protection (reference = 6 months)				
One year	0.202	0.169	0.232	−0.130, 0.534
More than 2 years	0.518	0.073	0.000	0.375, 0.662
Acquaintances vaccinated (reference = 30%)				
60%	0.173	0.186	0.353	−0.192, 0.537
90%	−0.002	0.088	0.978	−0.174, 0.169
The probability of respondents/acquaintances infected (reference = 1/100,000)				
6/100,000	−0.027	0.117	0.817	−0.257, 0.203
100/100,000	0.502	0.080	0.000	0.346, 0.659

with previous findings for the general public (18), risk tolerant students preferred to be administered vaccines at second level medical centers over third level county hospitals. One possible explanation is that the need for convenience triumphs over perceived vaccination administration risks at second level health facilities (18).

There are some limitations of our study. The sampling of this study occurred concurrently with the DCE survey for the Qingdao general public (18). Compared to online surveys, our study was a DCE conducted face-to-face, but due to the COVID-19 travel and social restrictions, our data was limited to one city in China. Further student DCE studies should be undertaken in other cities. In addition, our sampling at vaccination centers may leave out those who are vaccine hesitant and future studies should focus on determining factors that can motivate these populations. While acknowledging face-to-face

TABLE 6 Sub-group analysis for student majors.

Attribute	β	SE	p-Values	β	SE	p-Values
Sub-group	Social sciences			Non-social sciences		
Vaccine effectiveness (reference =40%)						
60%	−0.151	0.048	0.001	−0.137	0.041	0.001
85%	0.052	0.051	0.311	−0.0270	0.044	0.541
Vaccine related side-effects (reference = 50/100,000)						
10/100,000	0.538	0.049	0.000	0.596	0.043	0.000
1/100,000	0.772	0.052	0.000	0.901	0.044	0.000
Vaccination sites (reference = level 1 village community health station)						
Level 2	0.104	0.051	0.040	0.168	0.048	0.000
Level 3	0.144	0.047	0.002	0.187	0.041	0.000
Duration of vaccine protection (reference = 6 months)						
One year	0.387	0.050	0.000	0.404	0.044	0.000
More than 2 years	0.166	0.048	0.001	0.231	0.042	0.000
Acquaintances vaccinated (reference = 30%)						
60%	−0.282	0.049	0.000	−0.385	0.043	0.000
90%	0.100	0.048	0.038	0.096	0.042	0.021
The probability of respondents/acquaintances infected (reference = 1/100,000)						
6/100,000	0.245	0.050	0.000	0.281	0.044	0.000
100/100,000	0.476	0.047	0.000	0.503	0.040	0.000

TABLE 7 Sub-group analysis for student risk preferences.

Attribute	β	SE	p-Values	β	SE	p-Values
Sub-group	Risk adverse			Risk tolerant		
Vaccine effectiveness (reference=40%)						
60%	−0.181	0.036	0.000	0.140	0.090	0.117
85%	−0.039	0.038	0.303	0.296	0.098	0.003
Vaccine related side-effects (reference=50/100,000)						
10/100,000	0.621	0.037	0.000	0.357	0.092	0.000
1/100,000	0.881	0.039	0.000	0.568	0.098	0.000
Vaccination sites (reference = level 1 village community health station)						
Level 2	0.125	0.038	0.001	0.318	0.098	0.001
Level 3	0.218	0.035	0.000	0.168	0.090	0.063
Duration of vaccine protection (reference = 6 months)						
One year	0.395	0.037	0.000	0.396	0.095	0.000
more than 2 years	0.234	0.036	0.000	0.050	0.092	0.591
Acquaintances vaccinated (reference = 30%)						
60%	−0.303	0.037	0.000	−0.443	0.098	0.000
90%	0.133	0.036	0.000	0.014	0.091	0.875
The probability of respondents/acquaintances infected (reference = 1/100,000)						
6/100,000	0.248	0.038	0.000	0.437	0.097	0.000
100/100,000	0.459	0.035	0.000	0.587	0.089	0.000

interviews may risk social desirability bias, especially for distrust of government or risk aversion items, our trained interviewers and privacy protocols attenuated this problem. We collected limited information with regard to student majors, and future studies should collect more detailed data on student majors.

Conclusion

Students have been identified as a major risk group during the 2022 outbreaks of COVID-19 in China. Our DCE study investigated Qingdao university student vaccination preferences for both intrinsic and extrinsic attributes. We found that most students exhibited preferences similar to the general public, but risk tolerant students exhibited clear preference heterogeneity for vaccination sites and duration of protection. In addition, our results revealed free riding issues, where high vaccination rates among acquaintances reducing the intention to vaccinate, especially for risk adverse subgroup students.

Our results inform universities and local governments across China on the implementation of their vaccination programs, especially for students. Understanding the existence of vaccination free riding and preference discrepancies between student sub-groups guide local governments to targeted COVID-19 vaccination campaigns for younger people and subsets of students. We recommend on-campus vaccination education programs to provide targeted messaging for different student cohorts, especially to address the risk of free riding. Such targeted programs are urgent with the return to on-campus teaching and to attenuate the risk of COVID-19 resurgence.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Nanjing Medical University Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

Author contributions

SW and AL contributed to the conception, design, and methodology of the manuscript. SW wrote the initial draft of the preparation, conducted the formal analysis of the data, including data curation, and visualization. EM, SN, AL, and TW contributed to the manuscript revision and supervision. AL contributed to the project's administration, data collection, and funding acquisition. All authors read and approved the final version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Parental preference for Haemophilus influenzae type b vaccination in Zhejiang Province, China: A discrete choice experiment

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Background: China is the only country in the world that has not included the Haemophilus influenzae type b (Hib) vaccine in its National Immunization Program, making it more difficult to eliminate Hib-related diseases through Hib vaccination. It is necessary to study parental preferences for Hib vaccination to optimize vaccine promotion strategies in China.

Objective: This study aimed to investigate Chinese parental preference for five attributes of Hib vaccination, i.e., the place of origin, effectiveness, adverse event, doctors' recommendation, and the price of full vaccination when making a decision to vaccinate their children under 2 years old.

Methods: A cross-sectional survey was conducted in two cities in Zhejiang Province from November to December in 2020 using a discrete choice experiment (DCE). A mixed logit model was used to estimate participating parents' preference for Hib vaccination attributes included in the DCE. Subgroup analysis and probability analysis were also conducted to capture the heterogeneity and trade-off of parental preference for Hib vaccination.

Results: Data from 6,168 observations were included in the analyses. Parents of children are, on average, more likely to voice a positive preference for Hib vaccination. Such attributes of Hib vaccination as effectiveness and doctor's recommendation have a significant positive influence on parents' preference for Hib vaccination, while imported vaccines, adverse events, and the price of full vaccination have a significant negative influence on parents' preference. Parents with different demographic characteristics also existed heterogeneities in preference for Hib vaccination. Parents will make a trade-off on price if the Hib vaccine has a good performance on effectiveness and safety.

Conclusion: The study found that, regardless of the place of origin of the Hib vaccine, parents with children under 2 years old prefer to compromise on price if the vaccine has a better effectiveness and safety profile. A proactive recommendation from doctors would strengthen their willingness for Hib vaccination. These findings help aid the development of communication strategies with parents for Hib vaccination in China.

KEYWORDS

Hib vaccination, discrete choice experiment, parental preference, mixed logit model, Chinese parents, immunization policy

Introduction

Haemophilus influenzae type b (Hib), a gram-negative cocobacillus bacterium, occurs mainly in children under 5 years of age (especially in children under 2 years of age) and is a common cause of morbidity and mortality in this group of children (1). Globally, ~8 million cases of pneumonia and meningitis and 371,000 deaths are attributed to Hib each year (2), which raises certain challenges for global public health. In China, the pooled carriage of Hib among healthy children in China is 5.87% (3), results from a study of PCR testing of nasopharyngeal secretions (NPS) in Zhejiang Province among children diagnosed with respiratory infections show a positive rate of Hib of 18.49% (4).

Vaccination has long been the most cost-effective means of preventing and controlling infectious diseases (5). Currently, Hib conjugate vaccines have the potential to reduce overall mortality in children by 4% (6). Thus, Hib vaccination is recognized as an effective way to prevent Hib infection, which has been reported regardless of the level of development and economic status of many countries (1, 7). The widespread use of the Hib vaccine worldwide has reduced the number of children who die from Hib infection by over 90% and is expected to eliminate Hib-related diseases (8). Despite the effectiveness of Hib vaccination in preventing Hib, many cases of invasive Hib disease are still reported each year due to unvaccinated, failed vaccinations, etc. Hib vaccine has a low vaccination rate according to available statistics from Immunization Program Information System in China (9), which has been well below the world average (10). As of 2016, the third dose of the Hib vaccine in China has been < 30%, while the global average reached about 70% (9).

China is currently the only country that has not included the Hib vaccine in its National Immunization Program (NIP) and is among the four countries with the highest number of Hib-related deaths worldwide (11). Specifically, vaccines provided to citizens in China are broadly divided into National Immunization Program (NIP) vaccines and Non-Expanded National Immunization Program (non-NIP) vaccines, where NIP refers to vaccines that the government provides free of charge to citizens and that citizens should be vaccinated in accordance with government regulations; NENPI, also known as category II vaccines, refers to other vaccines that are vaccinated by citizens at their own expense and on a voluntary basis. China has now expanded NIP (including one dose of Bacille Calmette-Guerin vaccine, four doses of the oral live attenuated polio vaccine, etc.) and NIP vaccination rates have reached high levels (12). On the contrary, although non-NIP vaccines play an important role as a supplement or limited alternative to NIP in controlling the corresponding infectious diseases and meeting the health needs of different populations, the voluntary and out-of-pocket nature of non-NIP results in a low vaccination rate (13). Chinese children's parents need to pay for Hib vaccination out of their own pocket, and if other factors interfere, which will undoubtedly lead to an insufficient vaccination rate compared with other countries (13, 14). Of all the vaccines in non-NIP, Hib vaccine coverage is relatively low in China compared with other non-NIP vaccines with similar costs, such as the varicella vaccine (15).

The Changchun Changsheng vaccine incident (CCVI, a vaccine safety and quality event that occurred in Changchun, China in 2018) that occurred in 2018 has caused Chinese parents to become more concerned about vaccinations, and more and more parents are proactively searching for information about the non-NIP vaccine online to determine whether to get their children vaccinated (16). Whereas, prior to the incident, parental decisions for uptake non-NIP vaccines were mainly informed by the recommendation of doctors or friends (14). The Chinese government has issued the Vaccine Administration Law following CCVI that requires doctors to communicate adequately with guardians or recipients during the vaccination process (see Article 45 of the Vaccine Administration Law)[1]. Specifically, doctors must communicate more with guardians prior to vaccination so that guardians know more about the

1 The National People's Congress of the People's Republic of China. Vaccine Administration Law of the People's Republic of China. 2019. Available online at: http://www.npc.gov.cn/npc/c30834/201907/11447c85e05840b9b12c62b5b645fe9d.shtml (accessed 30 September 2022).

vaccine and vaccination and to confirm that their choice to vaccinate their child is well-informed. In the case of non-NIP vaccines, doctors need to introduce more detail about the vaccine and the benefits of vaccination to ensure that the parent's decision to vaccinate is voluntary. These regulations will enhance parents' awareness of vaccines and potentially change their vaccination habits. It is, therefore, necessary to investigate parental preference of Hib vaccination, which can guide health care professionals to start structuring vaccine conversations with parents.

Discrete choice experiment (DCE), a quantitative attribute-based survey method, is widely used in public health to assess community views and preferences and to measure benefits (utility) (17, 18). The result of DCE can assist policymakers in understanding which characteristics or features of public health programs citizens have the highest preferences (17, 18). Existing studies have widely applied DCE to investigate preferences for different vaccines [COVID-19 vaccination (19), human papillomavirus vaccination (20), infant meningococcal vaccination (21), etc.] on numerous characteristics (effectiveness, cost, etc.). Rare studies applied this method to look at the factors influencing parental preference for Hib vaccination.

In this study, we aim to look at factors affecting the preferences of parents with children aged under 2 years old for Hib vaccination in Zhejiang Province, and conduct a systematic analysis of parental preferences through subgroup analysis drawing on the theory of DCE. To the best of our knowledge, this study represents the first DCE work to investigate parental preference for Hib vaccination in China. As mentioned above, the background that the Hib vaccine was not included in the Chinese NIP and the increased awareness of parents about vaccination encourages us to explore parent preferences for Hib vaccination based on the current situation, which serves as a stepping stone for future research in Hib vaccination in China. The second objective of our study is to propose several insights and policy advice in terms of effectiveness, adverse events, doctor's recommendations, and place of origin of Hib vaccines based on the results of all analyses, which can provide a reference for adjusting and optimizing Hib vaccine immunization strategies in China in the future.

Materials and methods

Sampling and study population

This study was conducted in two cities of Shaoxing and Wenzhou in Zhejiang, a developed province in the east of China. And then two districts/counties with per capita GDP ranking in the upper and lower quartiles (P_25, P_75) in 2019 and providing Hib vaccines were selected from each city. Four vaccination clinics were then selected by convenient sampling (i.e., two from the rural area and two from the urban area) in each district/county. Priority is given to vaccination clinics that can supply both domestic and imported Hib vaccines. A total of 16 vaccination clinics were invited to participate in the study. The survey was administered online *via* Wenjuanxing (WJX, https://www.wjx.cn/), an online survey company in China between November and December of 2020. Father or mother of children under age 2 (i.e., born between November 1st of 2018 and November 1st of 2020) was recruited in the observation room after routine vaccination with informed consent, and grandparents and other family members of children were excluded. The sample size was determined according to the equation of $N > 500 \times \frac{c}{(t \times a)}$ (17), where the largest number of levels c among different attributes in this study was 4, and the number of choice sets t and the number of alternatives in each set a was 8 and 2, respectively. Therefore, the minimum value of N could be estimated as $(500 \times 4)/(8 \times 2) = 125$. To ensure that a sufficient number of valid questionnaires are collected, we invited 120 parents in each city (i.e., 15 parents in each vaccination clinic) to file the questionnaire. The study was approved by the *Chinese Center for Disease Control and Prevention Institutional Review Board (#201944).*

Experiment and questionnaire design

In the discrete choice experiment, participants are asked to complete a series of questions, and each of which corresponds to a hypothetical scenario (22). Each scenario contains 2 or more attributes with different definitions that have different levels. After the participant understands each attribute and its level in a hypothetical scenario, they need to make a choice between 2 or more options. Participants' preferences for the different levels of each attribute and their willingness to make trade-offs between attributes can be analyzed according to their choices across multiple scenarios (18).

Following methodological guidelines of DCE (23), we first identified the important attributes and levels that influence parental preference for Hib vaccination through a literature review related to Hib vaccination. A study in Thailand, one of the last countries to include the Hib vaccine in the NIP, also found that despite the low burden of Hib-related disease in the country, the adverse event and effectiveness of the vaccine still had a significant influence on parental preference for Hib vaccination (24). Furthermore, although Pneumococcal Conjugate Vaccine (PCV), as a non-NIP vaccine in China, has a higher price than the Hib vaccine, vaccination rates in economically developed Shanghai showed that much higher rates for the first dose of the Hib vaccine significantly lower than the PCV vaccine (25). Accordingly, the factors besides price such as parental knowledge about Hib vaccination and whether or not a doctor recommends it, also are major factors underlying the low coverage (26–29). Based on previously published

TABLE 1 Attributes and levels on the discrete choice experiment.

Attribute	Definition	Attribute level
Place of origin	Type of vaccine manufacturer	Domestic product
		Imported product
Effectiveness (%)	The percentage of children that will be protected against a Hib infection when vaccinated	75%
		85%
		95%
Adverse event	The percentage of vaccinated children that will suffer from severe side effects due to Hib vaccination	5/1 million doses (low adverse event)
		15/1 million doses (moderate adverse event)
		25/1 million doses (high adverse event)
The price of full vaccination	Price per child for full Hib vaccination	200 yuan
		400 yuan
		600 yuan
		800 yuan
Doctor's recommendation	Whether doctors recommend vaccinations for children	Recommendation
		No recommendation

TABLE 2 Attributes and levels on the discrete choice experiment.

Attribute	Hib vaccine A	Hib vaccine B
Place of origin	Imported product	Domestic product
Effectiveness (%)	85%	75%
Adverse events	5/1 million doses (Low)	25/1 million doses (High)
The price of full vaccination	800 yuan	400 yuan
Doctor's recommendation	No recommendation	Recommendation
First stage: Which vaccine would you prefer?	☐	☐
Second stage: In reality, would you vaccinate your child with the option you chosed above?	YES	
	NO	

literature regarding DCE studies on vaccination (27–30), we initially identified 17 attributes, which may influence vaccination decisions. In addition, we conducted face-to-face interviews with 17 key stakeholders (i.e., 4 experts from the national, provincial, and local Center for Disease Control and Prevention, 4 vaccination clinic staff, 8 parents of children, and 1 expert from the DCE field) to assess the appropriateness of attributes and its levels, and rank the attributes by the order of importance. Finally, we selected five attributes, i.e., the place of origin, effectiveness, adverse event, the price of full vaccination, and doctor's recommendation. The levels of these five attributes are listed in Table 1.

After defining the attributes and attribute levels, the relative importance of these attributes in the view of parents was evaluated by offering two different vaccination choices with different combinations of attribute levels. Among the five determined DCE attributes, two attributes have two levels, two attributes have three levels and one attribute has four levels, thus 144 possible scenarios ($2^2 \times 3^2 \times 4^1$) and a total of 10,296 possible pair-wise choices ($\frac{144\times143}{2}$) were generated in a full factorial design. Based on the DCE design package in SAS software, 24 manageable choice sets were obtained using a sequential orthogonal factorization design technique. To minimize the cognitive burden on participants, the 24 choice sets were further divided equally into three blocks, and each block included 9 pair-wise choice sets. In each block, two choice scenarios (pairs 2 and 9) were set to be the same for checking whether the data met internal consistency, i.e., whether the participants made the same answer for the two choice scenarios.

To maximize the information received from the participants, a pair-wise binary two-stage response DCE design was applied in this study following Marshall et al. (31) and Cheng et al. (32). In the first stage, each participant was asked to choose the preferred choice from two alternative vaccination options. Subsequently, in the second stage, each participant was further confirmed whether they would, in reality, vaccinate their child with the Hib vaccine selected in stage 1. Table 2 shows the example of a choice set, and each participant was asked to respond in both stages.

In the final version of the electronic questionnaire, the socio-demographic characteristics of participants and their knowledge about the Hib vaccine were collected in addition to the designed DCE questions, and the questionnaire is included in the Supplementary material.

Survey and data collection

After completing the questionnaire design, a pilot study was conducted to check the comprehensibility, acceptability, and effectiveness of the electronic questionnaire prior to the formal study, and the existing problems were further addressed in the formal study.

The subjects of this study were only the father or mother of the children aged 0–2 years (born on or after November 1st, 2018), excluding grandparents and other family members, and the whole investigation process was divided into two stages: pre-investigation and formal investigation. To check the comprehensibility, acceptability, and effectiveness of the complete electronic questionnaire, the convenience sampling method was adopted in the pre-investigation stage. A vaccination clinic in Beijing (Jianwailang Home Community Health Service Center, Chaoyang District, Beijing) was selected to carry out the pre-investigation, and the existing problems in the pre-investigation were further modified.

In the process of investigation, for each participant, a professional investigator would give one-on-one guidance to each participant to scan the QR code of the electronic questionnaire and fill in it by using mobile phones or other convenient mobile devices. Specifically, the team of investigators was formed by the vaccination clinic itself, and they need to be uniformly trained to be competent for this investigation. Each investigator works on three tasks: First, the significance of the investigation, the DCE questions, and other questions should be explained in detail to each participant. Secondly, before filling in the questionnaire, the investigator should explain the contents of the informed consent, and inform the participants that the questionnaire will be filled out anonymously, and the relevant information will not involve personal privacy and confirm the participants' willingness to participate in this investigation. For participants who agree to participate in this investigation, they should be asked to fill out the questionnaire truthfully. Finally, the investigator should fill in the vaccination clinic code correctly so that the number of completed questionnaires for each clinic can be checked in real-time in the database, and the questionnaire administration time for each participant should be limited to 20–30 min. After the successful completion of the pre-investigation, a formal investigation was carried out in 16 vaccination clinics in Zhejiang Province.

Statistical analysis

We used a most promising state-of-the-art discrete choice model, the mixed logit model (20, 30, 33), to estimate parental preferences for the different levels of attributes. It considered repeated choices by the same participant and allowed for random coefficients at the respondent level. Participants' preferences for all levels of each attribute (including the reference group) were estimated using effect coding. Specifically, the mixed logit model is constructed based on a random utility theory framework. The utility for the participant i derives from choosing alternative j in choice scenario t can be calculated as follows:

$$U_{ijt} = X_{ijt}\beta_i + \varepsilon_{ijt}$$

where X_{ijt} denotes a vector of observed attributes of alternative j in choice scenario t (i.e., Hib vaccination preferences attributes and corresponding levels); β_i represents a vector of individual-specific coefficients that reflect the preferability of the attributes; the multiplication of X_{ijt} and β_i represents the fixed utility of participant i choosing alternative j in choice scenario t; ε_{ijt} denotes a random utility of participant i choosing alternative j in choice scenario t.

Among the five designed DCE attributes, the price is coded as a continuous variable and the other four attributes are coded as dummy variables. Thus, the utility U_{ijt} that participant i derives from choosing alternative j in choice scenario t can be calculated as:

$$\begin{aligned} U_{ijt} = {} & \beta_0 \textit{imported product} + \beta_1 \textit{effect } 85 + \beta_2 \textit{effect } 95 \\ & + \beta_3 \textit{moderate adverse event} + \beta_4 \textit{high adverse event} \\ & + \beta_5^{*} \textit{recommendation} + \beta_6 \textit{price} + \beta_7 \textit{ASC\_None} + \varepsilon_{ijt} \end{aligned}$$

In the equation, *ASC_None* is an alternative specific constant for choosing not to vaccinate (i.e., opt-out) (34), and the reference group is set up as follows: imported product, effectiveness with 75%, low adverse event, and no recommendation for the doctor' advice.

We first estimated the main effects mixed logit model to assess parental preferences for the different levels of attributes compared with the reference group. To consider preference heterogeneity, each coefficient was presented as having a mean and a standard deviation, and the mean denotes the overall average preference, and the standard deviation is the individual-specific preference. We also performed subgroup analyses from 4 perspectives to capture differences in Hib vaccination preferences among participants with different characteristics (child residence, parental highest educational attainment, occupation, past history of experiencing adverse events for child). Results from the main effects mixed logit model was also employed to analyze the percentage change in the probability of choosing that specific alternative compared to the base alternative by changing the level of a given attribute. Initial data obtained from the electronic questionnaires were pre-processed using Python software, and all analyses were performed using Stata 15.

TABLE 3 Demographic characteristics.

Demographic information	All samples		Consistent samples		Inconsistent samples		Statistical performance	
	$n = 257$		$n = 219$		$n = 38$			
	n	%	*n*	%	*n*	%	chi-squared	*p*-value
Parent							0.494	0.482
Relationship with child								
Father	44	17.1	39	17.8	5	0.1		
Mother	213	82.9	180	82.2	33	0.9		
Highest education attainment							3.666	0.453
Junior high school and below	40	15.6	35	16	5	0.1		
High school	60	23.3	55	25.1	5	0.1		
College	74	28.8	60	27.4	14	0.4		
Bachelor	82	31.9	68	31.1	14	0.4		
Master and above	1	0.4	1	0.5	0	0		
Age, years old							0.287	0.866
<25	28	10.9	23	10.5	5	0.1		
25–34	184	71.6	157	71.7	27	0.7		
≥35	45	17.5	39	17.8	6	0.2		
Occupation							0.721	0.396
Healthcare related profession	36	14	29	13.2	7	0.2		
Non-healthcare related profession	221	86	190	86.8	31	0.8		
Monthly income/per[a]							6.893	0.229
<¥2,500	19	7.4	19	8.7	0	0		
¥2,500 – ¥4,999	49	19.1	42	19.2	7	0.2		
¥5,000 – ¥9,999	116	45.1	95	43.4	21	0.6		
¥10,000 – ¥19,999	47	18.3	40	18.3	7	0.2		
¥20,000 – ¥34,999	12	4.7	12	5.5	0	0		
≥¥35,000	14	5.4	11	5	3	0.1		
Gender							0.659	0.417
Boy	117	45.5	102	46.6	15	0.4		
Girl	140	54.5	117	53.4	23	0.6		
Residence							0.497	0.974
Urban	86	33.5	73	33.3	13	0.3		
Rural	125	48.6	107	48.9	18	0.5		
Mobility	30	11.7	25	11.4	5	0.1		
Not available	11	4.3	10	4.6	1	0		
None	5	1.9	4	1.8	1	0		
Birth order							0.756	0.685
First born	144	56	123	56.2	21	0.6		
Second born	109	42.4	92	42	17	0.4		
Third born	4	1.6	4	1.8	0	0		
Past history of experiencing adverse events following vaccination							3.097	0.078
Yes	48	18.6	37	16.9	11	28.9		
No	209	81.3	182	83.1	27	71.1		

[a] ¥1 = $ 0.1565 (November 9, 2021).

Results

Study participants

A total of 257 parents of children aged 0–2 years old participated in the study. To ensure internal consistency of the data, i.e., the participants filled in the electronic questionnaire rationally, the results of the choice test for all participants in the duplicated choice tasks were examined, and 38 out of all participants failed in the consistency test. The characteristics of participating parents and their children are shown in Table 3. Based on comparisons with demographic characteristics of participants, there are no statistically significant differences between the participants who failed in the consistency test and those who passed the consistency test. A total of 219 participants who passed the consistency test were included in the data analysis. Most participants were mothers of children, aged between 25 and 34 years, had attained high educational attainment, had earned between 5,000 RMB (yuan) and 9,999 RMB (yuan) monthly, employed by non-healthcare institutions. Fewer children of the participants who were transient population, third child, had experienced adverse events in previous vaccinations.

Parental preferences for Hib vaccination

To determine whether there is a difference in the DCE results based on all samples (i.e., consists of consistent samples and inconsistent samples) and consistent samples, we constructed mixed logit models in these two different

TABLE 4 Mixed logit estimates on Hib vaccination preferences.

Attribute	Consistent samples				All samples			
	β^i	SE	95% CI		β^i	SE	95% CI	
Mean								
***Place of origin:* domestic product (ref.)**								
Imported product	−0.189	0.129	−0.442	0.064	−0.122	0.109	−0.335	0.091
***Effectiveness (%):* effectiveness 75% (ref.)**								
Effectiveness 85%	0.799***	0.116	0.573	1.026	0.760***	0.104	0.555	0.964
Effectiveness 95%	2.061***	0.193	1.683	2.439	1.913***	0.166	1.589	2.238
***Adverse events:* low adverse event (ref.)**								
Moderate adverse event	−0.725***	0.129	−0.977	−0.473	−0.659***	0.112	−0.879	−0.440
High adverse event	−1.168***	0.150	−1.463	−0.874	−1.073***	0.129	−1.326	−0.819
***Doctor's recommendation:* Not recommended (ref.)**								
Recommended	0.468***	0.119	0.235	0.701	0.431***	0.105	0.226	0.636
Price	−0.001***	0.000	−0.001	0.000	−0.001***	0.000	−0.001	0.000
ASC (opt-out)	−9.284***	1.369	−11.967	−6.601	−9.560***	1.388	−12.280	−6.840
SD								
***Place of origin:* domestic product (ref.)**								
Imported product	1.479***	0.160	1.165	1.794	1.290***	0.131	1.033	1.547
***Effectiveness (%):* effectiveness 75% (ref.)**								
Effectiveness 85%	−0.035	0.163	−0.355	0.284	0.016	0.155	−0.288	0.321
Effectiveness 95%	1.586***	0.185	1.225	1.948	1.511***	0.167	1.183	1.839
***Adverse events:* low adverse event (ref.)**								
Moderate adverse event	−0.013	0.171	−0.348	0.323	0.045	0.175	−0.299	0.389
High adverse event	−0.407	0.270	−0.936	0.121	0.473	0.260	−0.036	0.981
***Doctor's recommendation:* no recommendation (ref.)**								
Recommendation	1.254***	0.143	0.974	1.533	1.176***	0.126	0.929	1.423
Price	0.002***	0.000	0.001	0.003	−0.002***	0.000	−0.003	−0.001
ASC (opt-out)	5.791***	0.739	4.342	7.240	6.527***	0.896	4.771	8.282
Samples		219				257		
Observations		5,256				6,168		
Log-likelihood		−1,082.9447				−1,308.6328		

i: **p*-value < 0.10; ***p*-value < 0.05; ****p*-value < 0.01.

datasets, respectively. Both models achieve convergence and their results are reported in Table 4, respectively. The main results were similar regardless of the inclusion or exclusion of the participants who did not pass the consistency test. Hence, we only analyze the DCE results based on the consistent samples as follows.

In the discrete choice analysis, the coefficients of four attributes (effectiveness, adverse events, doctor's recommendation, price) at all levels were significantly different from the reference group (p-value < 0.05), suggesting these four attributes were meaningful on parental preference for Hib vaccination (Table 4). On the contrary, the coefficient of imported products is not significantly different from domestic products revealing that it was not meaningful to participants on the preference of Hib vaccination.

The relative preferences of participants for different levels of attributes are important in explaining the experimental results of the DCE. The coefficient of effectiveness with different levels showed that the positive influence of effectiveness with 95% is greater than effectiveness with 85% compared with effectiveness with 75%. Similarly, the coefficient of adverse events with different levels showed that the negative influence of the high adverse event on parental preference for Hib vaccination is greater than the moderate adverse event. Parents also had strong preferences for Hib vaccination for doctor's recommendation and Hib vaccines with low price. Out of all five attributes, the adverse events exist homogeneous preferences (p-values > 0.05 in the estimated standard deviation of the mean coefficients), and the remaining four attributes all have unobservable preference heterogeneity. When we examined the coefficient of ASC-None, we found a significant negative influence. The result indicated that parents are, on average, more likely to voice a preference to choose Hib vaccination for their children, regardless of the level presented by the other attributes.

Variation in the parental preference for Hib vaccination

To capture differences in Hib vaccination preferences among participants with different characteristics, we performed subgroup analyses from 3 perspectives (occupation, parental highest educational attainment, past history of experiencing adverse events for child), and all results can be found in the Supplementary Tables A1–A3.

Subgroup analyses revealed several heterogeneities in preferences for Hib vaccination across the following perspectives (in the Supplementary Tables A1–A3). Unlike the overall results, the doctor's recommendation and price do not influence the parental choice for the Hib vaccination for their children who experienced adverse events in the past vaccinations, and only effectiveness and the adverse event can drive their decision. When parents are healthcare-related practitioners, their preference for Hib vaccination is influenced only by effectiveness and adverse events. Parents in other occupations are additionally influenced by price and doctor's recommendation in their preferences for Hib vaccination. Moreover, parents with junior high school education or below preferred domestic products. Among parents with a bachelor and above and children with adverse events in the past vaccinations the results showed that price and doctors' advice were not meaningful to them.

Probability analyses

Probability analysis, a simulation method, is also utilized to analyze the percentage change in the probability of choosing that specific alternative compared to the base alternative by changing the level of a given attribute. Figure 1 illustrates these changes from three perspectives: changes in price, changes in doctor's recommendation, and changes in effectiveness and adverse events. Taking Figure 1A as an example, the dark blue bars mean that the probability of participants choosing the Hib vaccine with risk_M drops by about 6, 16, and 26% when the cost changes under three different cases (from 800 to 200 yuan; from 800 to 400 yuan; from 800 to 600 yuan), respectively. The other bars can be understood in the same way.

In relation to the levels of price (as shown in Figure 1A), when the price drops by 200 from 800 yuan, parents are 29.13% more likely to be willing to accept a Hib vaccine with 75% effectiveness. When the doctor's recommendation changed from not recommending to recommending for Hib vaccination under different prices (800, 600, and 400 yuan), parents are 18.45, 39.33, and 63.70% more likely to choose Hib vaccination for their children, respectively (as shown in Figure 1B). For the trade-off between effectiveness and the adverse event (as shown in Figure 1C), parents are 85.23% more likely to be willing to trade a low adverse event for a vaccine with a high adverse event when the effectiveness of the vaccine is increased from 75 to 95%, and 46.42% more likely to be willing to trade 95% effectiveness for a vaccine with 75% effectiveness when the adverse event decreases from high to low.

Discussions

Principal findings

Among all non-NIP, Hib vaccine coverage is relatively low in China compared with other paid vaccines with similar costs [i.e., overall coverage of 61.1% for the full process varicella vaccination (15)]. In addition to the key factor that the Hib vaccine is part of non-NIP, there are a variety of other factors that come into play, such as parental knowledge, the cost of

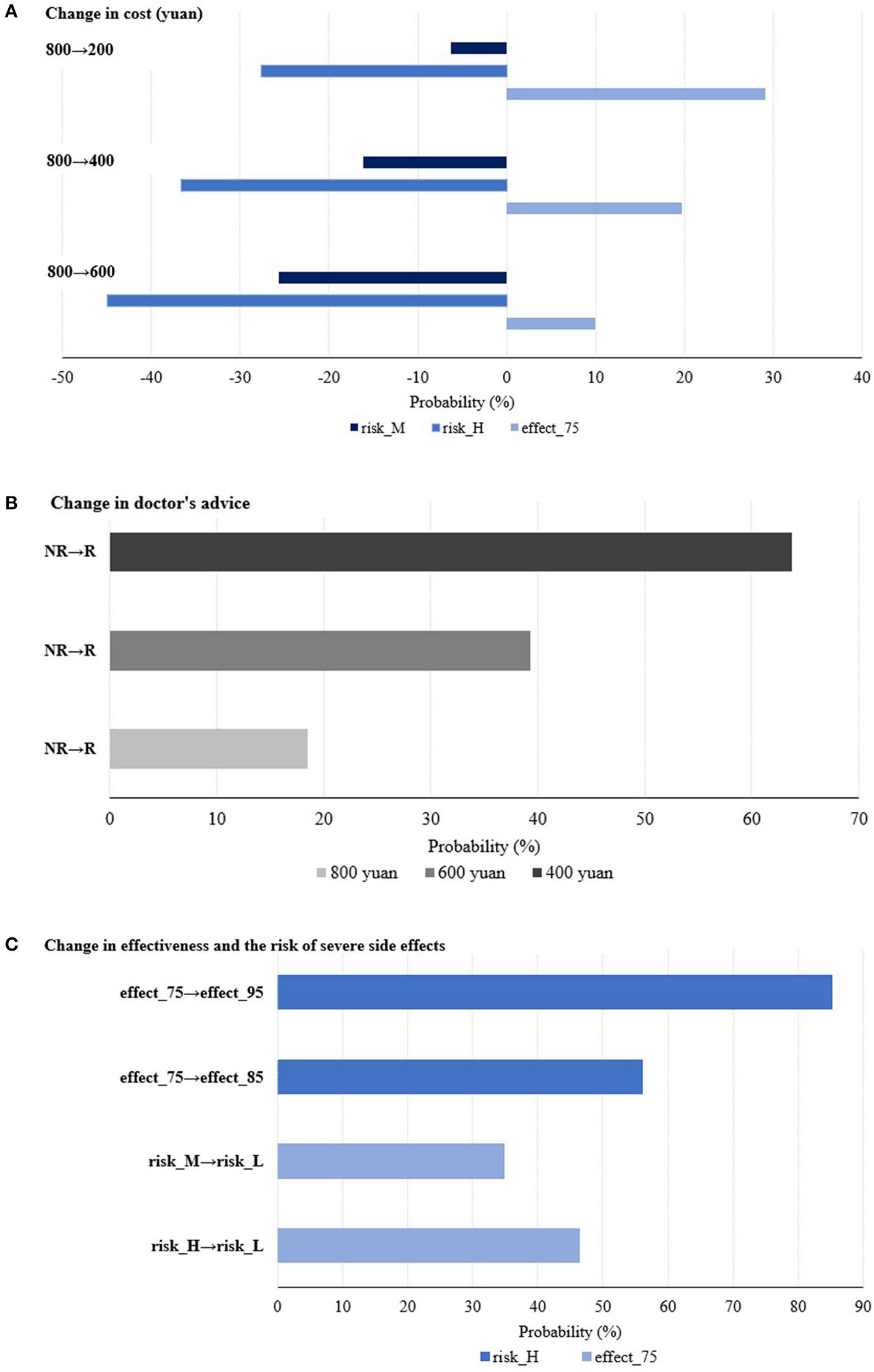

FIGURE 1
Simulated preferences for Hib vaccination under various potential cases.

the vaccine, and whether or not the doctor recommends it. Despite prior studies investigated the four vaccine attributes on people's preference for vaccination (20, 30, 31, 35), the doctors' recommendation was ignored. Due to the crisis of confidence caused by the CCVI event and the low awareness of the Hib vaccine among Chinese health care providers may lead to changes in parental preference for vaccination (36, 37), doctor's recommendation was also considered in our study. Therefore, this study investigated parental preferences for Hib vaccination on four vaccine attributes (origin of vaccines, effectiveness, adverse event and price) and one non-vaccine attribute (doctor's recommendation). The results show that even though the Hib vaccine requires payment, Chinese parental attitudes toward vaccinating their children with the Hib vaccine are still positive. This finding is similar to the result of other scholars on the willingness to vaccinate EV71 vaccines at a similar price (38). In line with the findings of existing studies (31), our study also shows that effectiveness and adverse event all have a significant influence on parental preference for Hib vaccination. However, our study reveals several new findings that doctor's recommendation has a significant positive influence, while imported vaccines do not influence parental preference for Hib vaccination.

Possible explanations and understandings

Results showed that the origin of the vaccine had no significant influence on parental preference for Hib vaccination, which deviates from our expectations and the findings of existing studies (39, 40). It could be influenced by complex factors such as increased positive media coverage of the vaccine prior to the investigation to counter the negative impact of CCVI. The finding could be a positive sign for the inclusion of the Hib vaccine in the NIP, there is after all only one imported Hib vaccine manufacturer in mainland China at present and it may be difficult to make the vaccination widely available. It is also a reminder that there is no need to deliberately emphasize the origin of the vaccine in the publicity of the vaccine.

We found that parents regard the effectiveness of the Hib vaccine as more important than its adverse event, contrary to the findings of a study by Chinese researchers on flu vaccines (41). Perhaps because their previous vaccination experience makes them unconvinced that the vaccine can have serious adverse events, and their perception of benefit from vaccination is not as clarified as that of medical professionals, they would prefer a Hib vaccine with more pronounced effectiveness. Regardless of parents' occupational and social roles, effectiveness and adverse events remained the two most important factors influencing parents' preference for Hib vaccination. Especially for parents whose occupation is healthcare-related, their preference for Hib vaccination is not influenced by the origin of the vaccine, doctor's recommendation and price, because they are more likely to make a choice based on their own cognitions. Additionally, for the price of Hib vaccination, parents will compromise on price due to effectiveness and safety. Lowering the price of the Hib vaccine would also assist in boosting its uptake, meaning that the NIP inclusion of the Hib vaccine in more economically developed or cost-effective areas is urgently needed.

Due to the crisis of confidence caused by the CCVI event and the low awareness of the Hib vaccine among Chinese health care providers (36, 37), the doctor's recommendation on the parental preference for Hib vaccination was also investigated. Previous non-NIP vaccination successes in China have largely been observed by parents following and trusting doctor's recommendations on vaccination (42, 43), similar findings were found in our study. But interestingly, the subgroup analysis showed that parents with higher socioeconomic levels are not significant to be influenced by doctor's recommendations, possibly because they have higher expectations of doctors' service capacity, suggesting the importance of doctors' improved service capacity. Adults' vaccination decisions are mostly irrational and behavioral interventions have influenced their vaccination preferences (44). So various pre-vaccination services should be used by doctors to recommend Hib vaccination and safety information to parents as in vaccination information packs for parents of newborns who are pregnant, parent education sessions held, etc., could be a very efficient intervention to increase Hib vaccination rates (45).

Factors, such as restrictions on the timing of Hib vaccination, the number of doses required, and the fact that the Department of Health does not assess non-NIP vaccination rates, may have led to the little incentive for doctors to recommend vaccines. Hib-containing combination vaccines or co-administration with other NIP vaccines has promoted the Hib vaccine coverage rate in China to a certain extent (46), which deserves further dissemination to change and optimize the current inflexible immunization strategy in China. Targeted incentives from the health sector are also needed to motivate doctors to proactively recommend Hib vaccination.

Implication for Chinese doctors and government

At present, Chinese citizens can only pay for the Hib vaccine, but it is very necessary to improve the coverage of the Hib vaccine in China. Therefore, the society and vaccination clinics should strengthen the publicity of the safety and effectiveness of the Hib vaccine and increase the enthusiasm of doctors to actively inform and recommend it (informing about the dangers of the disease caused by Hib and the benefits of Hib vaccination), which is a high guideline to increase the willingness to vaccinate with Hib vaccine (47). For the Chinese government, although the Hib vaccine is not included in NIP vaccines, it does not mean that Hib vaccination is not important and not advocated in China, in recent years the Chinese authorities have been attempting to develop plans to implement Hib vaccination in the NIP (46, 48). Therefore, we also call on government officials to make some changes based on the key findings from this study. First, with reference to foreign practices of periodic monitoring of the safety and quality of vaccines, government officials could adequately disclose the safety data and safety survey results of vaccines to ensure parents' confidence in the quality of domestic vaccines. Second, a relevant co-immunization with other vaccines policy from the authorities as soon as possible is also necessary. It would help avoid parents from missing or forgetting the Hib vaccination schedule due to repeated clinic visits, and it would also reduce to some extent the hindrance and concern of doctors in recommending the Hib vaccine. Finally, the Chinese government has, as a recent reform measure, allowed vaccination clinics to charge a fixed fee for medical services from parents who choose to have their children vaccinated with non-nip vaccines (see Article 49 of the Vaccine Administration Law)[1]. However, the and doctors are allocated only a small percentage of it, which is not conducive to doctors' initiative. Doctors may therefore be more motivated to recommend non-NIP vaccine if the fee allocation percenntage could be increased.

Limitations

In this study, the influence of parental attitudes and cognitions on Hib vaccination also is investigated through parental evaluation of individual attributes. We also effectively observe and analyze the trade-offs and decisions made by parents in Hib vaccine attribute changes using DCE according to their repeated choice results in various hypothetical scenarios. It is no denying that this study exists some limitations. Different from other similar studies (31, 49), we did not examine the parental willingness to pay for Hib vaccination. Because the current cost level of Hib vaccines produced by different manufacturers is 80–200 yuan/dose, which is at a relatively low level among the more popular paid vaccines. Thus, a study of willingness to pay on this basis can lead to some large errors. Additionally, due to the relatively low coverage rate of Hib vaccination in China, this study only surveyed the two cities with higher levels of disposable income in China (Wenzhou and Shaoxing). Admittedly, this work helps us to get positive results more efficiently, but the findings may be limited in extrapolation.

Conclusions

Effectiveness, adverse events, price and doctor's recommendation are significant attributes when parents are making the decision of whether to choose Hib vaccination for their child. Chinese parental preference for Hib vaccination that emphasizes parents are more willing to compromise on price if the vaccine is more effective and safer. And doctors' proactive recommendations for Hib vaccination enhance parental perceptions of the importance of the Hib vaccine. Regardless of the place of origin of Hib vaccines, parents prefer to choose Hib vaccines that have better effectiveness and safety profile and are cheaper for their children. Furthermore, subgroup analysis reveals that parents with different demographic characteristics existed heterogeneities in preference for Hib vaccination. These significant findings will contribute to the development and optimization of future immunization strategies for Hib vaccination in the future in China.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Chinese Center for Disease Control and Prevention Institutional Review Board (#201944). The patients/participants provided their written informed consent to participate in this study.

Author contributions

XW and YF contributed equally to the problem of the study, preprocessed data, performed the experiment, significantly to analysis and manuscript preparation, performed the data analyses, and wrote the manuscript. QZ, LY, and MC prepared and wrote ethics application materials, designed the discrete choice experiment questionnaire, and collected data. PL and SLiu helped design the discrete choice experiment questionnaire and helped perform the analysis with constructive discussions. SLi contributed to the problem of the study. JZ contributed to the problem of the study and revised the manuscript, and provided financial support. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.967693/full#supplementary-material

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COVID-19 vaccines reduce the risk of SARS-CoV-2 reinfection and hospitalization: Meta-analysis

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The addictive protection against SARS-CoV-2 reinfection conferred by vaccination, as compared to natural immunity alone, remains to be quantified. We thus carried out a meta-analysis to summarize the existing evidence on the association between SARS-CoV-2 vaccination and the risk of reinfection and disease. We searched MedLine, Scopus and preprint repositories up to July 31, 2022, to retrieve cohort or case-control studies comparing the risk of SARS-CoV-2 reinfection or severe/critical COVID-19 among vaccinated vs. unvaccinated subjects, recovered from a primary episode. Data were combined using a generic inverse-variance approach. Eighteen studies, enrolling 18,132,192 individuals, were included. As compared to the unvaccinated, vaccinated subjects showed a significantly lower likelihood of reinfection (summary Odds Ratio—OR: 0.47; 95% CI: 0.42–0.54). Notably, the results did not change up to 12 months of follow-up, by number of vaccine doses, in studies that adjusted for potential confounders, adopting different reinfection definitions, and with different predominant strains. Once reinfected, vaccinated subjects were also significantly less likely to develop a severe disease (OR: 0.45; 95% CI: 0.38–0.54). Although further studies on the long-term persistence of protection, under the challenge of the new circulating variants, are clearly needed, the present meta-analysis provides solid evidence of a stronger protection of hybrid vs. natural immunity, which may persist during Omicron waves and up to 12 months.

KEYWORDS

SARS-CoV-2, COVID-19, vaccination, meta-analysis, Omicron (B.1.1.529), reinfection

Introduction

Clarifying the frequency and predictors of SARS-CoV-2 reinfections is crucial to determine the course of the pandemic, and to optimize restriction and vaccination policies (1–3). Solid evidence is currently available on the frequency of reinfections after the emergence of the Omicron variant: a recent proportion meta-analysis including 15 million subjects recovered from a first infection estimated an overall reinfection rate of 3.3% in the first 3 months of Omicron predominance, likely increasing (2). However, the potential addictive protection conferred by hybrid immunity, generated by the combination of prior infection and vaccination, as compared to the sole natural immunity, remains to be fully disclosed (4, 5). A few population-based studies suggested that reinfection is less likely in vaccinated vs. unvaccinated subjects, but the magnitude of the association varied across studies, which differed for patients' characteristics, exposure risk, type of SARS-CoV-2 vaccine received, definition of reinfection adopted, and extent of measured confounding (4, 6–8). In a recent meta-analysis, the overall reinfection rate among vaccinated subjects was quantified to be as low as 0.32%, as compared to 0.74% among previously infected, unvaccinated individuals, but these estimates were obtained from raw, unadjusted data (2). Additionally, only limited data are available on the time course of natural and hybrid immunity (9), and the extent of its waning, particularly due to Omicron infections, is not yet well characterized (4, 9).

We carried out a meta-analysis to summarize the existing evidence from adjusted analyses on the association between SARS-CoV-2 vaccination and reinfection, in subjects who recovered from a first episode of SARS-CoV-2 infection.

Methods

Bibliographic search, data extraction and quality assessment

The reporting of this meta-analysis was guided by the standards of the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 Statement (10). We searched MedLine and Scopus databases, up to July 31, 2022, for studies evaluating the risk of SARS-CoV-2 reinfection (either asymptomatic or symptomatic and requiring hospital admission) among vaccinated subjects of all ages (with hybrid immunity resulting from a combination of natural and vaccine immunization), vs. unvaccinated subjects (with natural immunity only). Vaccinated subjects were defined as those receiving ≥ 1 dose of the COVID-19 vaccines currently approved ≥ 14 days before the reinfection. The following search strategy was adopted, without language restrictions: (coronavirus* or coronovirus* or coronavirinae* or Coronavirus* or Coronovirus* or Wuhan* or Hubei* or Huanan or "2019-nCoV" or 2019nCoV or nCoV2019 or "nCoV-2019" or "COVID-19" or COVID19 or "WN-CoV" or WNCoV or "HCoV-19" or HCoV19 or CoV or "2019 novel*" or Ncov or "n-cov" or "SARS-CoV-2" or "SARSCoV-2" or "SARSCoV2" or "SARS-CoV2" or SARSCov19 or "SARS-Cov19" or "SARSCov-19" or "SARS-Cov-19" or Ncovor or Ncorona* or Ncorono* or NcovWuhan* or NcovHubei* or NcovChina* or NcovChinese*) AND (reinfection* or re-infection* or second episode or recurrence* or recrudescence* or relapse* or RCOVID19) (2). The reference lists of reviews and retrieved articles was also screened, for additional pertinent papers (11). Given that several relevant clinical databases have been shared in public preprint repositories in the context of a public health emergency, we also searched for potential studies among those submitted in medRxiv.org. In case of re-analyses published from the same cohort, we extracted the data of the publication with the longer follow-up or, if the length of follow-up was identical, with the largest sample size.

Inclusion criteria were: (a) cohort or case-control design; (b) laboratory confirmation of SARS-CoV-2 initial episode through a positive reverse-transcriptase polymerase chain reaction (RT-PCR) test, and/or an initial positive serology investigated with the use of an anti-trimeric spike IgG enzyme-linked immunosorbent assay (ELISA) (12); (c) data available to compare SARS-CoV-2 reinfection by vaccination status in subjects who recovered from a primary infection; (d) explicit reinfection definition criteria. In accordance with CDC (12), a reinfection was defined by the presence of:

(a) two positive PCR samples detected ≥ 45 days apart with ≥ 1 negative RT-PCR test collected between the first and second episode (13), and/or confirmation of infection with two different phylogenetic strains by viral genomic sequencing;

(b) two positive PCR samples detected ≥ 45 days apart in subjects with a symptomatic second episode or in close contact with a laboratory-confirmed COVID-19 case (12);

(c) a positive PCR test ≥ 45 days after the first positive serology (detection of anti-S1 domain of spike protein IgG antibodies using an enzyme-linked immunosorbent assay—ELISA) (12, 14).

Each included article was independently evaluated by 2 reviewers (MEF, CAM), who extracted the main study characteristics and measures of effect. In case of discrepancies in data extraction, a third author was contacted (LM), and consensus achieved through discussion.

Individual study quality was evaluated using an adapted version of the Newcastle Ottawa Quality Assessment Scale, assessing the comparability across groups for confounding factors, the appropriateness of outcome assessment, length of follow-up and missing data handling and reporting (15).

Data analysis

The units of the meta-analysis were single comparisons of vaccinated vs. unvaccinated subjects in predicting (a)

TABLE 1 Characteristics of the included studies.

No.	References	Journal	Country	Design	Population	% vacc.	Mean age (SD)	Mean f-up (days)	Dominant strain	Reinfection definition and time-lag	Raw data[a]	Covariates
1	Bager et al. a1 [b] (27)	Lancet Infect Dis	Denmark	Cohort	General	65.8	31.0 (27.4)	120	Delta	2 PCR + > 60 days	783/80 426 vs. 1103/69,885	Raw data extracted
2	Bager et al. a2 [b] (27)	Lancet Infect Dis	Denmark	Cohort	General	81.2	29.0 (18.5)	120	Omicron	2 PCR + > 60 days	1520/31 403 vs. 622/7266	Raw data extracted
3	Cavanaugh et al. (21)	MMWR	USA	Case-control	General	20.3	NR	NR	NR	PCR + /Ag test May–Jun21 (1st episode: Mar-ec 20)	67/275 vs. 179/463	Age, gender, time from 1st infection
4	Cerqueira-Silva et al. (26)	Lancet Infect Dis	USA	Case-control	General	35.5	36.0 (11.1)	60	Gamma	2 PCR + > 90 days	6584/59,064 vs. 14 566/97 856	Comorb, time from 1st infection, severity of 1st infection
5	Eythorsson et al. (6)	JAMA Netw Open	Iceland	Cohort	General	25.5	34.0 (19.0)	287	Omicron	2 PCR + > 60 days	320/2938 vs. 1007/8598	Age, gender, time from 1st infection
6	Flacco et al. (28)	Front PublicHealth	Italy	Cohort	General	43.5	41.6 (21.9)	277	Omicron	2 PCR + ≥ 45 days (≥ 1 PCR−)	386/88,576 vs. 343/30,690	Age, gender, comorb, severity of 1st infection
7	Hall et al. (29)	Lancet	UK	Cohort	HCW	47.5	45.6 (14.2)	275	NR	2 PCR + ≥ 90 days + serology/genomic)	NR	Age, gender, ethnicity, time from 1st infection, workplace, contact frequency
8	Hammerman et al. (7)	New Engl J Med	Israel	Cohort	General	56.0	39.3 (17.1)	270	Delta	2 PCR + > 90 days	354/83,356 vs. 2,168/65,676	Age, gender, comorb. ethnicity, socio-economic status
9	Jang et al. (30)	J Med Virol	Korea	Cohort	General	76.1	NR	242	Omicron	2 PCR + ≥ 45 days	19,943/12,270,241 vs. 19,513/3,638,932	Age, gender, strain immunologic status
10	Levin-Rector et al. (22)	Clin Infect Dis	USA	Case-control	General	54.4	NR	NR	Delta	2 PCR + > 90 days	965/5,228 vs. 1,436/4,376	Age, gender, time from 1st infection
11	Lewis et al. a1 [c] (31)	JAMA Netw Open	USA	Cohort	General	51.2	35.0 (20.7)	225	Delta	2 PCR + > 90 days	298/52,683 vs. 1,105/41,833	Age, gender, time from and severity of 1st infection
12	Lewis et al. a2 [c] (31)	JAMA Netw Open	USA	Cohort	HCW	66.3	41.0 (17.0)	225	Delta	2 PCR + > 90 days	47/2,131 vs. 227/746	Age, gender, time from and severity of 1st infection
13	Malhotra et al. (32)	JAMA Netw Open	India	Cohort	HCW	75.3	36.6 (10.3)	233	Delta	2 PCR + ≥ 90 days	56/1,445 vs. 60/472	Age, gender, work category
14	Medic et al. (4)	Lancet Reg Health	Serbia	Case-control	General	46.2	45.9 (18.7)	340	Omicron	Rapid Ag test or 2 PCR + ≥ 90 days	3,404/10,220 vs. 3,815/11,417	Age, gender, comorb., time from 1st infection
15	Murugesan et al. (33)	PloS One	India	Cohort	HCW	76.9	33.7 (10.9)	259	Delta	2 PCR + ≥ 90 days	12/791 vs. 16/658	Raw data extracted
16	Nisha et al. (34)	J Fam Commun Med	India	Cohort	HCW	36.3	30.3 (10.5)	270	NR	2 PCR + > 90 days (≥ 1 PCR−)	103/1,684 vs. 24/225	Age, gender, comorb, work category

(Continued)

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TABLE 1 (Continued)

No.	References	Journal	Country	Design	Population	% vacc.	Mean age (SD)	Mean f-up (days)	Dominant strain	Reinfection definition and time-lag	Raw data[a]	Covariates
17	Nordstrom et al. (8)	Lancet Infect Dis	Sweden	Cohort	General	50.0	38.8 (17.9)	60	Delta	PCR + Dec 20-Oct 21 (1st episode before 24 May 21)	1,077/765,064 vs. 2,470/765,064	Age, gender, comorb., time from 1st infection, marital status, work category
18	Nunes et al. (23)	Vaccines	South Africa	Case-control	HCW	80.0	37.4 (9.2)	NR	Omicron	2 PCR + > 90 days	43/116 vs. 9/23	Study site
19	Plumb et al. a1[b] (24)	MMWR	USA	Case-control	General	48,4	NR	NR	Delta	2 PCR + > 90 days	487/2,183 vs. 950/2,418	Age, gender, race, time from 1st infection
20	Plumb et al. a2[b] (24)	MMWR	USA	Case-control	General	48,4	NR	NR	Omicron	3 PCR + > 90 days	971/3,442 vs. 1,353/3,456	Age, gender, race, time from 1st infection
21	Spicer et al. (25)	J Pediatric	USA	Case-control	General	20.5	15.1 (1.7)	246	Delta	2 PCR + > 90 days	20/855 vs. 342/3,307	Raw data extracted

HCW, healthcare workers; SD, standard deviation; % vacc., % of vaccinated individuals; Comorb., Comorbidities; PCR, oro-nasopharyngeal swabs tested through reverse transcription polymerase chain reaction; PCR + , Positive RT-PCR; PCR−, Intermediate negative RT-PCR between two positive tests; Ag, Antigen; NR, Not reported.

[a]Raw data: Number of vaccinated, reinfected subjects/Total number of vaccinated subjects vs. Number of unvaccinated, reinfected subjects/Total number of unvaccinated subjects.

[b]Same publication providing separate data for Delta and Omicron waves.

[c]Same publication providing separate data for general population and healthcare workers.

SARS-CoV-2 reinfection; (b) severe COVID-19 disease—requiring hospital admission with no use of an intensive care unit; (c) critical/lethal COVID-19 disease—requiring admission in an intensive care unit and/or causing death (2). The likelihood of each outcome was assessed: (a) using ≥ 45 days as the minimum time-lag between two positive episodes; (b) adopting a more stringent time-lag of 90 days (2); (c) including only studies with adjusted estimates. When data were available, we also performed several additional meta-analyses stratified by: (d) number of vaccine doses ("fully vaccinated" subjects—those receiving ≥ 2 doses of mRNA-1273, BNT162b2, ChAdOx1 nCoV-19, BBV152, BBIBP-CorV, Gam-COVID-Vac, CoronaVac, or 1 dose of JNJ-78436735 ≥ 14 days before reinfection—or "partially vaccinated" subjects—those receiving 1 dose of mRNA-1273, BNT162b2, ChAdOx1 nCoV-19, BBV152, BBIBP-CorV, Gam-COVID-Vac, or CoronaVac ≥ 14 days before reinfection—vs. unvaccinated) (13). When data were available, we also extracted separate estimates for those who received 3 doses of mRNA-1273, BNT162b2, ChAdOx1 nCoV-19, BBV152, BBIBP-CorV, Gam-COVID-Vac, or CoronaVac vaccines ("boosted subjects"); (e) time between first episode and reinfection (<6 vs. ≥ 6 months); (f) dominant viral strain (Delta or Omicron); (g) exposure risk (healthcare workers or general population); (h) study design (cohort or case-control).

Data were combined using a random-effect generic inverse variance approach (16, 17), in order to account for between-study heterogeneity (18). If a study reported the results of different multivariable models, the most stringently controlled estimates (those from the model adjusting for more factors) were extracted. If different models controlled for the same number of covariates, the model containing the most clinically meaningful covariates was used for the analysis (19). When a study only reported separate estimates by vaccine dose, the overall estimate of risk was computed from the separate relative risks using the fixed-effect model for generic inverse-variance outcomes (19).

Between-study heterogeneity was quantified using the I^2 statistic. Potential publication bias was assessed graphically, using funnel plots [displaying the Odds Ratios—ORs from individual comparisons vs. their precision (1/SE)], and formally, using Egger's regression asymmetry test (16).

All meta-analyses were performed using RevMan software, version 5.3 [The Cochrane Collaboration, (20)].

Results

Of the 3,470 papers initially retrieved, seven case-control (4, 21–26) and 11 cohort studies (6–8, 27–34) were included in the analyses (**Supplementary Figure 1** and **Supplementary Table 1**). Three studies contributed with two dataset (24, 27, 31), as the same publication provided separate data for healthcare workers and the general population (31), and for Delta and Omicron waves (24, 27): this led to a total of 21 datasets that were included in the analyses (**Table 1**).

Six studies were carried out in Europe (4, 6, 8, 24, 27–29), six in the USA (21, 22, 24–26, 31), five in Asia (7, 30, 32–34) and one in South Africa (23). Thirteen studies evaluated the general population (4, 6–8, 21, 22, 24–28, 30, 31), and six assessed the healthcare workers (23, 29, 31–34). In most studies, the analyses were adjusted for age, gender, and comorbidities, as a minimum set of potential confounders of the association between vaccination status and reinfections (4, 6–8, 21, 23, 26, 28–32, 34).

The mean age of the participants ranged from 15 to 46 years, and the mean follow-up ranged from a minimum of 60 up to 340 days. In 13 studies (4, 7, 21–26, 29, 31–34) the minimum time-lag between infection and reinfection was set at 90 days, and only three (28, 29, 34) strictly followed the CDC criteria to define a reinfection (≥1 intermediate negative PCR and/or viral genomic sequencing) (12). Most reinfections were reported during the Delta (7, 8, 22, 24, 25, 27, 31–33) and the Omicron waves (4, 6, 23, 24, 27, 28, 30).

The methodological characteristics of the included studies are summarized in **Table 2**: the selection of the cohort of patients, the ascertainment of the exposure, and the evaluation of the comparability of subjects were adequate in all studies, while 15 out of 18 adequately addressed the items pertaining to outcome assessment and follow-up (length and missing data).

TABLE 2 Methodological quality of the included studies according to the Newcastle Ottawa Scale.

References	Selection (Max. score 4)	Comparability (Max. score 2)	Outcome (Max. score 3)
Bager et al. (27)	4	2	3
Cavanaugh et al. (21)	4	2	3
Cerqueira-Silva et al. (26)	4	2	3
Eythorsson et al. (6)	4	2	3
Flacco et al. (28)	4	2	3
Hall et al. (29)	4	2	3
Hammerman et al. (7)	4	2	3
Jang et al. (30)	4	2	3
Levin-Rector et al. (22)	4	2	2
Lewis et al. (31)	4	2	3
Malhotra et al. (32)	3	2	3
Medic et al. (4)	4	2	3
Murugesan et al. (33)	4	2	3
Nisha et al. (34)	4	2	3
Nordstrom et al. (8)	4	2	2
Nunes et al. (23)	3	2	2
Plumb et al. (24)	4	2	3
Spicer et al. (25)	4	2	2

Twenty-one datasets including a total of 18,132,192 individuals were included in the overall meta-analysis comparing the risk of SARS-CoV-2 reinfection in vaccinated vs. unvaccinated subjects (**Table 3**) (4, 6–8, 21–34). In 20 out of 21 datasets, the vaccinated subjects were significantly less likely to be reinfected, with a summary OR of 0.47 (95% confidence interval—CI – 0.42–0.54) (**Figure 1**). When the only study reporting a significantly higher risk among vaccinated subjects (and no data on underlying comorbidities) was excluded (6), the estimates were virtually identical (OR: 0.45; 95% CI: 0.39–0.50). Also, the results did not substantially change after the exclusion of the three studies with unadjusted estimates (OR: 0.47; 95% CI: 0.39–0.56) (25, 27, 33), and when only the 17 datasets with a more conservative time-lag of 90 days were considered (OR: 0.47; 95% CI: 0.41–0.54) (4, 7, 21, 23, 24, 26, 29, 31–34).

When the analyses were stratified by number of doses, the summary OR of reinfection was lower among fully vaccinated than partially vaccinated subjects (summary OR 0.45 and 0.58, respectively). The confidence intervals, however, largely overlapped. In the analyses restricted to the subjects who received three doses (a booster dose), the summary OR was comparable to that of the fully vaccinated individuals (OR: 0.46; 95% CI: 0.29–0.73). As shown in **Table 3**, the association between vaccination and reinfection did not show a substantial variation by length of follow-up: the summary OR of the studies with a follow-up shorter than 6 months (OR: 0.52; 95% CI: 0.40–0.67) was comparable with the OR (0.45; 95% CI: 0.34–0.59) of the studies with a longer follow-up (up to 340 days).

The likelihood of a reinfection remained significantly lower among vaccinated subjects both in the studies that were carried out during Delta predominance (summary OR: 0.40; 95% CI: 0.31–0.50) (7, 8, 19, 22–24, 27–29) and during Omicron predominance (OR: 0.58; 95% CI: 0.48–0.60) (2, 4, 6, 23, 24, 27, 30). Again, in the analyses stratified by risk of exposure (general population or healthcare workers) and by study design (cohort or case-control) the likelihood of reinfection was comparably, significantly lower among vaccinated subjects, with summary ORs ranging from 0.44 to 0.54, and overlapping confidence intervals.

The Egger test was not significant (p = 0.3), and the funnel plot displaying the ORs of the individual comparisons vs. the logarithm of their SE (precision) did not show asymmetry, suggesting the absence of publication bias (**Supplementary Figure 2**).

A total of seven datasets and 2,312,703 individuals provided specific data and were included in the meta-analysis comparing the risk of severe/lethal COVID-19 of the vaccinated vs. the unvaccinated subjects (8, 22, 24, 26, 29, 32). Compared with the unvaccinated, those receiving ≥ 1 dose were significantly less likely to develop a severe disease, once reinfected (OR: 0.45; 95% CI: 0.38–0.54—**Table 3** and **Figure 2**). The risk remained comparably and

TABLE 3 Risk of SARS-CoV-2 reinfection and severe/critical COVID-19 among vaccinated vs. unvaccinated subjects, overall, and stratified by definition of reinfection, number of vaccine doses, length of follow-up, predominant strain, study design and risk exposure.

Analyses	N. datasets (total sample)[a]	Pooled estimates: OR (95% CI)	*P*-value	I^2, %	Raw data[b]: No. of events	Vaccinated subjects	No. of events	Unvaccinated subjects
SARS-CoV-2 reinfection—all studies (4, 6, 8, 21–34)	21 (18, 132, 192)	0.47 (0.42 − 0.54)	< 0.001	98	37,440	13,462,121	134,598	4,670,071
- Adjusted estimates only (4, 6, 8, 21–24, 26, 28–32, 34)	17 (17, 937, 601)	0.47 (0.41 − 0.54)	< 0.001	98	35,105	13,348,646	132,525	4,588,955
1. Time-lag ≥ 90 days [c] (4, 7, 21–26, 29, 31–34)	15 (373, 109)	0.44 (0.36 − 0.54)	< 0.001	97	13,411	223,473	109,540	149,636
- Adjusted estimates only (4, 21–24, 26, 29, 31, 32, 34)	13 (367, 498)	0.46 (0.37 − 0.56)	< 0.001	97	13,379	221,827	109,182	145,671
2. Number of vaccine doses: [d]								
- Partially vaccinated subjects (4, 8, 23, 24, 26, 28, 30–32)	11 (5, 248, 720)	0.58 (0.44 − 0.77)	0.004	98	5,820	729,103	127,701	4,509,617
- Fully vaccinated subjects (4, 8, 21–24, 26, 28, 30–32)	13 (17, 036, 021)	0.45 (0.40 − 0.50)	< 0.001	95	28,508	12,521,565	129,316	4,514,456
- Boosted subjects (3 doses) (4, 24, 30)	4 (11, 365, 430)	0.46 (0.29 − 0.73)	0.001	99	1,675	7,709,207	25,631	3,656,223
3. Length of follow-up:								
- <6 months (< 120 days)—all studies (8, 26, 27)	4 (1, 876, 028)	0.52 (0.40 − 0.67)	< 0.001	99	9,964	935,957	18,761	940,071
- Adjusted estimates only (8, 26)	2 (1, 603, 758)	0.47 (0.30 − 0.74)	0.001	99	7,661	824,128	17,036	862,920
- ≥6 months (≥ 120 days)—all studies (4, 6, 7, 25, 28–34)	12 (16, 317, 474)	0.45 (0.34 − 0.59)	0.005	98	24,943	12,514,920	28,620	3,802,554
- Studies with adjusted estimates only (4, 6, 7, 28–32, 34)	10 (16, 311, 863)	0.47 (0.35 − 0.63)	0.05	99	24,911	12,513,274	28,262	3,798,589
4. Predominant viral strain:								
- Delta variant (B.1.617.2)—all studies (8, 22, 24, 25, 27, 31–33)	10 (1, 948, 597)	0.40 (0.31 − 0.50)	< 0.001	97	4,099	994,162	9,877	954,435
- Adjusted estimates only (8, 22, 24, 31, 32)	7 (1, 792, 675)	0.38 (0.30 − 0.49)	< 0.001	96	3,284	912,090	8,416	880,585
- Omicron variant (B.1.1.529)—all studies (4, 6, 23, 24, 27, 28, 30)	7 (16, 107, 318)	0.58 (0.48 − 0.70)	< 0.001	97	26,587	12,406,936	26,662	3,700,382
- Adjusted estimates only (4, 6, 23, 24, 28, 30)	6 (15, 951, 396)	0.59 (0.48 − 0.73)	< 0.001	96	25,772	12,324,864	25,01	3,626,532
5. Risk of exposure:								
- General population—all studies (4, 6, 8, 21, 22, 24–28, 30, 31)	15 (18, 123, 901)	0.47 (0.41 − 0.53)	< 0.001	98	37,179	13,455,954	134,262	4,667,947
- Adjusted estimates only (4, 6, 8, 21, 22, 24, 26, 28, 30, 31)	11 (17, 930, 759)	0.46 (0.37 − 0.55)	< 0.001	98	34,856	13,343,270	132,195	4,587,489
- Healthcare workers—all studies (23, 29, 31–34)	6 (8, 291)	0.50 (0.41 − 0.61)	< 0.001	0	261	6,167	336	2,124
- Adjusted estimates only (23, 29, 31, 32, 34)	5 (6, 842)	0.49 (0.40 − 0.61)	< 0.001	0	249	5,376	320	1,466

(Continued)

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TABLE 3 (Continued)

Analyses	N. datasets (total sample)[a]	Pooled estimates: OR (95% CI)	*P*-value	I^2, %	No. of events	Raw data[b]: Vaccinated subjects	No. of events	Unvaccinated subjects
6. Study design:								
- Cohort—all studies (6, 8, 25, 27–34)	14 (18, 014, 945)	0.44 (0.36 − 0.54)	< 0.001	98	24,919	13,381,593	29,000	4,633,352
- Adjusted estimates only (6, 8, 28–32, 34)	10 (17, 820, 354)	0.44 (0.33 − 0.57)	< 0.001	98	22,584	13,268,118	26,917	4,552,236
- Case-control—all studies (4, 21–24, 26)	7 (117, 247)	0.54 (0.48 − 0.61)	< 0.001	89	12,521	80,528	105,598	36,719
Severe or critical/lethal COVID-19 [e] (8, 22, 24, 26, 29, 32)	7 (2, 312, 703)	0.45 (0.38 − 0.54)	< 0.001	91	1,411	1,536,917	2,657	775,786
1. Number of vaccine doses: [d]								
- Partially vaccinated subjects (8, 24, 26, 32)	5 (982, 721)	0.35 (0.21 − 0.60)	0.02	91	474	48,4471	3,693	498,250
- Fully vaccinated subjects (8, 22, 24, 26, 32)	6 (597, 193)	0.34 (0.24 − 0.49)	< 0.001	93	1,629	296,197	3,620	300,996

[a]Three studies (24, 27, 31) contributed with more than one dataset, thus the number of references does not always match the number of datasets included in each analysis (see "Results" for further details).
[b]Number of events/Total number of previously infected and vaccinated subjects vs. Number of events/Total number of previously infected and unvaccinated subjects.
[c]The risk of SARS-CoV-2 reinfection was computed: (1) using ≥ 45 days as the minimum time-lag between two positive episodes; (2) adopting a more stringent time-lag of 90 days (see Methods for further details).
[d]Partially vaccinated subjects: 1 dose of mRNA-1273, BNT162b2, ChAdOx1 nCoV-19, BBV152, BBIBP-CorV, Gam-COVID-Vac, or CoronaVac ≥ 14 days before reinfection; fully vaccinated subjects: ≥ 2 doses of mRNA-1273, BNT162b2, ChAdOx1 nCoV-19, BBV152, BBIBP-CorV, Gam-COVID-Vac or CoronaVac, or 1 dose of JNJ-78436735 ≥ 14 days before reinfection; boosted subjects: 3 doses of mRNA-1273, BNT162b2, ChAdOx1 nCoV-19, BBV152, BBIBP-CorV, Gam-COVID-Vac, or CoronaVac vaccines.
[e]Severe COVID-19: disease requiring hospital admission with no use of an intensive care unit; critical/lethal COVID-19: disease requiring admission in an intensive care unit and/or causing death. OR, Odds ratio; CI, confidence interval.

significantly lower when only the subset of studies evaluating partial vaccination (OR: 0.35; 95% CI: 0.21–0.60) or those evaluating full vaccination (OR: 0.34; 95% CI: 0.24–0.49) vs. no vaccination, were included.

Discussion

This meta-analysis, which included the data of more than 18 million previously infected and recovered subjects, has two main findings. First, as compared to natural immunity alone, the addition of vaccination approximately halved the odds of severe COVID-19, and the degree of protection was similar after a single or multiple doses. Second, the likelihood of reinfection was also reduced by approximately 50% among the vaccinated, and this finding was consistent in all stratified analyses, either extracting estimates adjusted for potential confounders or unadjusted, with follow-ups shorter or longer than 6 months, adopting different reinfection definitions, in both case-control and cohort studies, in the general population and healthcare workers alone, after a single or multiple vaccine doses, and irrespective of the predominant strain.

Preliminary evidence suggested that the protection conferred by hybrid immunity against reinfection was similar, or only marginally better, than the infection-induced or vaccine-induced immunity alone (5, 35). More recently, however, a proportion meta-analysis including 15 million previously infected and recovered individuals reported markedly lower rates of reinfection among vaccinated vs. unvaccinated subjects (0.32% vs. 0.74%), but these findings were based upon raw data and needed confirmation from adjusted estimates (2). The present meta-analysis expanded the previous and included 15 studies that adjusted the analyses for age, gender, comorbidities, and other potential confounders, providing solid evidence of a stronger protection of hybrid vs. natural immunity, which may persist during Omicron waves and up to 12 months.

Indeed, concerning the waning of the immunity, a 20% decline in the effectiveness of vaccination against first infection after 6 months was first showed in a meta-analysis including studies up to December 2021 (36). Then, evidence of waning protection both with hybrid and natural immunity 4 months after immunization was reported in some large prospective studies, which showed corresponding upward trends in reinfection absolute rates during time (5, 8, 9). In the present meta-analysis, the reinfection rates of the cohort studies with follow-up longer than 6 months were not distinctly higher (0.17 and 0.65 × 100 individuals in vaccinated and unvaccinated subjects, respectively), as compared to those with short follow-up (0.39 and 0.50 × 100 individuals in vaccinated and unvaccinated subjects, respectively). Additionally, we did not observe a substantial reduction of the protection when the follow-up lasted 6–11 months: pooling the 12 datasets with a

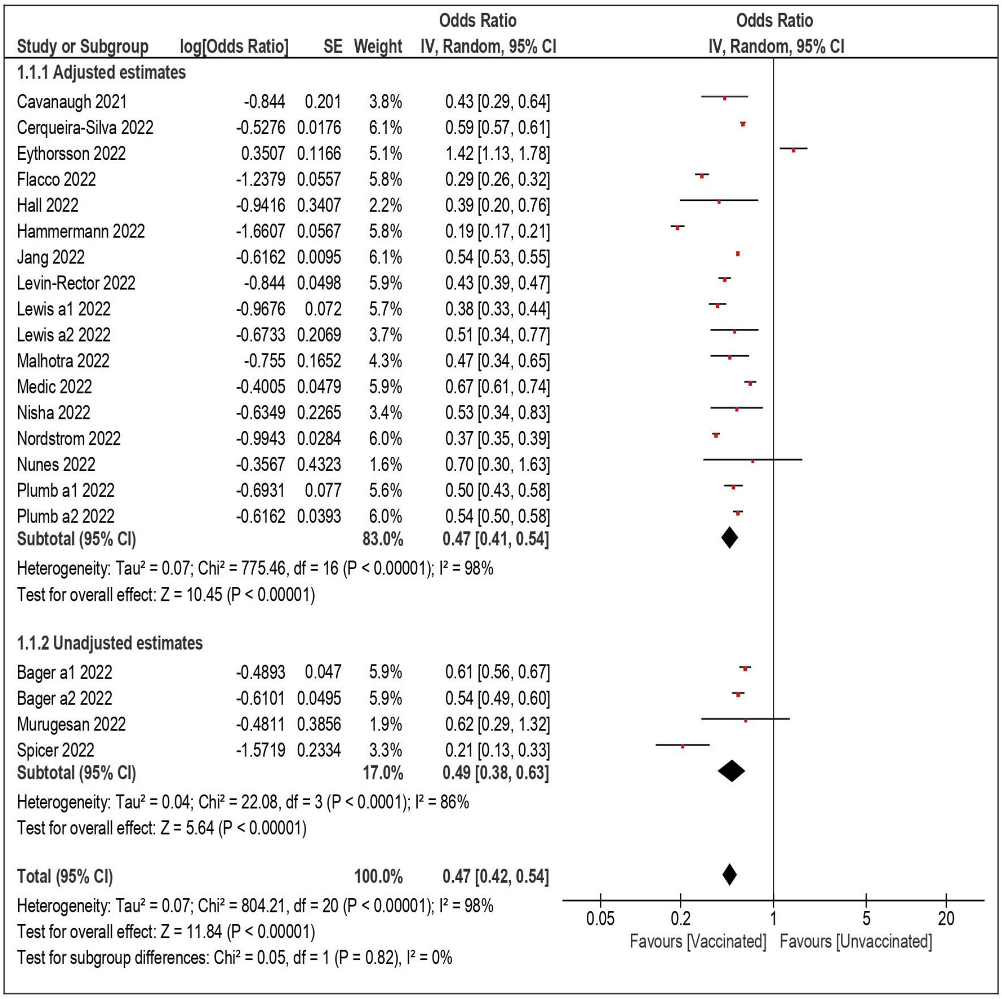

FIGURE 1
Risk of SARS-CoV-2 reinfection among vaccinated vs. unvaccinated subjects.

longer follow-up, the odds of reinfection were approximately 50% lower among the vaccinated. Inevitably, this information remains preliminary, as it is based upon studies in which the follow-up lasted up to 12 months, and the use of viral genomic sequencing was uneven.

These findings may offer a contribution to help planning tailored immunization strategies for previously infected subjects: if, on one side, the marked increase in the absolute number of reinfections with time is concerning, the significantly lower relative risk still observed among vaccinated subjects may be reassuring, thus vaccinating also this population may definitely play a role to control the pandemic (4). In this scenario, the strong protective effect exerted by a single dose (if confirmed during longer follow-up and toward different strains) might be taken into account when designing tailored vaccination schedules directed to lower-priority groups (4, 5). It should be also considered, however, that the degree of additional protection specifically conferred by further boosters (three or more doses) still remains uncertain, as our stratified meta-analyses did not show a clear benefit of a 3- vs. a 2-dose schedule.

The second main finding of the present meta-analysis was the significant reduction of the risk of hospitalization due to severe COVID-19 that was observed among the vaccinated subjects, either receiving one or more doses. This was crucial, as the primary aim of COVID-19 vaccination is to reduce the pressure on the healthcare systems preventing severe disease and hospitalization (37). Unfortunately, however, most of the studies included in the meta-analyses of this outcome were carried out before the emergence of Omicron strain. Therefore, this finding requires confirmation from more recent data with longer follow-up, as the large increase in the number of reinfections during the Omicron wave, and in turn the consequences on the healthcare systems still needs to be carefully evaluated.

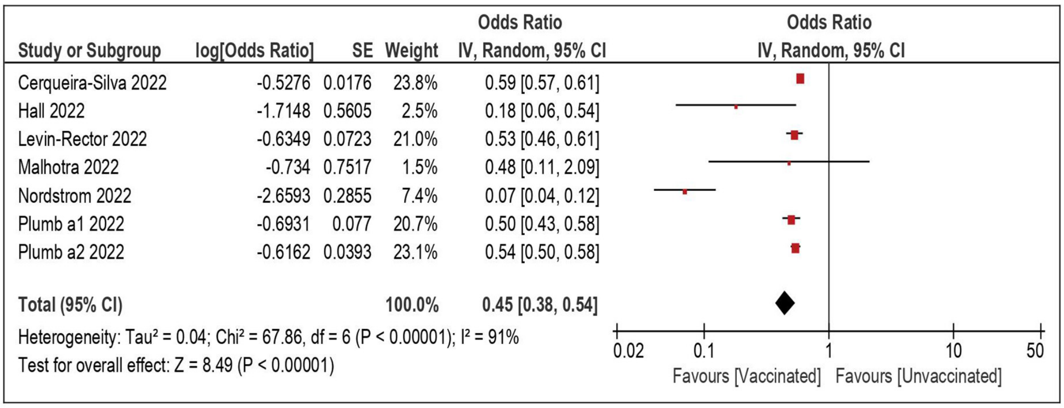

FIGURE 2
Risk of severe/lethal COVID-19 among vaccinated vs. unvaccinated subjects.

In the first phases of the pandemic, there was uncertainty on the criteria to define a reinfection, especially on the time interval between the first and second episodes, and most initial studies defined a reinfection as a new PCR test occurring ≥ 90 days after complete resolution of the first infection (4, 7, 21–26, 29, 31–34). However, the CDC later expanded the definition, including also the subjects with COVID-19-like symptoms and detection of SARS-CoV-2 RNA ≥ 45 days since first infection (12). In the present analysis, we did not find substantial differences when a 90-day or a 45-day cutoff was adopted, suggesting that a low proportion of reinfections was missed using the longer threshold. Indeed, a recent cohort study reported a mean time between the first and second infection of 349 days, with less than 15% of the reinfections occurring in the first 6 months since the first episode (28).

Some limitations must be considered when interpreting the present findings. First, most meta-analyses showed an intermediate-to-high level of heterogeneity. However, a certain degree of heterogeneity across studies was inevitable, given the large variation in terms of setting and baseline patients characteristics. Also, when the analyses were repeated adopting a fixed approach, none of the results substantially differed (except for CIs, which were typically tighter). Second, although most studies provided analyses at least adjusted for age, gender, and several underlying comorbidities, some extent of residual confounding cannot be completely ruled out, as for any observational study (38). Third, the risk of reinfection could have been overestimated in several of the included studies adopting less stringent criteria to define a reinfection (2). Conversely, if previously infected people tended to seek fewer testing due to their presumed acquired natural immunity, the reinfection rate could have been underestimated (4). A sensitivity analysis based upon the average number of PCR tests as a proxy of health-seeking behavior would have increased the precision of our estimates (2), but these data were unfortunately not available. Fourth, it might have been interesting to evaluate if the results differed according to the sequence of events, whether vaccination was administered before or after the first infection. Unfortunately, however, the exact timeline of events could be determined only in two studies (4, 31), in which all the infections occurred before the start of the vaccination campaign.

Acknowledging these caveats, this meta-analysis showed that, among the subjects that recovered from a first SARS-CoV-2 infection, vaccination was associated with a significant and substantial reduction of the risk of both reinfection and severe COVID-19. This finding was confirmed when the analyses were adjusted for potential confounders, up to 12 months of follow-up, and after any vaccine dose. Further studies on the long-term persistence of protection, and assessing the reinfection and hospitalization rates under the challenge of the new circulating variants, are strongly warranted.

Data availability statement

The data presented in this study are available upon reasonable request from the corresponding author.

Author contributions

MF and LM: concept and design and statistical analysis. MF, CA, VB, and ER: acquisition, analysis, or interpretation of data. MF, CA, and LM: drafting of the manuscript. CD, PV, and LM: critical revision of the manuscript for important intellectual content. PV and LM: supervision. LM: full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.1023507/full#supplementary-material

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Patients with inflammatory bowel disease are more hesitant about Coronavirus disease 2019 vaccination

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Despite the impact of the Coronavirus Disease 2019 (COVID-19) pandemic, vaccine hesitancy remains common in the general public and patients with Inflammatory Bowel Diseases (IBD). We sought to examine the reasons for vaccine hesitancy in patients with IBD. In this case-control study, we performed a retrospective chart review of 1,349 IBD patients and 215 non-IBD patients seen at University of Maryland Medical Center, a tertiary referral medical center, between March 2020 and October 2021. Data obtained included demographics, vaccination records, disease history, number of IBD-related surgeries, and IBD medications. 813/1,349 (60.3%) IBD patients received at least one dose of either the Pfizer/BioNTech, Moderna, or Johnson & Johnson vaccines. In a multivariate logistic regression, COVID vaccination was found to be positively associated with older age (p-value = 1.65e-5), female sex ($p = 0.00194$), Asian and White races (p = 0.02330, 0.00169), number of clinic visits (p = 1.11e-08), and biologic use (p = 7.82e-5). There was no association between vaccination and other types of vaccination nor with the use of other IBD medications. There was a negative association between vaccination status and the total number of IBD related surgeries ($p = 0.02857$). In non-IBD patients, only the number of clinic visits was positively associated with COVID-19 vaccination. Although the majority of IBD patients are immunosuppressed, COVID-19 vaccination rate was only 60.3%. Younger adults, males, African Americans, and those requiring IBD-related surgeries were less likely to receive COVID-19 vaccine. Healthcare providers need to recognize these potential risk factors for COVID-19 vaccine hesitancy.

KEYWORDS

vaccine hesitancy, immunosuppression, COVID-19, inflammatory bowel disease, vaccines

Introduction

When Coronavirus disease 2019 (COVID-19) vaccines became available, adults who were on immunosuppressive medications were among the earlier groups recommended by the Centers for Disease Control and Prevention to receive the vaccines. Among these groups were patients diagnosed with Inflammatory Bowel Diseases (IBD), which includes Crohn's Disease and Ulcerative Colitis. These are diseases of innate and adaptive immune system dysregulation leading to chronic intestinal inflammation. An estimated 3.1 million adults (1) in the United States live with IBD and many patients require immunosuppressive medications such as corticosteroids, immunomodulators, anti-Tumor Necrosis Factors, and other biologic agents. These medications have been associated with increased susceptibility to infections (2–5). Consequently, the fear of COVID-19 infection in patients with IBD is more pronounced, especially in those taking immunosuppressants (6). Despite the global impact of the COVID-19 pandemic, vaccine hesitancy remains in both the general public (7, 8) and the IBD population (9).

Vaccine hesitancy in IBD patients is not a novel concern to gastroenterologists. Prior studies have shown that IBD patients are less likely to receive vaccinations made necessary from their immunocompromised state (10). Some concerns from the past have transferred to COVID-19 vaccines. Studies in the United States (U.S.) and Europe reported COVID-19 vaccination intent among IBD patients as rates ranging from 54 to 96.4% (9, 11–14). Many IBD patients voiced concerns that the nature of their disease may trigger worse adverse side-effects from the COVID-19 vaccine and/or the vaccine will cause an IBD flare. Others were concerned about the overall efficacy and validity of the vaccines (15, 16). However, consensus among physicians is in support (17) of vaccination of all IBD patients as data shows COVID-19 vaccines available in the U.S. are safe (18–21) and effective (22–25) for these patients.

Recent studies have shown that the rate of COVID-19 infection in IBD patients is similar to the rate of infection in the general population (26–28). They have also shown that risk factors for adverse COVID-19 outcomes in IBD patients are also similar to the risk factors of the general population which include age and comorbidities (29–33). There have been varying reports of the effects of IBD therapies on COVID-19 infection outcomes. Some studies have found that IBD medications are not associated with more adverse COVID-19 infections (34). However, several other studies have shown 5-ASA/Sulfasalazine (31, 35) systemic corticosteroids (31, 32, 35, 36) and thiopurines (35) may be associated with worse clinical outcomes. Interestingly, anti-TNF drugs and biological therapies have not been shown to be associated with worse clinical outcomes (32, 34, 36).

Therefore, given the vulnerable nature of IBD patients in the setting of the ongoing COVID-19 pandemic, it is important to address any vaccine hesitancy seen in patients with inflammatory bowel disease and use this information to then increase rates of vaccination. We sought to investigate the barriers to vaccination by examining rate of vaccine hesitancy in patients with IBD as well as associated demographic and socioeconomic risk factors.

Materials and methods

This study was a single-center, retrospective analysis of 1,349 patients with IBD who were seen at the University of Maryland Medical Center between March 2020 and October 2021. 215 non-IBD patients, also seen in the same clinic, were used as the control group. The period between January 2020 and October 2021 was selected to account for the disruption of the pandemic on patients' clinic appointments. This period maximizes patient capture and ensures inclusion of those who presented to clinics infrequently; patients on therapies like mesalamine are seen yearly. Furthermore, as this was a retrospective chart review on an electronic medical record system, we were able to obtain current vaccine records even in patients only seen prior to when vaccines were first made available in January 2021. The diverse control group encompasses every patient seen at the clinic without IBD. They range from patients presenting for common and general gastroenterological needs to those with cancer and/or end stage diseases. Their medication use also vary, and can range from no medications to immunosuppressants/chemotherapy.

Data was obtained by performing a chart review of the electronic health record, *Epic*®. The data that was collected included demographics (age, sex, race, marital status, employment, insurance type), substance use (tobacco, alcohol, illicit drugs), IBD diagnosis, year of diagnosis, number of years since diagnosis, number of IBD-related surgeries, and IBD therapy received between October 2020 and 2021 including biologics, steroids, mesalamine, thiopurines or methotrexate. The number of IBD clinic visits and IBD-related gastroenterology procedures between October 2020 and 2021 were also reported (Table 1). Information was obtained on prior COVID-19 infection and recommended vaccines including the influenza vaccine, 23-valent pneumococcal polysaccharide vaccine, 13-valent pneumococcal conjugate vaccine, recombinant zoster vaccine, and COVID-19 vaccines. Patients were recorded as having received a COVID-19 vaccine if they received at least one dose (the first dose of the two-dose series for the Pfizer/BioNTech or Moderna COVID-19 vaccines, or the single dose Johnson & Johnson COVID-19 vaccine) (Table 2).

Multiple regression analysis was used to assess the relationships between several clinical and demographic factors, and likelihood of receiving a COVID vaccine, and both models and odd's ratios were calculated using a GLM (generalized

TABLE 1 Patient demographics including IBD history.

	IBD patients	Non-IBD patients	*P*-value
	Total (*n* = 1349)	Total (n = 215)	
Age, mean (IQR)	43.9 (31–55.5)	53.35 (43–64.5)	3.083e-13
Female, *n* (%)	711 (52.7)	141 (65.6)	0.0005077
Race, *n* (%)			3.445e-10
White	1,031 (76.4)	118 (54.9)	
Black	252 (18.7)	82 (38.1)	
Hispanic	35 (2.6)	8 (3.7)	
Asian	29 (2.1)	6 (2.8)	
American Indian/Alaska Native	1 (0.0007)	0	
Unknown	1 (0.0007)	1 (0.47)	
Marital Status, *n* (%)			0.8008
Single	685 (50.8)	112 (52)	
Married	663 (48.9)	103 (47.9)	
History Of Substance Use, *n* (%)			
Alcohol Abuse			0.3933
Never	1,248 (92.5)	203 (94.4)	
Current	74 (5.5)	7 (3.3)	
Former	27 (2.0)	5 (2.3)	
Tobacco Abuse			0.4328
Never	873 (64.7)	130 (60.4)	
Current	344 (25.5)	60 (27.9)	
Former	132 (9.8)	25 (11.6)	
Illicit Drug Abuse			0.5424
Never	1,123 (83.2)	173 (80.5)	
Current	158 (11.7)	30 (14.0)	
Former	68 (5.0)	12 (5.6)	
Employment Status, *n* (%)			0.0002292
Employed	870 (64.5)	109 (50.7)	
Insurance, *n* (%)			2.547e-05
Commercial	1,011 (74.9)	147 (68.4)	
Medicaid	139 (10.3)	11 (5.1)	
Medicare	191 (14.1)	57 (26.5)	
None	8 (0.006)	0 (0)	
IBD phenotype, *n* (%)			
Crohn's Disease	908 (67.3)		
Ulcerative Colitis	391 (29.0)		
Indeterminant Colitis	50 (3.7)		
Years Since Diagnosis, mean (IQR)	14.71 (6–21)		
IBD therapy, *n* (%)			
Biologics	992 (73.5)	4 (1.9)	2.2e-16
Steroids	232 (17.2)	24 (11.2)	0.0239
Immunomodulators	224 (16.6)	7 (3.3)	3.904e-09
5-Aminosalicylates	233 (17.3)	3 (1.4)	4.813e-13
Clinic visits in 1 year, mean (IQR)	1.82 (IQR 1-2)	1.5 (IQR 1-2)	0.00196
IBD-related surgeries, mean	0.8218		
Endoscopic procedures, mean	0.551	0.619	0.328

IQR, Interquartile Range.

TABLE 2 Vaccination and COVID history.

Vaccination, *n* (%)	IBD Patients	Non-IBD Patients	*P*-value
COVID-19	813 (60.3)	145 (67.4)	0.2154
Influenza	1,170 (86.7)	170 (79.1)	0.01043
PCV13/ PPV23			2.2e-16
Yes	929 (68.9)	76 (35.3)	
No	381 (28.2)	120 (55.8)	
Not Indicated	14 (1.0)	87 (40.5)	
Unknown	25 (1.9)	9 (4.2)	
Shingles			4.283e-14
Yes	248 (18.4)	42 (19.5)	
No	793 (58.8)	76 (35.3)	
Not Indicated	303 (22.5)	10 (4.7)	
Unknown	5 (0.4)	9 (4.2)	
Prior COVID-19 Infection, *n* (%)	98 (7.3)	24 (11.2)	0.1551

PCV13, 13-valent pneumococcal conjugate vaccine; PPV23, 23-valent pneumococcal polysaccharide vaccine.

linear model). All variables compared were considered as factors except for age, number of clinic visits and procedures, and years since diagnosis. Two group differences for various factors were compared using Fisher's exact test. All tests were performed using the R "stats" package, version 4.0.4.

Results

60.3% (813/1349) of IBD patients received at least one dose of either the Pfizer/BioNTech (BNT162b2), Moderna (mRNA-1273), or Johnson & Johnson (JNJ-78436735) vaccines (Table 2). In a multivariate regression, COVID vaccination was found to be positively associated with a number of factors including older age (OR 1.022, p-value = 1.65e-5), female sex (OR 1.46, $p = 0.00194$), Asian and White races (OR 2.84, 1.66, p = 0.02330, 0.00169), number of clinic visits in the past 12 months (OR 1.37, p = 1.11e-08), and biologic use (OR 1.78, p = 7.82e-5; Table 3). This was true while controlling for IBD type; marital status; insurance (Commercial vs. Medicaid vs. Medicare); employment status; years since diagnosis; and tobacco, alcohol, and substance use history. Years since diagnosis and age were not found to have a significant interaction suggesting older age independently predicts likelihood of vaccination. There was a negative association between vaccination status and the total number of IBD related surgeries a patient had undergone (OR 0.890, $p = 0.02857$). There was no association between COVID vaccination and the number of endoscopic procedures in the past 12 months, employment status, other types of vaccination (influenza vaccine, 23-valent pneumococcal polysaccharide vaccine, 13-valent pneumococcal conjugate vaccine, recombinant zoster vaccine), or with the use of other IBD medications. 992 patients with IBD received a biologic agent, but only 232, 224, and 233 received steroids, thiopurines or methotrexate, or 5-ASA agents, respectively, suggesting the difference in use may be responsible for the lack of significant relationship between vaccination status and non-biologic treatments. In contrast, age, race, sex, marital status, use of biologic, insurance type, and employment status had no relationship with likelihood of vaccination in those patients without IBD. Only the number of clinic visits a patient had was positively associated with likelihood of receiving a COVID vaccine (OR 1.54, $p = 0.00383$).

Discussion

Our study examined COVID-19 vaccination rates in a diverse, adult IBD and non-IBD population from a single institution in the state of Maryland. 60.3% (813/1349) of our IBD population received the vaccine, which is lower than the 88.4% of the general, adult U.S population and 95% of the Maryland population (as of April 04, 2022) (37). In our study, 67.4% (145/215) of non-IBD patients were vaccinated.

In prior studies of IBD patients, factors such as female gender, younger age, minority race, lack of prior vaccinations, shorter duration of IBD diagnosis, and current steroid therapy, appear to be negative determinants of COVID-19 vaccination in IBD patients (15, 38, 39). Whereas older age (13, 40), male gender (9, 13), White race (13), prior COVID-19 infection (13), prior routine vaccinations (12, 40, 41), current biologics (9, 13), and immunomodulators use (38), and higher education levels (13, 40) were associated with greater incidences of COVID-19 vaccination.

In prior studies examining the relationship between race in IBD patients and vaccination rates, the patient populations investigated were predominantly White. We included a more diverse patient population. Our study also showed that White

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TABLE 3 Logistic regression describing predictors of COVID vaccination.

Variable	Odd's Ratio	95% Confidence Interval	*P*-value
Age	1.02	[1.01,1.03]	1.65e-05
Male gender (relative to female)	0.683	[0.537,0.869]	0.00194
IC (relative to CD)	1.82	[0.896,3.90]	0.109
UC (relative to CD)	0.983	[0.741,1.31]	0.905
Number of IBD related surgeries	0.890	[0.801,0.988]	0.026
Numbers of clinic visits	1.37	[1.23,1.52]	1.11e-08
Numbers of procedures	1.06	[0.901,1.25]	0.500
Years since diagnosis	1.00	[1.00,1.00]	0.406
Positive biologic status	1.78	[1.34,2.38]	7.82e-05
American Indian or Alaskan Native race (relative to Black)	1.17e06	[9.15e-73,NA (undetectable upper bound)]	0.987
Asian race (relative to Black)	2.84	[1.19,7.38]	0.0233
White race (relative to Black)	1.66	[1.21,2.28]	0.00169
Other race (relative to Black)	1.03	[0.463,2.27]	0.951
Married (relative to unmarried)	1.11	[0.846,1.46]	0.446
Commercial insurance	0.545	[0.212,2.47]	0.987
Medicaid insurance	0.269	[0.0877,1.26]	0.275
Medicare insurance	0.413	[0.0744,1.96]	0.987
Employed	6.92e-07	[NA (undetectable lower bound),8.81e+71]	0.988
Unemployed	4.49e-07	[NA (undetectable lower bound), 5.72e+71]	0.987

race was associated with increased vaccination for COVID-19 in IBD patients. But we also demonstrated that Asian race was associated with increased vaccine acceptance, which had not been previously reported. Interestingly, African American race was not a negative determinant of COVID-19 vaccination, as previously demonstrated. However, African American IBD patients were less likely to be vaccinated relative to White and Asian patients. When compared to African American non-IBD patients, African American IBD patients were equally as likely to receive the COVID-19 vaccine. Concentrated efforts must continue to address the many health disparities which have become more accentuated during the pandemic.

Interestingly, in contrast to the other study, our study showed that female IBD patients were more likely to be vaccinated for COVID-19. Our study had 711 (52.7%) female IBD patients and 141 (65.6%) female non-IBD patients. Women in both groups were more likely to be vaccinated against COVID-19 than men. It is possible that non-IBD women were found to be more likely than non-IBD men to be vaccinated for COVID as women comprised a significantly larger portion of the non-IBD population in our study (65.6%).

We found that IBD-related surgeries were negatively associated with COVID vaccination suggesting that patients with history of severe IBD disease may be more hesitant about getting vaccinated. One possible explanation is that the patients fear the vaccine may exacerbate their disease and therefore lead to more traumatic surgeries. Another potential explanation is that patients with more severe disease and more IBD related surgeries may be more likely to be non-compliant with medication (42, 43). Those less compliant with medications are also likely to be less compliant with recommended vaccinations, such as the COVID-19 vaccine.

Interestingly, we did not find an association between prior vaccinations and COVID vaccination in IBD patients as other studies have shown. It is unlikely that IBD patients have an aversion to vaccinations in general as they are significantly more likely than non-IBD patients to receive other types of vaccinations (influenza, pneumococcal, shingles). And, oppositely, non-IBD patients are more likely to be vaccinated for COVID-19 than the routinely recommended vaccines. The IBD patients' reluctance may be due to the relative novelty of the COVID-19 vaccine versus the other vaccinations that have been available for a significantly longer period. Therefore, assumptions should not be made regarding patients' willingness to be vaccinated for COVID based on their vaccination history.

Our study also showed that biologic use was positively associated with COVID-19 vaccine. However, other immunosuppressive medications did not show any relationship as other studies have. This may be because a higher proportion of patients were on biologics (992, 73.5%) at this institution given it is a large tertiary care referring center, and only 232 (17.2%), 224 (16.6%), and 233 (17.3%) received either steroids, thiopurines or methotrexate, or 5-ASA agents, respectively.

We did not find an association between steroid use and COVID-19 vaccination. This may represent a dichotomy of perception of the patients: some may perceive that a COVID-19 vaccination might exacerbate their acute flare, and some may perceive that because they are in an acute flare, they wish to prevent a worse COVID-19 infection outcome.

In congruence with prior studies, older age appears to be associated with more likelihood of being vaccinated for COVID-19 in IBD patients. Age was not a predictor in non-IBD patients. This is likely due to the IBD patients' perception of higher risk for severe outcomes of COVID-19 infection given the evidence that the disease has a higher likelihood of negatively impacting the older population. Another reason why older IBD patients have higher rates of vaccination may be because they have had longer exposure and interaction to the healthcare system and this has required them to have regular contact with their health care providers.

This study also highlights the importance of regular visits with IBD patients, especially those who are immunosuppressed. We demonstrated that both IBD and non-IBD patients with more clinic visits over the 12-month period were more likely to be vaccinated against COVID-19. Clinic visits present opportunities for patients to ask questions regarding the vaccine and how COVID-19 infection can impact their disease. It is possible that patients who have higher numbers of clinic visits represent patients that are in an acute phase of their disease. Therefore, these patients may perceive a heightened risk and vulnerability to COVID-19, leading them to receive vaccinations for COVID-19. In addition, number of clinic visits was the only factor that was positively associated with vaccination in non-IBD patients, which further demonstrates its importance across both populations. Therefore, communication between physician and patient is one of the best contributing factors to getting vaccinated. Unfortunately, it has become easy for patients to be lost to follow-up during the pandemic. As providers, we must continue to educate our patients during clinic or telemedicine visits on the importance of obtaining a COVID-19 vaccine. Often, health maintenance conversations surrounding vaccines can be pushed to the end of the appointment or never spoken about given time restraints. We must continue to make this a priority during appointments given the ongoing global pandemic.

One limitation of this study is relying on the accuracy of the electronic medical record (EMR) for variables including vaccination status; marital status; employment status; and history of tobacco, alcohol, and illicit substance use. Data recorded are based solely on information disclosed by the patient.

In conclusion, greater vaccination efforts should be made for IBD patients, specifically targeting patients that are male, younger in age, African American, and have history of multiple IBD-related surgeries. In addition, efforts should be made to continue regular visits with patients when indicated to improve communication, educational opportunities, and thus increase COVID-19 vaccination uptake.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

As this was a retrospective chart review study, individual informed consent was waived and oversight of the protocol was governed by the University of Maryland, Baltimore Human Research Protections Office. All patient data collected were de-identified of any protected health information.

Author contributions

HK and KP are co-first authors and both planned the study, collected the data, and wrote the manuscript. KP submitted the study. MA performed data analysis and also wrote the manuscript. MBe, EZ, MBo, PP, and LS collected the data. UW was the Principal Investigator who planned and organized the study. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Lowering COVID-19 vaccine hesitancy among immigrants in Norway: Opinions and suggestions by immigrants

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Even though COVID-19 vaccine has been proved effective, vaccine uptake and coverage has been and still is a great concern across different immigrant groups. Vaccine hesitancy remains a barrier to accept the vaccine among immigrants across the globe—including Norway—despite higher rates of hospitalizations and deaths. This study aimed to explore the opinions and suggestions of immigrants on how to lower the COVID-19 vaccine hesitancy among immigrants in Norway. Qualitative interviews were conducted with 88 persons with different immigrant background. Data was analyzed using framework analysis, utilizing "3Cs model of vaccine hesitancy" as a theoretical framework. The analysis yielded five main themes related to factors that may lower the vaccine hesitancy among immigrants in Norway: (1) Effective cultural communication, (2) Vaccine advocacy through community engagement, (3) Motivating factors, (4) Collaborative efforts *via* government and healthcare, and (5) Incentives for vaccination. This study enhanced our understanding of factors that according to immigrants themselves may lower the vaccine hesitancy. The insights obtained in this study can contribute to a better understanding of the current status of vaccine uptake among immigrants and can further give directions on how to improve vaccine uptake in these groups in Norway.

KEYWORDS
COVID-19, immigrants, vaccine hesitancy, opinions, suggestions, Norway

Introduction

In several countries, the COVID-19 pandemic has disproportionately affected immigrants due to different range of vulnerabilities, including socioeconomic barriers such as occupational exposure (bus/taxi drivers, cleaning industry etc.) with no possibility of home office, overcrowded housing, lack of or low health literacy, co-morbidities leading to higher rates of hospitalization and death in these groups, as compared to the general population in the respective countries (1–5).

The development and rolling out of COVID-19 vaccine have been a great public health achievement. High vaccination coverage induces indirect protection to the overall community or herd immunity, by decreasing the transmission rates, and thus also decreasing the risk of infection among the most susceptible and vulnerable in the community (6). However, the success of the vaccine program depends on ensuring that all members of society have equal and prompt access to the vaccine (1). Although awareness regarding COVID-19 vaccine can often be high in high income countries, it seems that many countries are still struggling to increase vaccination coverage among those who are hesitant about the vaccine (7). Vaccine hesitancy, here understood *as delay in acceptance or refusal of vaccination despite availability of vaccination services, is a complex phenomenon, dependent on the context, and associated with various social and physical factors* (8). It remains a significant challenge to public health and a barrier to succeed with the disease containment strategy (7, 9). Recent studies have reported that immigrants are more hesitant to accept the COVID-19 vaccine, in comparison to the general population (10–18). To the extent that vaccine hesitancy is reflected in vaccination coverage and uptake, the following numbers might throw some light on the problem. In Sweden, the lowest vaccination coverage was reported among immigrants born in low- or middle-income countries (North Africa: 59%, other African countries: 44%) as compared to those born in Sweden (91%) (16, 17). In the UK, despite high availability of vaccines, the proportion who have chosen not to take the vaccine was higher among Blacks (71.8%), Pakistani and Bangladeshi (42.3%) in comparison to White British (15.2%) (10). Racial disparities with COVID-19 vaccine uptake have also been reported in a study conducted in the US, in which Black Americans were least likely to accept the vaccine as compared to other groups (12).

In a survey from Norway, it was reported that COVID-19 vaccine uptake varied between different immigrant groups. Immigrants from Eastern Europe, Western Asia and Africa had significantly lower uptake than the general population. The authors linked such difference to length of residence in Norway, education levels, and contact with Norwegians (19). Further, a recent Norwegian study on COVID-19 vaccination coverage by immigrant background, reported that immigrants had lower vaccine uptake, which varied from 45% (Latvia, Bulgaria, Poland, Romania, and Lithuania) to 92 % (Vietnam, Thailand, and Sri Lanka). The authors suggested that the difference in vaccination coverage to some extent could be explained by income and education (20). In another study, it was found that vaccination coverage in European countries ranged from 24.3 to 98.1% and ranged between 44.0 and 89.2% among European-born immigrants in Norway. Higher vaccination coverage was found among immigrants with a longer stay of residence in Norway than those with a shorter stay (21). Furthermore, lower vaccination uptake was also reported among health professionals with immigrant background in Norway (22). In a nation-wide registry study among healthcare workers, the vaccination rate was 9-percentage point lower among immigrant health workers (85%) compared to healthcare workers with non-immigrant background. The overall vaccination rate varied between health workers with immigrant background. The lowest vaccination rates were found among those born in Somalia (78%), followed by Eritrea (77%), Poland (76%), Romania (75%), Lithuania (72%), Serbia (72%) and Russia (71%) (22). We assume that a great deal of these differences in vaccination coverage and uptake are due to vaccine hesitancy.

Various studies have reported reasons for vaccine hesitancy among immigrants such as in Danish study, it was pointed out that hesitancy may be caused by lack of information about vaccine due to language barriers and limited digital competencies (23). Among younger immigrants, of whom several were not afraid of getting infected with virus or already had been infected, there was a tendency to deem vaccination as an unimportant measure. Moreover, some had received misinformation of infertility as the long-term side effect (23). Similar findings were reported in studies from Sweden and the UK, in addition to having the distrust on institutions (10, 11, 24–26).

A study on the impact of vaccine misinformation in the UK and the US suggests that some migrant communities may be more susceptible to COVID-19 vaccine misinformation, particularly where language barriers and social exclusion contribute to a deficit of accurate and accessible information (27). In previous work, we have explored the barriers to COVID-19 vaccination among immigrants in Norway and found out that immigrants were hesitant to receive the vaccine because of fear of side effects, long-term complications, misinformation of vaccine contents, conspiracy theories and lack of professional guidance on vaccine safety (28).

In line with this, Njoku et al. (29) discuss various ethnic inequities and structural barriers that can lead to lower vaccine acceptance, such as immigration status, lack of a centralized system, complicated vaccine scheduling, difficulties in reaching a vaccination site, language difficulties and inaccurate translations, poor digital access, and lack of trusted point of access in immigrant-specific areas. Indeed, vaccine hesitancy is a complex concept, varying across time, place and situations. Still, because vaccination is the most promising solution for the COVID-19 pandemic, such hesitation may influense vaccine utptake, create difficulties in obtaining adequate vaccine coverage in some immigrant groups and thus pose a threat to immigrants health (29).

In the present paper, we explored immigrants' perspectives, opinions, and experiences regarding interventions with a potential to lower vaccine hesitance and thus increase the uptake of COVID-19 vaccine among immigrants in Norway. Increasing vaccine uptake among immigrants is of significant importance in Europe. However, to our knowledge, so far there has been no study in Europe that has explored

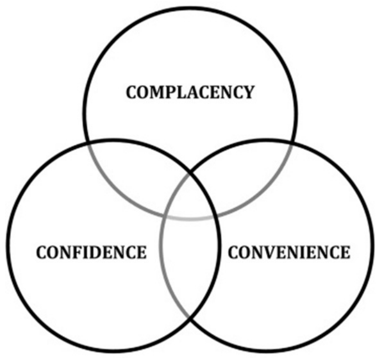

FIGURE 1
"3Cs model of vaccine hesitancy" (8).

immigrants' perspectives on interventions to increase their vaccine uptake.

Theoretical framework

WHO's Strategic Advisory Group of Experts (SAGE) on immunization has proposed a 3Cs-model (complacency, convenience, and confidence, Figure 1) (8) has been proposed in order to understand the concept of vaccine hesitancy and its determinants. *Complacency* occurs when the perceived risks of vaccine-preventable diseases is perceived as low. Vaccination is therefore not considered as a necessary preventive measure. In turn, complacency is influenced by factors such as health/life responsibilities. *Convenience* is another detrimental factor that affects the decision to get vaccinated. It depends on the quality of service that is made available, such as vaccine delivery at a particular time and place, appeal of immunization services, affordability, language, and health literacy, as well as the cultural context. Further, in the 3C-model, *confidence* means the ability to trust the effectiveness and safety of the vaccine, which in turn is influenced by the reliability and competence of the health care services and government's motivation for installing a vaccination program (8).

In on our study, *complacency* could be understood as "no need", *convenience* could be referred to the contextual factors, such as appeal, affordability of services, health literacy and social support. Further, *confidence* could imply "lack of trust in vaccine and/or services.

As vaccine hesitancy results from complex decision-making processes that to varying degrees are influenced by each of the factors constituting the 3Cs model (8), we believe that these factors in many instances also can be overlapping. Indeed, the descriptions of the 3Cs above as well as Figure 1 show that these categories are not mutually exclusive. Nonetheless, we argue that the 3Cs-model can be of great value in identifying factors that may lower vaccine hesitancy. MacDonald et al. do, however, not discuss the overlap among these 3Cs in their model.

Methods

To gain knowledge about factors that can help in lowering the vaccine hesitancy among immigrants, we conducted a qualitative exploratory study.

Recruitment and participants

The study was conducted in several counties of Norway and included those who met the inclusion criteria: men and women, over the age of 18 and who were either born outside of Norway [immigrant (30)] or had at least one parent born outside of Norway [Norwegian born to immigrant parents (30)].

To recruit participants, the Norwegian Institute of Public Health (NIPH) hired Opinion, a research consultancy firm. Out of the 55 participants recruited by this firm, 28 were recruited by snowballing and *via* networks like Facebook and other social media. In addition, five participants were recruited *via* contacts in various organizations. Three informants were recruited by the moderator on the streets in Oslo. The other 34 participants were recruited by the researchers from NIPH using purposive and snowballing methods**.** Saturation was achieved when no new patterns, ideas and opinions were found during the course of last interviews (31).

To attain the information-rich data, the study included a diverse sample of immigrant groups, including those groups who had higher hospitalizations and mortality due to COVID-19 disease as compared to other groups and the general population (2).

A total of 89 participants (Table 1), from ten different countries, were included in the study. These were Afghanistan (12), Bosnia/Serbia (6), Eritrea (6), Iraq (12), Pakistan (12), Poland (11), Somalia (12), Sri Lanka (6), Syria (6), Turkey (6). The age of participants varied from 19 to 78 years. There were 39 men and 50 women. The length of residence among participants varied between 1 and 48 years and a few were born in Norway. Several of the participants had completed secondary education while some had university education. They worked in different sectors like health services, transport, kindergartens, restaurants, IT, education sector or they ran their own businesses. However, some of the participants were laid off from their jobs due to the pandemic and a few were students and pensioners. Some of the participants were engaged in voluntary work in their local communities and had contributed to the dissemination of information about the pandemic in their respective communities. Further, the knowledge of Norwegian society and language skills varied among the participants, according to the length of residence in Norway.

TABLE 1 Characteristics of study participants.

Variables	Frequency ($n = 89$)
Gender	
Male	39
Female	50
Age, years	
19–50	69
51–78	20
Country of origin	
Afghanistan	12
Bosnia/Serbia	6
Eritrea	6
Iraq	12
Pakistan	12
Poland	11
Somalia	12
Sri Lanka	6
Syria	6
Turkey	6

Data collection

Six researchers from NIPH conducted 34 interviews. Immigrants from Pakistan, Somalia and Iraq were interviewed in their mother tongue (by researchers with Pakistani, Somali, and Iraqi background, while those from Poland, Afghanistan and Eritrea were interviewed in Norwegian. One Iraqi participant was interviewed in Norwegian on his preference.

Two moderators from Opinion conducted 54 interviews, 53 were individual interviews (31), while one was dyadic interview (conducted with two participants) (32). Five interviews were conducted in the participant's mother tongue using interpreters, 2 were conducted in English and the remaining were conducted in Norwegian. All interviews took place during the ongoing COVID-19 pandemic in Norway, and after the roll out of a vaccination program, between March-May 2021.

The interviews were conducted using an interview guide prepared by number of researchers working in the field of migration and health at NIPH and Opinion. The guide consisted of open-ended questions, and covered the broad topics, including, knowledge about vaccines, concerns and attitudes about vaccine in their community, opinions and suggestions on what would encourage the people of their community to get vaccinated, and what according to them can help lowering vaccine hesitancy among their community members, and were followed by probing questions.

The interviews, which lasted between 30 and 90 min, were conducted digitally *via* Zoom or Teams or by telephone. One dyadic interview was conducted face to face. All the interviews were audio recorded.

Ethical considerations

All the participants were sent information about the study prior to their participation. Prior to each interview, information regarding the study and the purpose of the study was explained to participants and consent was sought orally (a professional interpreter was used when necessary). The Regional Ethics Committee for Medical and Health Research in Norway has assessed that the topics investigated in this research project fall outside the Health Research Act. The research project therefore does not have an ethical approval from the Regional Ethics Committee in Norway. However, the ethical aspects of the current research project have been assessed by NIPH and found to be acceptable. In consultation with the Privacy Ombudsman at NIPH and Opinion, we have also assessed whether the data collection in this study required a complete Data Protection Impact Assessment (DPIA), of which it was concluded that this was not necessary.

Data analysis

All the interviews were transcribed verbatim into Norwegian by two moderators from Opinion and five researchers from NIPH. The data analysis was done manually by framework analysis (33) using "3Cs model of vaccine hesitancy" (8) (Figure 1) as a framework.

The analysis process included five steps (33). In the first step, familiarization, the transcriptions were read and reread to become familiar with the material, to get an overview and become aware of recurring themes. In step two, five main themes were generated in dialogue with the original "3Cs model of vaccine hesitancy". That is, the themes were generated from the data considering the theoretical framework as a correspondence. In the third step, indexing, data corresponding to a particular theme was identified and pooled. In step four, charting, the indexed data from stage three were placed in the thematic framework. The themes were discussed by the researchers among themselves several times, addressing the credibility of the findings. In the final stage of mapping and interpretation, the key themes in the thematic framework were described and interpreted in the results section. Two of the themes overlapped within the three categories of the 3Cs model (complacency, confidence, and convenience), as shown in Figure 2. This overlap is explained and discussed in the discussion section.

FIGURE 2
Factors lowering vaccine hesitancy among immigrants. Figure adapted from "3Cs model of vaccine hesitancy" (8).

Results

The analysis yielded five main themes that represented factors which may lower the vaccine hesitancy among immigrants in Norway. These themes were: (1) Effective cultural communication, (2) Vaccine advocacy through community engagement, (3) Motivating factors, (4) Collaborative efforts *via* government and healthcare (HC), and (5) Incentives for vaccination. Themes 1 and 2 were overlapping in the framework of "3Cs model of vaccine hesitancy" (Figure 2), and also formed the basis for our discussion.

Effective cultural communication

Participants mentioned that vaccine hesitancy and skepticism can be lowered by effective communication among different immigrant groups in their respective languages. They further stated that addressing the medical and religious concerns of these groups along with targeting false information on social media will create awareness of vaccine safety. They also suggested involvement of public figures and leaders in campaigning for vaccine safety, especially people who have been vaccinated and are trusted in the Norwegian society.

> *In Skien, every person who gets vaccinated, makes a video in their native language to recommend the vaccine. We can use these videos in social media and suggest people to take vaccine.* (F, 50 years)

> *I think it is important that it comes from a local network, including someone who speaks the language. I think it is important to have an open dialogue about these conspiracy theories and perceptions, "Why are you sceptical of the vaccines? What is the cause? Do you have any reason? ≫ I do not think it should be downplayed, then, that people feel that unrest. That unrest exists among both the younger and older generations, but for some it may simply be a lack of knowledge. So, I think it's important to use local people and also translate content about what this vaccine means and have open discussions about it... that you could, for example, have a workshop or something where you talk openly about what the vaccine means and why you are so afraid to take it* (F, 29 years)

> *... when it comes to vaccination, I think that the communication could have been better adapted to culture* (M, 29 years)

Participants suggested that providing detailed information about vaccine, that is, the benefits of receiving the vaccine in their own language and free of cost availability will be beneficial, especially if it gets circulated within their local networks and places where they often meet. The participants also mentioned targeting false information by having an open dialogue with group of immigrants about the potential perceptions related to concerns and conspiracy theories.

> *I think people need more detailed information about the vaccine. Most people do not believe in vaccine, and it is important that they are informed about it. Now we have made brochures and hung them up in different places where people often meet.* (M, in his 30s)
> *... for very many it is not enough to say that the vaccine is safe. They feel that they are not treated well, when they are told that, just like children, you see. They want accurate detailed information, not just the general "vaccine is safe".* (F, 33 years)

Some participants raised the concern about long history of skepticism related to any vaccine in their home country, which ultimately influence their decision making. They suggested to target these concerns and assure people of their community that vaccine is safe, by providing examples in their language, even if the vaccine for COVID-19 disease is made in short span of time.

> *There has been skepticism about the vaccines in Poland for many years. This applies not only to the corona vaccine, but also to other vaccines, so it is in a way an extension of what has been already there, and at the same time so many things happened in a short time. So, people are starting to get confused. This should be addressed.* (M, 37 years)

Vaccine advocacy through community engagement

Some participants suggested vaccine advocacy through engagement of community leaders, for example by including imams or other religious leaders in creating awareness about the benefits of receiving vaccine. This will counter the skepticism of many individuals who follow imams. Some participants also suggested about sharing their positive experiences of taking other vaccines in their home countries. This will indirectly increase the trust in COVID-19 vaccine and its safety. Further, one participant mentioned about sharing the information about vaccine from the governmental websites to their local Facebook groups to create awareness about vaccine and thereby lowering vaccine hesitancy.

> *I have also shared information regarding vaccination during Ramadan from Oslo municipality page on Facebook because there are many who wonder about this. In addition, I have asked two Afghan imams for their opinions regarding vaccination when fasting, and they both said that "it goes perfectly well, not only vaccination, but also that you can take other medicines". It is very important to convey such information about vaccine because there are still many who are skeptical to vaccine.* (M, 40 years)

As per several participants, trust building is an important factor for the success of vaccination program among immigrant communities. They mentioned that health professionals, especially those with a similar background and who speaks the same language, play a crucial role in creating trust, for example by providing adequate and clear medical advice regarding vaccination. One participant mentioned that immigrants do trust advice of health professional with similar background.

> *I would not say it is safe or unsafe if the health professionals say it is safe and I will listen to them. What gave me trust and assurance was when health professionals found out that Johnson and AstraZeneca were not completely safe, and they stopped it. It made me feel even safer… and I have no problems in being vaccinated"* (M, 58 years).

Motivating factors

Participants mentioned several motivating factors that can help in lowering vaccine hesitancy, including receiving detailed information about vaccine, information about others who have already been vaccinated and the people they trust, also that vaccination is available free of cost for everyone in the community, and that getting vaccinated will contribute to normalizing day to day life (pre-COVID-19).

Some participants mentioned that people in their communities will feel reassured if someone with a similar background has taken the vaccine, and without negative consequences, provided that the source of information is reliable. This will also contribute to the spread of a positive message about vaccine within their communities and hence lower the vaccine hesitancy.

> *I have experienced that good news or medical advice spreads faster in the local community. If you know someone who has taken the vaccine and they are having that conversation with you, it will be more natural to hear them than someone from the authorities. So, if I was able to vaccinate people with minority backgrounds then I would have started with those who have the most contact with others because then they can tell and spread it further. It is reassuring to see a person who has similar background as you and speaks the same language as you, who have taken the vaccine and says that it has gone well.* (F, 20 years)

Another participant mentioned that the spread of information that vaccination will take us a long step toward an everyday life like before the pandemic will be a motivating factor for receiving the vaccine and lowering the hesitancy.

> *I think if the vaccine is effective and contributes to everyday life being normalized again, then I think it is good to get vaccinated* (F, in her 30s).

Another motivating factor was that either they themselves have worked in the healthcare or they have family members or friends who have worked in the healthcare services for a long time. This may allow easy access to the information that can counter vaccine related concerns and doubts. A few participants also mentioned that having an underlying disease can be motivating factor to take the vaccine, in order to prevent getting seriously ill with COVID-19 disease.

Collaborative efforts *via* government and healthcare

Some participants suggested that the Norwegian government and healthcare authorities should work together against the spread of misinformation that creates vaccine hesitancy by providing sufficient and adapted information tailored to the different immigrant groups.

The participants also stated that it is important that government and healthcare authorities work together in disseminating information about vaccine safety in different immigrant communities. If they together promote the vaccine, most people in their community will take it, they said.

Trust in the government as well as trust in the health professional's assessment increases the likelihood of success of vaccination programs among immigrants. Some participants, especially those with longer stay of residence, told that they do have high level of trust in both government and healthcare, because of good previous experiences. They further mentioned that their trust level increased when the government and healthcare authorities decided to stop giving AstraZeneca after it was clear that it could cause severe side-effects.

> *I trust the Norwegian government, and I am sure that they will not allow the vaccine without knowing the usefulness and effect of the vaccine. For example. The blood clots that came from the AstraZeneca vaccine caused people to fear and worry about the vaccine. But the good thing was that they stopped the vaccine immediately and continued with other safe vaccines.* (M, 35 years)

Incentives for vaccination

Several participants mentioned that they during the pandemic have taken or would take vaccine in order to travel, especially to their home countries. Some participants mentioned that they partly live in Norway, partly in their homelands. Their strong connection with their homelands and the possibility of being able to visit their family if vaccinated would act as an incentive for vaccination.

> *I have already received the first dose, and everyone I know I want to get vaccinated. Because we hope that when we are vaccinated it will be possible … to travel to our country and easier to prevent quarantine or be in shorter quarantine.* (F, 45 years)

For several of our participants, prospects of traveling would be an incentive for vaccination. Other incentives were access to restaurants, cinemas, and museums, which all during the pandemic required vaccine certificate for entry. Such incentives may increase the vaccination rates and hence indirectly reduce vaccine hesitancy.

> *You cannot travel without a vaccine and since they like to travel, they will have to get vaccinated.* (M in his 40s)

Discussion

There is substantial evidence that among immigrants, COVID-19 vaccine hesitancy is high (11, 12, 14, 15, 29). Moreover, there has been a substantial increase in the misinformation about COVID-19 vaccination, especially among immigrants (34). This seems to hold true for immigrants in Norway as well (28).

The aim of this study was to explore immigrants' perspectives, opinions, and experiences regarding interventions with a potential to lower vaccine hesitance and thus increase the uptake of COVID-19 vaccine among immigrants in Norway. As a framework to our analysis we used the "3Cs model of vaccine hesitancy" (8) and five main theme were yielded: effective cultural communication, vaccine advocacy through community engagement, motivating factors, collaborative efforts *via* government and health and incentives for vaccination.

In broad terms, our study shows that to lower hesitancy and in this way enhance uptake, people at risk (immigrants) should feel that they need vaccine. Through adequate information, people may understand that they need vaccine to reduce their risk of severe illness. Adequate information may be provided through effective cultural communication, vaccine advocacy through community engagement and motivating factors.

Our findings also show that people at risk should trust the people providing information. It is then more likely that they will take the given information seriously and make an effort to become vaccinated. These factors might increase when engaging in collaboration, that is, by vaccine advocacy through community engagement and collaborative efforts *via* government and healthcare, provided that the people at risk do not feel exploited or serve as a kind of alibi.

Further, our study shows that the contextual factors are favorable for lowering vaccine hesitancy. Appeal, health literacy and social support may increase when people are collaborating as people then get to know each other, exchange views and experiences and can support each other in making decisions, that is, through effective cultural communication, vaccine advocacy through community engagement and collaborative efforts *via* government and healthcare. These findings are all in line with the 3Cs model (8).

Furthermore, the themes overlapped within the framework model. Overlap can be explained as such, vaccine advocacy through community engagement may have effect on all Cs of the framework model. That is, vaccine advocacy may increase the "confidence" and "convenience" and decrease the "complacency". Furthermore, effective cultural communication may have effect on two categories of the model, that is, may increase the "confidence" and decrease the "complacency", thereby lowering the vaccine hesitancy'. These are discussed below.

It is essential that information related to vaccine is both culturally tailored and provided in different languages (1). This is elaborated in a study conducted in the UK: to reach specific target groups, it is necessary to present detailed information on side-effects and contraindications not only in multiple languages, but in a culturally appropriate and understandable manner (25), which is in line with our findings. Further, Deal et al. (25) suggested that the information must be in such a way that it does not stigmatize any community, because stigmatization could have a negative impact on trust and engagement. Still, such efforts should go along with specific campaigns to counter misinformation. These strategies may help in decreasing the "complacency" and increasing the "confidence" in the 3Cs model.

Further, adequate information is likely to both increase "confidence" and decrease "complacency" in the framework model and have a positive effect on vaccine hesitancy. Regarding contextual factors, we should, however, be aware of historical oppression as well as current disparities in care that have been linked to the mistrust in the healthcare system among immigrants (35). This resonates with a Norwegian study, which found that many immigrants mostly listen to others who speak their mother tongue and, further, prefer to listen to people in their own environment rather than to representatives of local or national authorities (36). Therefore, campaigns specifically targeted at gaining trust among immigrants may increase the likelihood of receiving the vaccine.

Collaborative efforts between government, healthcare workers and representatives from the targeted local community may increase the "confidence" in the framework model as people who deliver the vaccine are more likely to be considered reliable and competent by the group in question. These efforts may include the implementing participants' suggestions as a part of a formal Tailoring Immunization Program (TIP) approach. TIP approach has been proven successful previously and has improved the immunization programs by understanding the perspectives of the low-coverage population in Europe (37). Moreover, in our study, the participants strongly highlighted a need for effective and culturally sensitive communication. They stated that healthcare professionals with a similar background, religious leaders, or other spokespersons from the inside of closed environments can most effectively provide information that can influence vaccine hesitancy. Moreover, some immigrant groups are strongly represented in the labor market, and it is likely that encouraging employers to motivate their employees to take vaccine and spread information about the vaccine safety in their respective milieus, may also aid in lowering vaccine hesitancy as many have a trustful relationship to their employers and therefore listen to their advice. However, such an initiative poses some ethical dilemmas that should be thoroughly investigated before this becomes a recommended strategy to increase vaccine uptake.

Our study showed that longer the stay of residence in Norway, the higher is the trust in the healthcare sector. Therefore, involving immigrants with longer stay of residence and those who are active in the community could be useful in the co-production of tailored interventions (to lower vaccine hesitancy and increase uptake) and in the dissemination of such interventions. Our participants suggested to involve trusted groups or community members to advocate the vaccine's safety, as they can widely promote relevant information in their own communities. They can also be useful for those designing vaccine advocacy campaigns. This is in line with other studies, which show that local community champions can act as information point both for their own community and for those designing tailored vaccine advocacy campaigns (1, 25).

Our analysis shows that vaccine advocacy through involving representatives from local communities has an effect on all Cs of the framework model. This is in line with a recent systematic review found that advocacy through community outreach programs and educational campaigns are promising strategies for improving vaccine uptake among immigrants in Europe (38). Furthermore, this kind of vaccine advocacy, which is ultimately based on adequate and appropriate information provided by highly trusted people, may increase not only "confidence", but also "convenience" as these people may be easy to reach and speak a language that people can easily understand. "complacency" is also likely to decrease, provided the champions adequately and correctly inform about the health hazards of COVID-19 infections.

Regarding motivating factors, some participants stated that knowing about vaccine safety and its effectiveness on reducing the spread of COVID-19 disease can increase the uptake. Others reported that spread of information *via* word-of-mouth and social media by individuals who have already taken the vaccine would lower the vaccine hesitancy. In line with other studies (25) motivating factors seem to increase "convenience" in the framework model by aiding the ability to understand the effectiveness of vaccine, and thus lower vaccine hesitancy.

Conclusion

This study provides some insights into immigrants' experiences, opinions, and suggestions on how vaccine hesitancy with regards to COVID-19 vaccine can be lowered in their respective groups. To our knowledge, this is the first study to explore these issues in a Norwegian context. Adequate knowledge provided in an effective and culturally sensitive way, combined with vaccine advocacy through community engagement may be important factors in creating disease awareness and lowering COVID-19 vaccine hesitancy. Further, there is need for establishing cooperation with religious leaders and trusted representatives and/or resource persons from the different affected communities in order to effectively reach out to the most vulnerable. This is especially important when it comes to counteracting misunderstandings and misinformation.

Our results, which are based on participants' subjective opinions and experiences, provides nuanced data specific to the immigrant population in Norway and can therefore be useful when designing approaches to lower vaccine hesitancy in these specific populations. In addition, our findings largely correspond to findings in other, international studies and thus contribute to the broader literature on how to address and allow for some general recommendations. When designing information campaigns on sensitive and critical issues like the COVID-19 pandemic, we strongly recommend a collaborative approach, a collaboration between local healthcare professionals and government officials pervaded by a direct dialogue between them and the targeted local communities; a dialogue in which all parties are listened to and willing to adjust to each other. In this way, specific concerns can be addressed, and dissemination of sufficient information is ensured so that informed decisions about COVID-19 vaccine can be made.

Data availability statement

The datasets presented in this article are not readily available because due to the nature of this research, participants of this study did not agree for their data to be shared publicly, so supporting data is not available. However, raw data will be made available on reasonable request to researchers from accredited research institutions, with any data that may risk loss of confidentiality redacted. Access to data will be limited to investigators who provide a methodologically sound proposal. To ensure compliance with the General Data Protection Regulation, data processing must be covered by the European Commission's standard contractual clauses for the transfer of personal data, which must be signed by the data requesters. Proposals and requests for data access should be directed to the corresponding author. Requests to access the datasets should be directed to PK, prabhjot.kour@fhi.no.

Ethics statement

The studies involving human participants were reviewed and approved by Privacy Ombudsman at Norwegian Institute of Public Health and Opinion. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

PK and TI contributed to conception and design of the study. PK carried out the data analysis, interpretation, and wrote the first draft of the manuscript. AG, AA, SQ, NS, ØV, and TI contributed to the further analysis and the write up of manuscript. All the authors contributed to manuscript revision, read and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Reduced antibody response to COVID-19 vaccine composed of inactivated SARS-CoV-2 in diabetic individuals

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Background: Patients with type 2 diabetes mellitus (T2DM) are at increased risk for COVID-19 related morbidity and mortality. Antibody response to COVID-19 vaccine in T2DM patients is not very clear. The present work aims to evaluate the antibody response to the inactivated SARS-CoV-2 vaccine in this population.

Methods: Two groups of subjects with no history of SARS-CoV-2 infection were included: 63 T2DM patients and 56 non-T2DM controls. Each participant received two doses of inactivated COVID-19 vaccine. IgG antibodies against the nucleocapsid (N) and spike (S) proteins of SARS-CoV-2 (anti-N/S IgG) and receptor binding domain (RBD) proteins (anti-RBD IgG) were quantitatively evaluated by the electrochemiluminescence immunoassays, respectively.

Results: It was observed that the positive rates and titers of anti-N/S IgG and anti-RBD IgG in T2DM patients were significantly lower than those in controls, respectively (anti-N/S: 85.7 vs. 98.2%, $P = 0.034$; 25.48 vs. 33.58 AU/ml $P = 0.011$; anti-RBD: 85.7 vs. 96.4%, $P = 0.044$; 15.45 vs. 22.25 AU/ml, $P = 0.019$). Compared to non-T2DM subjects, T2DM patients with uncontrolled glycemia showed lower positive antibody rates and titers (anti-N/S IgG: 75% and 13.30 AU/ml; anti-RBD IgG: 75% and 11.91 AU/ml, respectively, all $P < 0.05$), while T2DM patients with controlled glycemia had similar positive antibody rates and titers (anti-N/S IgG: 94.3% and 33.65 AU/ml; and anti-RBD IgG: 94.3% and 19.82 AU/ml, respectively, all $P > 0.05$).

Conclusion: In the analysis performed, the data indicate that T2DM patients with uncontrolled glycemia showed a lower level of IgG antibodies compared to non-diabetic controls and individuals with controlled glycemia when immunized with the inactivated COVID-19 vaccine.

KEYWORDS

T2DM patients, COVID-19, vaccination, inactivated SARS-CoV-2, impaired antibody response

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Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a global healthcare crisis, since as of 30 October 2022, at least 627 million confirmed cases and 6.5 million deaths were reported globally (1). COVID-19 also affects other patients or causes other medical issues (2–7). Compared to healthy individuals, those who had underlying chronic diseases, including hypertension, type 2 diabetes mellitus (T2DM), chronic obstructive pulmonary disease, cerebrovascular or cardiovascular disease, and others have increased fatality rate after infection with COVID-19 (8–10). COVID-19 occurred in diabetic patients is usually more severe than in non-diabetic patients (11–13). Thus, diabetic patients are among the critical subpopulations for prevention of COVID-19 (14, 15).

Diabetic patients are at increased risk for various infections (16), suggesting that the immunity in diabetic patients is to some extents compromised. Studies showed that the antibody response to hepatitis B vaccine is impaired in diabetic patients (17–19). However, the antibody response to influenza vaccines appears to be not impaired in people with T2DM (20, 21). These studies indicate that diabetic patients may present different immune response to different vaccines.

Since December 2020, several COVID-19 vaccines, composed of inactivated SARS-CoV-2, mRNA encoding the full-length spike (S) protein of SARS-CoV-2, viral-vector based vaccine encoding the S protein, or recombinant S proteins, have been applied in human to prevent the pandemic of COVID-19 (22–25). Recently, several studies reported the antibody response to mRNA or viral-vector vaccine against COVID-19 in diabetic patients with inconsistent results (26–29). COVID-19 vaccines composed of inactivated SARS-CoV-2 have been demonstrated to be effective and are also widely used in the world (24, 25, 29–32). However, the immunogenicity of inactivated COVID-19 vaccine in diabetic patients is not very clear (33). The present study aims to evaluate the antibody response to the inactivated SARS-CoV-2 vaccine in this population.

Materials and methods

Participants

China issued the first license for COVID-19 vaccine (Aikewei, Beijing Institute of Biological Products/Sinopharm, Beijing, China) composed of inactivated SARS-CoV-2 on December 30, 2020, and the second inactivated COVID-19 vaccine (CoronaVac, Sinovac Life Sciences, Beijing, China) on February 5, 2021, for emergency use in adult individuals at the age 18–60 years. The recommended vaccination requires two vaccine doses at an interval 2–4 weeks. During the first three-month period of vaccination campaign, the vaccines were mainly used in individuals who were at the frontier lines for controlling the pandemic of COVID-19, such as healthcare worker and other populations at high risk for infection of SARS-CoV-2 (24, 25, 34). Since April 1, 2021, COVID-19 vaccines have been administered among all general populations at the age of 18–60 years, and the vaccines have been then applied in adults over 60 years old and children at the age of 3–17 years. The COVID-19 vaccines initially used in China were mainly composed of inactivated SARS-CoV-2 adsorbed on adsorbed on aluminum hydroxide adjuvant (Aikewei or CoronaVac) (35, 36).

This was a cross-sectional study. Two groups of participants with no history of SARS-CoV-2 infection were included, and each participant received two doses of inactivated COVID-19 vaccines (Aikewei or CoronaVac). The patient group was composed of the individuals with T2DM who were out-patients in the department of endocrinology at Nanjing Drum Tower Hospitals between March 10 and September 24, 2021. The diagnosis of T2DM was based on the criteria (37). The inclusion criteria included: (1) $\geq$18 years older, (2) immunized with two doses of COVID-19 vaccine composed of inactivated SARS-CoV-2, within 2–10 weeks before recruitment. Patients who met any of following conditions were excluded from the study: (1) with autoimmune disease, (2) with malignant tumor, (3) with history of administration steroid hormones or other immunosuppressive agents within recent 3 months, (4) ongoing medication with any immunosuppressive agent, (5) Type 1 Diabetes, and (6) pregnancy. The control group consisted of age and sex matched subjects who had no history of diabetes and had normal fasting blood glucose; they were healthcare workers in Nanjing Drum Tower Hospital. All the subjects in the control group underwent regular yearly health examinations at least in the last 3 years, and no one showed the fasting blood glucose over 6.4 mMol/L. The inclusion and exclusion criteria were same as those mentioned above. The blood samples were collected between March 10 and September 16, 2021.

This study was approved by the institutional review board (IRB) of Nanjing Drum Tower Hospital (No. 2021-606-02). Written informed consent was obtained from each participant.

Sample size calculation

Considering that the positive rate of anti-RBD IgG was 97% in the non-T2DM subjects based on the results of clinical trials (33, 34) and assumed 80% in the T2DM patients, we calculated that 46 patients per group would be required, with a power of 80% and a type I error rate of 0.05, by using a χ^2-test. On the basis of an expected dropout of 10%, we planned to enroll 52 subjects per group.

Blood sample collection

Fasting blood samples were taken by venipuncture from each participant. In addition to the necessary laboratory tests such as clinical biochemistry and glycosylated hemoglobin, serum or plasma samples left over after clinical testing were aliquoted and stored at −30°C.

Detection of anti-SARS-CoV-2 antibody

Two chemo-luminescence immunoassay kits for anti-SARS-CoV-2 antibody, SARS-CoV-2 IgG kit and surrogate neutralization assay kit (iFlash 3000 chemiluminescence immunoassay analyzer, Shenzhen YHLO Biotech, China), were used to measure the levels of anti-SARS-CoV-2 antibodies as described elsewhere (38, 39). The SARS-CoV-2 IgG kit detects total IgG antibodies to the combination of nucleocapsid (N) and S proteins of SARS-CoV-2 (anti-N/S IgG), and the surrogate neutralization assay kit measures the IgG antibody specific to the receptor binding domain (RBD) of the S protein (anti-RBD IgG). The surrogate neutralization activity correlates well with the inhibition of SARS-CoV-2 infection in the cell culture (39). Based on the manufacturer's instructions, the measured results with values ≥10.0 arbitrary units (AU)/ml were considered positive for the antibodies, and the results below 10.0 AU/mL as negative.

Statistical analysis

Categorical data were presented as percentages and continuous data were presented as means ± standard deviation or median (25–75th percentile). The characteristics of participants with and without diabetes were compared by unpaired Student's t'-test for ages, by Mann-Whitney U-test for time interval (days) after the 2nd vaccine dose, and by χ^2-test for sex and the positive rates of anti-N/S IgG and anti-RBD IgG. Seropositivity and Clopper-Pearson 95% confidence intervals (CI) were calculated. The antibody levels were compared by Mann-Whitney U-test. The χ^2-test was used to compare the seropositivity of anti-N/S IgG and anti-RBD IgG between the subjects without diabetes and diabetic patients with high glycemia or with controlled glycemia. The amount of anti-N/S IgG and anti-RBD IgG in the sera of vaccinated individuals with high glycemia was compared to that in vaccinated individuals without high glycemia by Kruskal-Wallis test. A two-sided P-value of <0.05 was considered significant. All statistical analyses were conducted using the SPSS 25.0 (version 25.0, SPSS, Chicago, IL, USA).

Results

Participant characteristics

A total of 119 participants who did not have history of SARS-CoV-2 infection were included in this study. Sixty-three subjects who had been diagnosed with T2DM were divided into the patient group and 56 subjects who did not have history of T2DM were divided into the control group. The demographic characteristics and relevant variables of these two groups are presented in Table 1. Overall, there was no statistical significance in these parameters between these two groups.

Antibody response to inactivated COVID-19 vaccine in subjects with or without T2DM

Table 1 presents the results of anti-N/S IgG and anti-RBD IgG in the T2DM patients and controls. The positive rate of anti-N/S IgG in the T2DM patients was 85.7% (54/63) (95% CI 74.6, 93.3%), and the positive rate of anti-RBD IgG was also 85.7% (54/63) (95% CI 74.6, 93.3%); these 54 patients were positive for both anti-N/S IgG and anti-RBD IgG. In the controls, 98.2% (55/56) (95% CI 90.4, 100.0%) were positive for anti-N/S IgG and 96.4% (54/56) (95% CI 87.7, 100.0%) were positive for anti-RBD IgG. The positive rates of anti-N/S IgG and anti-RBD IgG in T2DM patients were significantly lower than those in the non-T2DM subjects, respectively (both P <0.05) (Table 1).

As shown in Figure 1, the median (interquartile range) level of anti-N/S IgG in T2DM patients was significantly lower than that in non-T2DM subjects (25.48 [8.89, 49.14] vs. 33.58 [25.11, 57.39] AU/ml, $p = 0.011$) (Figure 1A), and similarly, the median level of anti-RBD IgG in T2DM patients was also significantly lower than that in non-T2DM subjects (15.45 [10.44, 24.34] vs. 22.25 [15.25, 32.09] AU/ml, $p = 0.019$) (Figure 1B).

Anti-N/S IgG and anti-RBD IgG antibodies in T2DM patients with controlled and uncontrolled glycemia

To further clarify whether the antibody response to COVID-19 vaccine is influenced by the uncontrolled glycemia, we compared the positive rates and the levels of anti-N/S IgG and anti-RBD IgG between T2DM patients who had controlled glycemia and those who had uncontrolled glycemia. Figure 2A shows that the positive rates of anti-N/S IgG and anti-RBD

TABLE 1 Comparison of demographic characteristics and antibody response between T2DM and non-T2DM participants.

Item	Total, $n = 119$	T2DM, $n = 63$ (%)	Non-T2DM, $n = 56$ (%)	Statistics	P
Sex				$\chi^2 = 2.358$	0.125
Male	62 (52.1)	37 (58.7)	25 (44.6)		
Female	57 (47.9)	26 (41.3)	31 (55.4)		
Age (years)	51.0 ± 9.7	50.4 ± 11.4	51.6 ± 7.3	$t' = 0.727$	0.469
Interval after 2nd dose (days)	32 (26, 47)	35 (26, 51)	29 (26, 40)	$Z = -1.437$	0.151
Median (P_{25}-P_{75})					
Anti-N/S IgG*				$\chi^2 = 4.504$	0.034
≥10 AU/ml	109 (91.6)	54 (85.7)	55 (98.2)		
<10 AU/ml	10 (8.4)	9 (14.3)	1 (1.8)		
Anti-RBD IgG*				$\chi^2 = 4.057$	0.044
≥10 AU/ml	108 (90.8)	54 (85.7)	54 (96.4)		
<10 AU/ml	11 (9.2)	9 (14.3)	2 (3.6)		

*Results with ≥10.0 AU/mL and <10.0 AU/mL indicate IgG antibody positive and negative, respectively.
N and S, nucleocapsid (N) and spike (S) proteins of SARS-CoV-2, respectively. RBD, receptor binding domain.

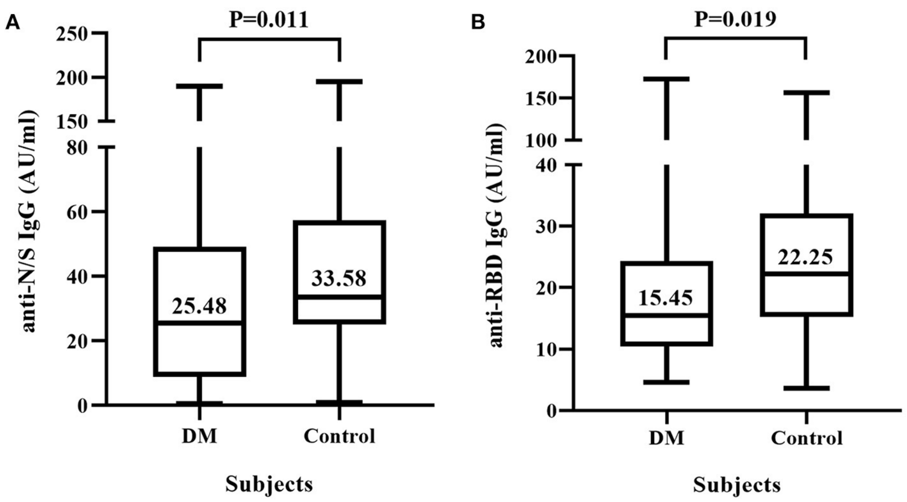

FIGURE 1
IgG antibody response to inactivated COVID-19 vaccine in diabetic mellitus (DM) patients and non-DM controls. Sixty-three DM patients and 56 non-DM subjects were each vaccinated with two doses of COVID-19 vaccine composed of inactivated SARS-CoV-2. **(A)** Titers of IgG antibody against the nucleocapsid (N) and spike (S) proteins of SARS-CoV-2 (anti-N/S IgG). **(B)** Titers of IgG antibody against receptor binding domain (RBD) of S protein (anti-RBD IgG).

IgG in the T2DM patients with fasting blood glucose ≥7 mMol/L were both 75.0% (95% CI 55.1, 89.3%), significantly lower than the rates (94.3% [95% CI 80.8, 99.3%]) in the patients with fasting blood glucose <7 mMol/L ($P = 0.030$), and lower than those (anti-N/S IgG 98.2% and anti-RBD IgG 96.4%) in the non-T2DM individuals ($P = 0.003$ and 0.009, respectively). However, compared to non-diabetic controls, T2DM patients with fasting blood glucose <7 mMol/L had similar positive rate for anti-N/S IgG (94.3 vs. 98.2%, $P = 0.676$) and for anti-RBD IgG (94.3.0 vs. 96.4%, $P = 1.000$) (Figure 2A).

The comparison of antibody titers between the T2DM patients with controlled and uncontrolled glycemia and the non-T2DM individuals showed that the median levels of anti-N/S IgG and anti-RBD IgG in the patients with fasting blood glucose ≥7 mMol/L were much lower than those in the patients with fasting blood glucose <7 mMol/L, respectively (anti-N/S IgG: 13.30 vs. 33.65 AU/ml, $P = 0.006$; anti-RBD IgG: 11.91 vs. 19.83 AU/ml. $P = 0.023$), and significantly lower than those in the non-T2DM individuals (anti-N/S IgG: 13.30 vs. 33.58 AU/ml, $P < 0.001$; anti-RBD: 11.91 vs. 22.25 AU/ml. $P = 0.001$) (Figures 2B,C). However, the titers

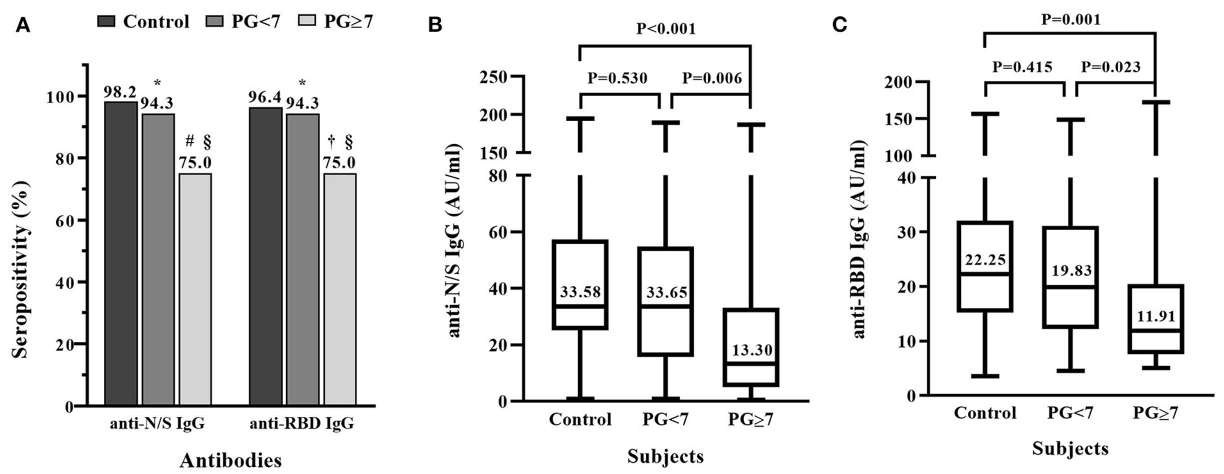

FIGURE 2
Comparison of IgG antibody response to inactivated COVID-19 vaccine in patients with diabetic mellitus (DM) who had controlled or uncontrolled fasting blood glucose and non-DM subjects. Thirty-five DM patients who had plasma glucose (PG) <7 mMol/L, 28 DM patients who had PG ≥7 mMol/L, and 56 non-DM subjects were each vaccinated with two doses of inactivated COVID-19 vaccine. **(A)** Positive rates of IgG antibody against the combination of nucleocapsid (N) and spike (S) proteins (anti-N/S IgG), and against receptor binding domain (RBD) (anti-RBD IgG). **P* > 0.05, compared to control; #*P* = 0.003, compared to control; †*P* = 0.009, compared to control; §*P* = 0.030, comparison of diabetic patients with PG <7 and ≥7 mMol/L. **(B)** Comparison of titers of anti-N/S IgG between controls and diabetic patients with PG <7 and ≥7 mMol/L, respectively. **(C)** Comparison of titers of anti-RBD IgG between controls and diabetic patients with PG <7 and ≥7 mMol/L, respectively.

of anti-N/S IgG and anti-RBD IgG between the patients with fasting blood glucose <7 and non-T2DM subjects were comparable, respectively (anti-N/S IgG: 33.65 vs. 33.58 AU/ml, $P = 0.530$; anti-RBD IgG: 19.83 vs. 22.25 AU/ml, $P = 0.415$) (Figures 2B,C).

Discussion

In the present study, we revealed that antibody response to COVID-19 vaccine composed of inactivated SARS-CoV-2 in T2DM patients was lower than that in non-T2DM subjects, and the antibody response in T2DM patients with uncontrolled glycemia was lower than that in T2DM patients with controlled glycemia. The data indicate that diabetic patients have reduced antibody response to inactivated COVID-19 vaccine, particularly in the patients with uncontrolled glycemia.

The participants included in this study were vaccinated with COVID-19 vaccine composed of inactivated SARS-CoV-2. Thus, the vaccinees were able to produce antibodies to all viral proteins of SARS-CoV-2. We used two types of assays to measure the antibody responses. One assay contains a combination of the N and S proteins of SARS-CoV-2, which can detect antibodies directed against both the N and S proteins. And the other assay contains the RBD domain only, which can detect antibodies specifically directed against RBD. Anti-RBD IgG antibodies are proved to be neutralizing against SARS-CoV-2 (39, 40). In the present study, 98.2% (55/56) and 96.4% (54/56) of the non-DM subjects showed anti-N/S IgG positive and anti-RBD positive, respectively after a full vaccination with two doses at an interval of 2–4 weeks (Table 1 and Figure 2), which is in agreement with the results in the clinical trials (33, 34). Thus, our data in the present study added more evidence that the inactivated COVID-19 vaccine efficiently elicited the non-neutralizing (anti-N) as well as neutralizing (anti-RBD) antibodies.

Diabetic patients are usually considered to be to some contents immunocompromised in both innate and adaptive immune responses. One of the common complications among diabetic patients is various infections (41). Clinical observations showed that COVID-19 patients who had underlying diabetes have an increased risk of severe disease and mortality (42, 43). This may be explained by the impaired antibody responses to the natural SARS-CoV-2 infection in diabetic patients (44), although others reported that diabetic patients with COVID-19 had same antibody responses as non-diabetic COVID-19 patients (45). In diabetic patients who were vaccinated with mRNA or viral vector-based COVID-19 vaccine, the antibody titers are relatively lower than that in non-diabetic subjects (26, 27). In our present study, we also observed that the antibody response to inactivated COVID-19 vaccine in diabetic patients was lower than that in subjects who had no diabetes. The impaired antibody response to inactivated COVID-19 vaccine was mainly seen in diabetic patients who had uncontrolled glycemia, whereas diabetic patients who had controlled glycemia showed similar antibody response as the non-diabetic subjects did (Figure 2). Our finding is in agreement with what reported by Marfella et al. that diabetic patients with poor glycemic control showed a weak immunity to mRNA vaccines (mRNA-BNT162b2 and mRNA-1273 vaccine) or a viral vector-based vaccine (ChAdOx1-S) (27). This suggests that uncontrolled glycemia may inhibit the immune response to COVID-19 vaccines. Indeed, compared to diabetic patients with controlled glycemia, those with poor glycemic control are at the increased risk of various infections (46).

The reduced antibody response (the seroconversion rate and antibody titers) to COVID-19 vaccine in diabetic patients observed in this study suggests that the protective efficacy and duration of protection against COVID-19 may be relatively lower, particularly in the patients with uncontrolled glycemia. Therefore, the issue of whether diabetic subjects with uncontrolled glycemia require more doses of COVID-19 vaccine, or a relatively shorter interval to receive booster immunization, to obtain the optimized protective efficacy merits further study. Alternatively, to have the full efficacy of the vaccine, diabetic patients with uncontrolled glycemia may delay the vaccination until their glycemia is controlled. Nevertheless, breakthrough infection occurred in diabetic patients who had already received COVID-19 vaccination is prone to have more severe COVID-19 than non-diabetic patients (47). Thus, other preventive measures, such as social distance and face masking, are still critical in diabetic subjects, even after COVID-19 vaccination.

There are several limitations in our study. First, it was single center study and the sample size was small. Second, the participants in this study received inactivated COVID-19 vaccines prepared by two manufacturers and we did not compare the antibody responses between these two inactivated vaccines. Third, although anti-RBD is considered to be neutralizing antibodies, we did not directly measure the neutralizing antibody response. Fourth, because of the limited number of patients with type 1 DM in the study period, we did not evaluate the antibody response to inactivated COVID-19 vaccines in such patients. Whether they have impaired immune response to COVID-19 vaccines requires further investigation.

In conclusion, after vaccinated with two doses of inactivated COVID-19 vaccines, T2DM patients with uncontrolled glycemia developed significantly lower anti-RBD IgG antibody levels than non-T2DM subjects and T2DM patients with controlled glycemia. Our results indicate that the vaccination schedule against COVID-19 requires further investigation to optimize the protective efficacy of COVID-19 vaccines.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Institutional Review Board (IRB) of Nanjing Drum Tower Hospital (No. 2021-606-02). The patients/participants provided their written informed consent to participate in this study.

Author contributions

YC, PS, ZH, and Y-HZ: conceptualized and designed the study. PS, YT, and WZ: performed the laboratory work. YC, YB, and ZH: recruited the study subjects. BX: participated in the design and performed the statistical analysis. YC and PS: drafted the manuscript. ZH and Y-HZ: critically revised the manuscript. All authors contributed to the interpretation of the results and agreed to the submitted version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Global COVID-19 vaccine acceptance rate: Systematic review and meta-analysis

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Background: A vaccine against COVID-19 is a vital tool in managing the current pandemic. It is becoming evident that an effective vaccine would be required to control COVID-19. Effective use of vaccines is very important in controlling pandemics and paving the way for an acceptable exit strategy. Therefore, this systematic review and meta-analysis aims to determine the global COVID-19 acceptance rate that is necessary for better management of COVID-19 pandemic.

Methods: This review was conducted based on Preferred Reporting Items for Systematic Reviews and Meta-Analysis protocols and considered the studies conducted on acceptance and/or hesitancy of COVID-19 vaccine. Articles were searched using electronic databases including PubMed, Scopus, Web of Science, Embase, CINAHL, and Google Scholar. The quality of the study was assessed using the Joanna Briggs Institute (JBI) critical assessment tool to determine the relevance of each included article to the study.

Results: Of the 6,021 articles identified through the electronic database search, 68 articles were included in the systematic review and meta-analysis. The global pooled acceptance rate of the COVID-19 vaccine was found to be 64.9% [95% CI of 60.5 to 69.0%]. Based on the subgroup analysis of COVID-19 vaccine acceptance rate by the World Health Organization's region, the countries where the study was conducted, occupation, and survey period, the prevalence of COVID-19 vaccine acceptance rate was 60.8% [95% CI: 56.3, 65.2%], 61.9% [95% CI: 61.3, 62.4%], 81.6% [95% CI: 79.7, 83, 2%] and 64.5% [95% CI: 60.3, 68.5%], respectively.

Conclusions: This review revealed the variation in the level of COVID-19 vaccine acceptance rate across the world. The study found that the overall prevalence of COVID-19 vaccine acceptance was 64.9%. This finding indicated that even if the COVID-19 vaccine is developed, the issue of accepting or taking the developed vaccine and managing the pandemic may be difficult.

KEYWORDS

vaccine acceptance, vaccine hesitancy, COVID-19, coronavirus, 2019, SARS-CoV-2, vaccine rejection, global

Introduction

Corona virus disease 2019 (COVID-19) has spread drastically throughout the world, since the first case of COVID-19 disease was reported in Wuhan, China (1), and has rapidly become a major public health concern (2). Vaccination has played a fundamental role in global public health, leading to increased life expectancy (3) and is one of the most cost-effective ways of avoiding the disease and currently prevents between two and three million deaths per year (4). It is becoming evident that an effective vaccine would be required to control COVID-19 (7). Effective use of vaccines is necessary to reduce the social and economic burden and to prepare the way for an acceptable exit strategy from the COVID-19 pandemic (8). Vaccination hesitancy and anti-vaccination movements are increasing and need critical attention (9–11). Similarly, a vaccine against COVID-19 is a vital tool in managing COVID-19 pandemic (5, 6).

Currently, vaccination rates have fallen and public confidence in vaccines has been inconsistent (6, 13) and various studies have reported a declining level of willingness to accept the COVID-19 vaccine (14). Globally, the intention of being vaccinated against the COVID-19 pandemic is declining from time to time (8). According to the World Health Organization (WHO), vaccine hesitancy has become an emerging global issue and has been identified as one of the top ten threats to global health in 2019 (12).

Although vaccines are developed against COVID-19, many factors compromise the acceptance of the vaccine against COVID-19 and become a public concern (13, 15). Furthermore, transparent and effective communication efforts are essential to reduce misinformation and vaccine hesitancy and build trust to ensure adequate vaccination coverage will be achieved (8).

Previously, several studies have been conducted and many literatures have been published to capture and address many issues regarding the COVID-19 pandemic. However, to the level of our knowledge, there is no adequate studies that have been investigated that provide the global pooled acceptance or hesitancy of the COVID-19 vaccine. Therefore, this systematic review and meta-analysis was aimed to determine the acceptance rate of the COVID-19 vaccine across the world, which is necessary to understand the acceptance or hesitancy of the vaccine in different contexts and can be an input for others pandemics.

Materials and methods

This systematic review and meta-analysis was conducted under the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (16).

Eligibility criteria

Studies that met the following inclusion criteria were included in the systematic review and meta-analysis. The inclusion criteria considered in this review include:-

- Study population: All populations regardless of their age, occupation, ethnicity, gender, etc.
- Outcomes: The articles aimed to determine COVID-19 vaccine hesitancy and/or acceptance that provided a quantitative outcome were included in the study.
- Language: Articles written in English.
- Types of articles: Peer-reviewed full text, original, and published articles.
- Publication year: Studies published since the emergency of COVID-19 to the study period (March 2020 to June 2022).
- Study regions / locations: Not specified (not limited).

However, articles not freely available, not peer-reviewed articles or preprints, editorial papers, reports, short communications, review articles, the article did not provide an outcome of interest and high risk of bias articles were excluded from this study.

Information sources and search strategy

Article searches were performed using main key terms or keywords such as COVID-19, vaccine hesitancy, vaccine acceptance and intention to take vaccine, and Medical Subject Headings (MeSH) in combination with Boolean logic operators ("AND," "OR," and "NOT"). The articles were searched from PubMed, Scopus, Web of Science, Embase, CINAHL, and Google Scholar. References within eligible articles were further screened for additional articles. The articles were searched from February 01 to March 29, 2021 and May 02 to June 26, 2022 on PubMed, Scopus, Embase, and Google Scholars, while the search on Web of Science, CINAHL, and Google was made from 15 February to 31 March 2021. Articles published from March 2021 to June 2022 were searched from the included electronic databases according to their own searching strategies (Supplementary File I).

Study selection

The study selection process was performed using the PRISMA flow chart, indicating the number of articles included in the systematic review and articles excluded from the study with the reasons of exclusion. Following the search for articles through the included electronic databases, duplicate articles were removed using the ENDNOTE software version X5 (Thomson Reuters, USA). After duplicated articles were removed, the authors (DM, YA, and YD) independently screened the articles based on their titles and abstracts by applying the inclusion criteria.

Furthermore, the full text of the relevant articles was further read in detail and the inclusion criteria independently evaluated by the authors (DM, YA, and YD). Any disagreements made with respect to the inclusion of studies were resolved by consensus after discussion. Finally, studies that met the criteria were included in the systematic review and meta-analysis.

Data extraction

The data were extracted by the authors (DM, YA, and YD) independently. Predetermined tabular format consisting of study characteristics including publication year, survey period, country where the study was conducted, number of respondents, and outcome (COVID-19 vaccine acceptance/hesitancy rate) using Microsoft Excel, 2016 (Supplementary File II). Any disagreement made between the authors was resolved through discussion after the same procedures were repeated.

Data quality assessment

The selected articles were subjected to a rigorous independent assessment using a standardized critical assessment tool, Joanna Briggs Institute (JBI) Critical Assessment Tools for prevalence studies (17). The evaluation tools have the following nine evaluation criteria/ parameters; (1) appropriate sampling frame; (2) proper sampling technique; (3) adequate sample size; (4) description of the study subject and setting description; (5) sufficient data analysis; (6) use of valid methods for identifying conditions; (7) valid measurement for all participants; (8) use of appropriate statistical analysis and (9) adequate response rate.

The authors (DM, YA, and YD) assessed the quality of the included studies. Based on the items in the above appraisal tool, the articles were classified as high quality (80% and above), moderate (60–80% score), and low quality (<60% score). Articles with a score $\geq$60% (articles has high and moderate quality) were included in the review, while those with low quality were excluded from the study. Finally, the disagreements made among the authors (DM, YA, and YD) were resolved by discussion and repeating the same procedures.

Outcome measures

The term "vaccine hesitancy" refers to "delay in acceptance or refusal of vaccines despite the availability of vaccine services (6, 18, 19)." In this review, for articles that did not provide general acceptance of the vaccine among study participants, the prevalence of vaccine acceptance was calculated based on the response of the participants. The participant responded strongly agree, agree, completely agree, accept, all, accept, some accept, and yes to the questions were considered as accepted. Finally, the prevalence was calculated based on the frequency of responses and the total number of respondents. The same principle was applied to studies which reported results based on the Likert scale and others (18) (Figure 1).

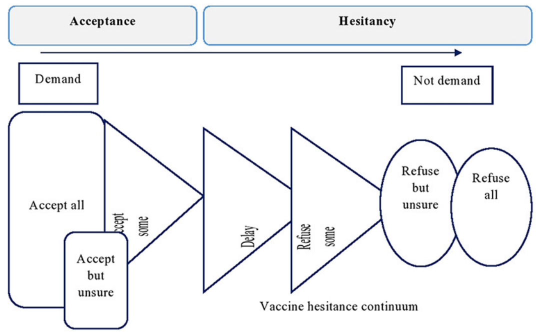

FIGURE 1
The continuum of vaccine hesitancy and acceptance of all vaccines. [Source (18)].

Statistical procedures and data analysis

The pooled acceptance rate of the COVID-19 vaccine was performed using Comprehensive Meta-Analysis (CMA) version 3.0 statistical software. Forest plots and random-effects models were used to determine and visualize the pooled acceptance rate of the COVID-19 vaccine. The Cochran Q-test (Q) and I-Squared test (I^2 statistics) were used to evaluate the heterogeneity between the included articles. Then, heterogeneity was classified into low (I^2 index $<$ 25%), medium (I^2 index ranging from 25 to 75%), and high heterogeneity (I^2 index $>$ 75%). The random-effects model was used to analyze the data. Furthermore, subgroup analysis was performed based on the year of publication, survey period (when the study was conducted), and study area.

Sensitivity analysis was used to determine the differences in pooled effects by dropping studies that were found to influence the summary estimates, including extreme sample sizes and outcomes.

Results

Study selection

A total of 6,021 short communications, original articles and editorial articles were searched through electronic databases from PubMed, Scopus, Web of Science, Embase, CINAHL, and

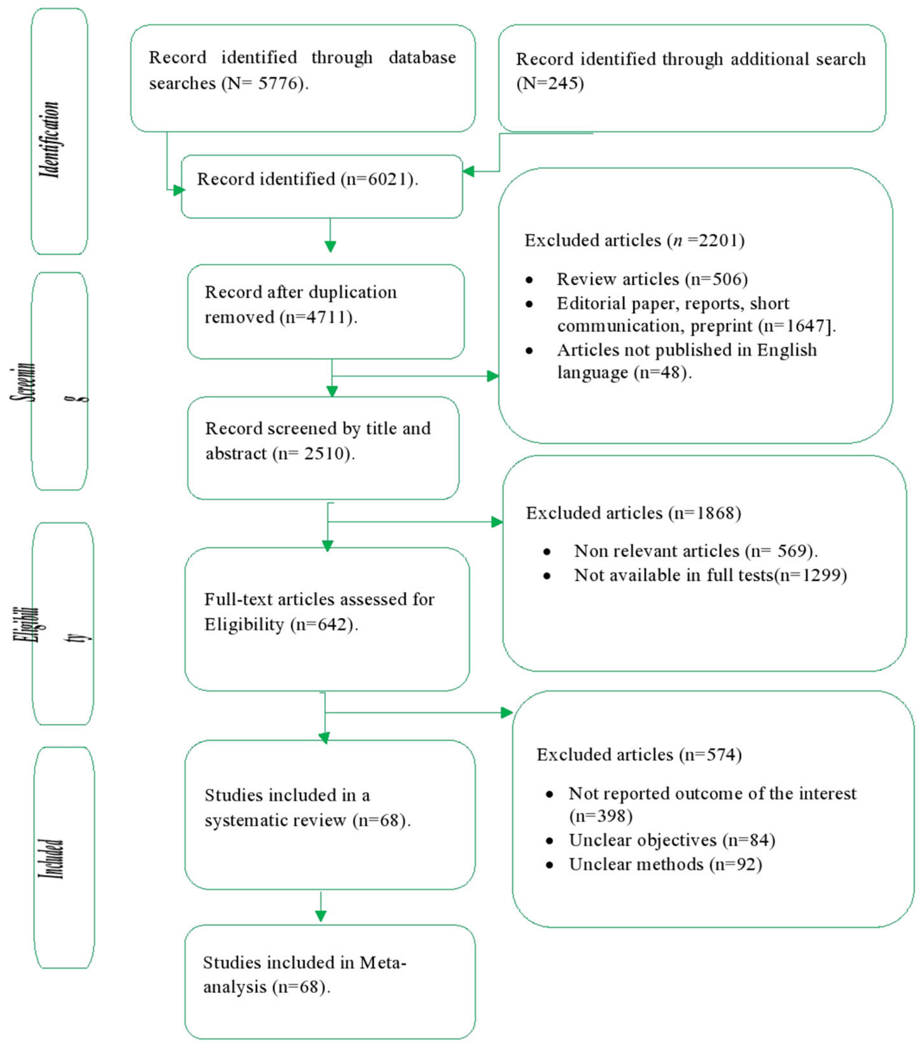

FIGURE 2
Study selection process of included articles for systematic review and meta analysis, 2021.

Google scholars. The articles were searched from February 01 to March 29, 2021 and May 02 to June 26, 2022 on PubMed, Scopus, Embase, and Google Scholars, while the search on Web of Science, CINAHL, and Google was made from 15 February to 31 March 2021. Then, 1,310 duplicate articles were excluded. Furthermore, 2201 articles were excluded after initial selection based on abstracts and titles. Furthermore, 599 articles were excluded after eligibility for full text articles ($n = 601$). Finally, a total of 68 articles were included in the systematic review and meta-analysis (Figure 2).

Characteristics of the included articles

Among the included articles, 35 (50%) had high quality, while the rest (50%) had moderate quality, based on the JBI critical appraisal tools for the prevalence study (17) (Supplementary file III). 143,111 study participants were included in 68 articles, which were published from 2020 to 2022. The included studies were conducted in 38 countries around the world (Figure 3).

Eight studies (14, 20–26) were conducted in China, six studies (27–32) in Saudi Arabia, four studies (2, 33–35) in United States, four studies (36–38) in United Kingdom, and four studies (39–42) in Turkey. Additionally, three studies were conducted in each Malaysia (43–45) and Kuwait (27, 46). Two studies conducted in each Qatar (47, 48), Italy (15, 49), Jordan (27, 50), Bangladesh (51, 52), Ethiopia (53, 54), Taiwan (55, 56), and Germany (57, 58).

However, only one study was conducted in each of the following countries; Republic of Congo (59), Japan (60), Poland (10), Cameroon (7), Israel (61), Mexico (62), Malta (63), Scotland (6), Indonesia (64), England (65), South Korea (66), Iran (67), Nigeria (68), Tunisia (69), Netherlands (70), Thailand

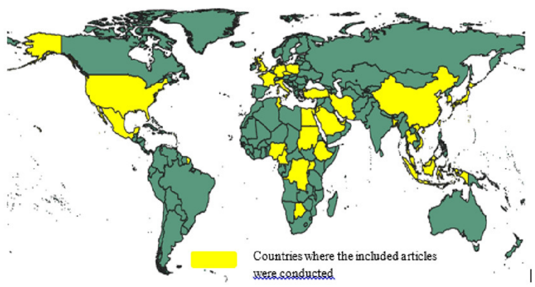

FIGURE 3
Countries of the world where the included articles were conducted.

(71), Vietnam (72), United Arab Emirates (73), Botswana (74), Sudan (75), Czechia (76), Uganda (77), France (78), and in Egypt (79).

The included studies were cross-sectional studies with a sample size ranging from 123 (63) to 23,582 (31) study participants. In general, the overall global acceptance rate of the COVID-19 vaccine, regardless of occupation, was 63.4% and ranged from 15.4% (7) to 95.6% (14) (Supplementary File IV).

COVID-19 vaccine acceptance

This systematic review and meta-analysis was performed using Comprehensive Meta-Analysis (CMA) version 3 statistical software to determine pooled COVID-19 vaccine acceptance and hesitancy rates.

The overall pooled prevalence/rate of COVID-19 vaccine acceptance

The pooled prevalence of COVID-19 vaccine acceptance rate was found to be 64.9% [95% CI: 60.5 to 69.0%]; $I^2 = 99.57\%$ with a p-value of <0.001 (Figure 4).

Subgroup analysis of the pooled prevalence of COVID-19 vaccine acceptance rate

Based on the subgroup analysis based on the World Health Organization's Region, the overall pooled prevalence of COVID-19 vaccine acceptance rate was 60.8% [95% CI: 56.3, 65.2%]. The lowest prevalence of COVID-19 vaccine acceptance rate was reported in the Eastern Mediterranean Region, accounting for 60.8% [95% CI: 43.4, 57.2%], whereas the highest prevalence was reported in the South East Asian Region, which accounted for 81.0% [95% CI: 59.9, 92.4%] (Figure 5).

Based on the countries where the study was conducted, the lowest prevalence of COVID-19 vaccine acceptance rate was reported in Cameroon, accounted for 15.4% [95% CI: 14.0, 16.9], while the highest prevalence [95.6% (95% CI: 93.8, 96.9%] was reported in Thailand followed by Indonesia [93.3% (95% CI: 91.8, 94.5%] (Figure 6).

Based on the study participants, the highest COVID-19 vaccine acceptance rate was reported among healthcare workers, which accounted for 71.4% [95% CI: 59.9, 80.7%], followed by students accounted for 64.7% [95% CI: 32.6, 89.2%]. The lowest prevalence of COVID-19 vaccine acceptance rate was reported among patients [51.8% (95% CI: 36.8, 66.6%] (Figure 7).

Based on the survey period, the pooled prevalence of COVID-19 vaccine acceptance was 64.5% [95% CI: 60.3, 68.5%]. Relatively, the lowest prevalence [57.9% (95% CI: 49.2, 66.2%)] of vaccine acceptance was reported from September to November 2020, whereas the highest prevalence [81.0% (95% CI: 57.3, 93.1%] was reported between September to November 2021 (Figure 8).

Sensitivity analysis

Sensitivity analysis was performed by removing low outcome, high outcome, and small sample sizes. However, the sensitivity analysis did not show a substantial change in the prevalence of COVID-19 acceptance compared to the pooled prevalence without sensitivity analysis [61.1% (95% CI 53.8 to 67.9%)] (Table 1).

Discussion

We conducted a systematic review and meta-analysis using data extracted from 68 studies conducted on 143,111 study participants. The study revealed that the pooled prevalence of COVID-19 vaccine acceptance was 64.9% [95% CI of 60.5 to 69.0%]. Some studies were conducted by the same authors across various countries (6, 27). The sensitivity analysis was employed to assess the cause of high heterogeneity and found no substantial difference in the prevalence of COVID-19 vaccine acceptance.

The utility of the vaccine to control COVID-19 pandemics depends on the acceptance of the vaccine (80, 81). Currently, vaccine hesitancy represents a serious threat to health. Similarly, the current study found that the global pooled prevalence of COVID-19 vaccine acceptance was 64.9% [95% CI of 60.5 to 69.0%], which was lower than the finding of the global survey, which reported about 71.5% of COVID-19 vaccine acceptance rate (62). The possible reason for the disparity in the prevalence estimate could be related to the variation in

Study name	Event rate	Lower limit	Upper limit	Z-Value	p-Value
Shekhar et al	0.360	0.345	0.375	-17.641	0.000
Malik et al	0.670	0.634	0.705	8.632	0.000
Ditekemena	0.559	0.544	0.574	7.566	0.000
Wong et al	0.945	0.930	0.957	22.072	0.000
Wong et al	0.422	0.394	0.450	-5.382	0.000
Kose et all	0.686	0.658	0.712	12.235	0.000
Yoda et al	0.657	0.628	0.684	10.233	0.000
Freeman	0.717	0.704	0.729	29.946	0.000
Williams et al	0.860	0.828	0.887	14.460	0.000
Alabdulla	0.605	0.594	0.616	18.432	0.000
Reiter	0.690	0.669	0.710	16.574	0.000
Wang et al	0.348	0.328	0.369	-13.531	0.000
Gerussi et al	0.408	0.369	0.448	-4.477	0.000
Sallam et al	0.318	0.249	0.396	-4.409	0.000
Feleszko et al	0.370	0.342	0.399	-8.390	0.000
Dinga et al	0.154	0.140	0.169	-30.819	0.000
Wang et al	0.913	0.900	0.924	30.057	0.000
Dror et al	0.750	0.724	0.775	15.863	0.000
Dickerson et al	0.290	0.253	0.330	-9.398	0.000
Lazarus et al	0.762	0.729	0.792	13.102	0.000
Gretch et al	0.618	0.529	0.699	2.592	0.010
Williams et al	0.775	0.756	0.793	23.189	0.000
Sallam et al	0.236	0.207	0.267	-13.851	0.000
Harapan et al	0.933	0.918	0.945	24.275	0.000
Akarsu et al	0.497	0.462	0.533	-0.165	0.869
Khubchandani et al	0.790	0.771	0.808	23.386	0.000
Chen	0.838	0.825	0.850	34.227	0.000
Palamenghi	0.590	0.559	0.620	5.672	0.000
Wang	0.522	0.500	0.544	1.995	0.046
Sallam et al	0.284	0.265	0.303	-19.438	0.000
Bell et al	0.558	0.530	0.585	4.095	0.000
Alwi et al	0.833	0.813	0.852	22.515	0.000
Achangwa et al	0.708	0.673	0.740	10.730	0.000
Nakhostin-Ansari et al	0.690	0.676	0.703	25.109	0.000
Mustapha et al	0.400	0.355	0.447	-4.167	0.000
Hossain et al	0.429	0.404	0.454	-5.475	0.000
Berihun et al	0.594	0.546	0.640	3.811	0.000
Alibrahim and Awad	0.738	0.724	0.751	29.325	0.000
Huang et al	0.844	0.833	0.855	39.829	0.000
Khiari et al	0.350	0.287	0.419	-4.176	0.000
Antwi-Berko et al	0.696	0.620	0.762	4.819	0.000
Qin et al	0.885	0.869	0.899	27.020	0.000
Sirikalyanpaiboon et al	0.956	0.938	0.969	16.765	0.000
Nguyen et al	0.604	0.566	0.641	5.268	0.000
Mohamed et al	0.645	0.620	0.670	10.714	0.000
Saddik et al	0.580	0.537	0.622	3.622	0.000
Tlale et al	0.734	0.722	0.746	32.651	0.000
Huang et al	0.749	0.721	0.775	14.665	0.000
Roberts et al	0.850	0.839	0.860	41.710	0.000
Barry et al	0.700	0.676	0.723	15.098	0.000
Raja et al	0.558	0.491	0.623	1.705	0.088
Paul et al	0.605	0.590	0.620	13.467	0.000
Boche et al	0.727	0.676	0.773	7.803	0.000
Riad et al	0.702	0.653	0.747	7.456	0.000
Nohl et al	0.570	0.543	0.597	5.023	0.000
Bongomin et al	0.701	0.648	0.749	6.945	0.000
Al-Mulla et al	0.626	0.581	0.669	5.357	0.000
İkiışık et al	0.547	0.497	0.596	1.839	0.066
Almaghaslah et al	0.224	0.197	0.253	-15.209	0.000
Yahia et al	0.618	0.576	0.658	5.386	0.000
Tsai et al	0.527	0.496	0.558	1.724	0.085
Han et al	0.891	0.877	0.904	30.190	0.000
Elharake et al	0.649	0.643	0.655	45.050	0.000
Vallée et al	0.713	0.652	0.767	6.337	0.000
Alfageeh et al	0.480	0.459	0.501	-1.849	0.065
Tao et al	0.774	0.751	0.795	19.209	0.000
Holzmann-Littig et al	0.917	0.909	0.925	44.458	0.000
Gallè et al	0.919	0.909	0.928	37.638	0.000
El-Elimat et al	0.374	0.357	0.391	-13.877	0.000
Saied et al	0.540	0.519	0.561	3.691	0.000
Ayhan et al	0.370	0.317	0.426	-4.451	0.000
	0.649	0.605	0.69	6.467	0.000

Heteriogeniety (I square)= 99. 574, a p-value of <0.001

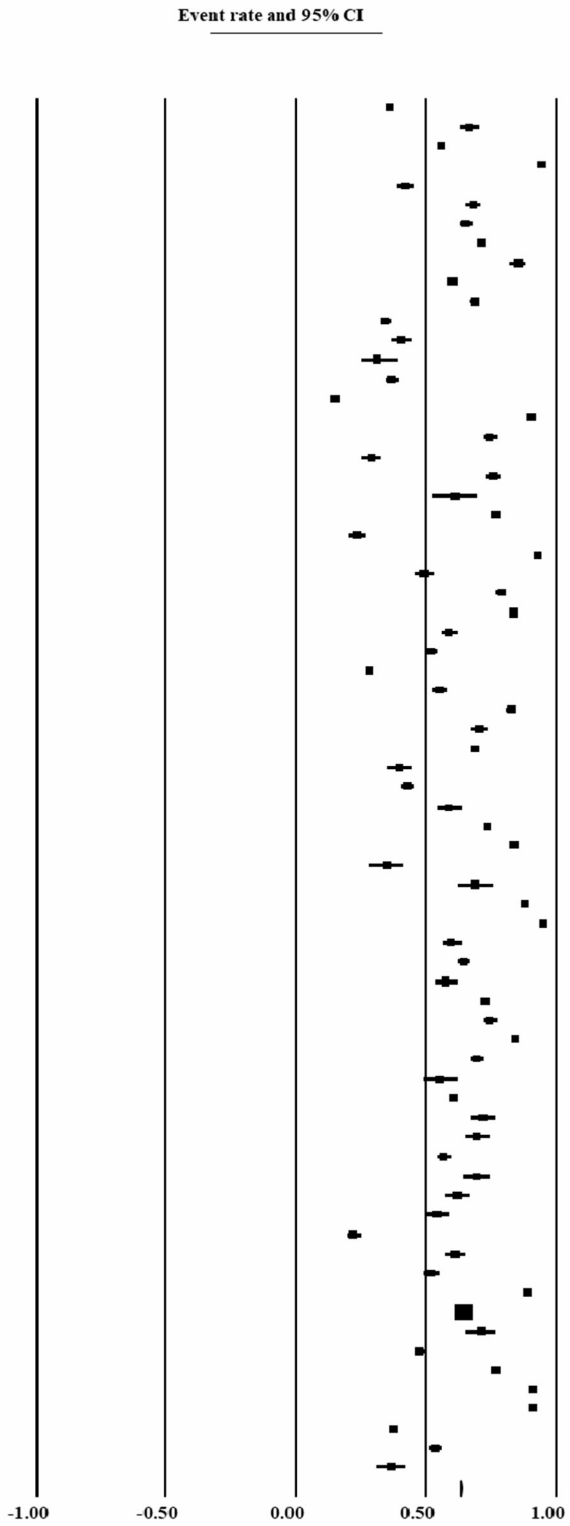

FIGURE 4
Forest plot shows the overall pooled COVID-19 vaccine acceptance rate, 2022.

Group by WHO region	Study name	Event rate	Lower limit	Upper limit	Z-Value	p-Value
AfR	Ditekemena	0.559	0.544	0.574	7.566	0.000
AfR	Dinga et al	0.154	0.140	0.169	-30.819	0.000
AR	Mustapha et al	0.400	0.355	0.447	-4.167	0.000
AfR	Berihun et al	0.594	0.546	0.640	3.811	0.000
AfR	Tlale et al	0.734	0.722	0.746	32.651	0.000
AfR	Boche et al	0.727	0.676	0.773	7.803	0.000
AfR	Bongomin et al	0.701	0.648	0.749	6.945	0.000
AfR		0.548	0.363	0.720	0.499	0.618
AfM	Shekhar et al	0.360	0.345	0.375	-17.641	0.000
AmR	Malik et al	0.670	0.634	0.705	8.632	0.000
AmR	Reiter	0.690	0.669	0.710	16.574	0.000
AmR	Lazarus et al	0.762	0.729	0.792	13.102	0.000
AmR	Khubchandani et al	0.790	0.771	0.808	23.386	0.000
AmR		0.664	0.458	0.823	1.571	0.116
EMR	Alabdulla	0.605	0.594	0.616	18.432	0.000
EMR	Sallam et al	0.318	0.249	0.396	-4.409	0.000
EMR	Sallam et al	0.236	0.207	0.267	-13.851	0.000
EMR	Sallam et al	0.284	0.265	0.303	-19.438	0.000
EMR	Nakhostin-Ansari et al	0.690	0.676	0.703	25.109	0.000
EMR	Alibrahim and Awad	0.738	0.724	0.751	29.325	0.000
EMR	Khiari et al	0.350	0.287	0.419	-4.176	0.000
EMR	Saddik et al	0.580	0.537	0.622	3.622	0.000
EMR	Barry et al	0.700	0.676	0.723	15.098	0.000
EMR	Raja et al	0.558	0.491	0.623	1.705	0.088
EMR	Al-Mulla et al	0.626	0.581	0.669	5.357	0.000
EMR	Almaghaslah et al	0.224	0.197	0.253	-15.209	0.000
EMR	Yahia et al	0.618	0.576	0.658	5.386	0.000
EMR	Elharake et al	0.649	0.643	0.655	45.050	0.000
EMR	Alfageeh et al	0.480	0.459	0.501	-1.849	0.065
EMR	El-Elimat et al	0.374	0.357	0.391	-13.877	0.000
EMR	Saied et al	0.540	0.519	0.561	3.691	0.000
EMR		0.503	0.434	0.572	0.091	0.927
EuR	Kose et al	0.686	0.658	0.712	12.235	0.000
EuR	Freeman	0.717	0.704	0.729	29.946	0.000
EuR	Williams et al	0.860	0.828	0.887	14.460	0.000
EuR	Gerussi et al	0.408	0.369	0.448	-4.477	0.000
EuR	Feleszko et al	0.370	0.342	0.399	-8.390	0.000
EuR	Dror et al	0.750	0.724	0.775	15.863	0.000
EuR	Dickerson et al	0.290	0.253	0.330	-9.398	0.000
EuR	Gretch et al	0.618	0.529	0.699	2.592	0.010
EuR	Williams et al	0.775	0.756	0.793	23.189	0.000
EuR	Akarsu et al	0.497	0.462	0.533	-0.165	0.869
EuR	Palamenghi	0.590	0.559	0.620	5.672	0.000
EuR	Bell et al	0.558	0.530	0.585	4.095	0.000
EuR	Antwi-Berko et al	0.696	0.620	0.762	4.819	0.000
EuR	Roberts et al	0.850	0.839	0.860	41.710	0.000
EuR	Riad et al	0.702	0.653	0.747	7.456	0.000
EuR	Nohl et al	0.570	0.543	0.597	5.023	0.000
EuR	İkiışık et al	0.547	0.497	0.596	1.839	0.066
EuR	Vallée et al	0.713	0.652	0.767	6.337	0.000
EuR	Holzmann-Littig et al	0.917	0.909	0.925	44.458	0.000
EuR	Gallè et al	0.919	0.909	0.928	37.638	0.000
EuR	Ayhan et al	0.370	0.317	0.426	-4.451	0.000
EuR		0.663	0.573	0.743	3.467	0.001
SEAR	Harapan et al	0.933	0.918	0.945	24.275	0.000
SEAR	Hossain et al	0.429	0.404	0.454	-5.475	0.000
SEAR	Sirikalyanpaiboon et al	0.956	0.938	0.969	16.765	0.000
SEAR	Paul et al	0.605	0.590	0.620	13.467	0.000
SEAR		0.810	0.599	0.924	2.707	0.007
WPR	Wong et al	0.945	0.930	0.957	22.072	0.000
WPR	Wong et al	0.422	0.394	0.450	-5.382	0.000
WPR	Yoda, et al	0.657	0.628	0.684	10.233	0.000
WPR	Wang et al	0.348	0.328	0.369	-13.531	0.000
WPR	Wang et al	0.913	0.900	0.924	30.057	0.000
WPR	Chen	0.838	0.825	0.850	34.227	0.000
WPR	Wang	0.522	0.500	0.544	1.995	0.046
WPR	Alwi et al	0.833	0.813	0.852	22.515	0.000
WPR	Achangwa et al	0.708	0.673	0.740	10.730	0.000
WPR	Huang et al	0.844	0.833	0.855	39.829	0.000
WPR	Qin et al	0.885	0.869	0.899	27.020	0.000
WPR	Nguyen et al	0.604	0.566	0.641	5.268	0.000
WPR	Mohamed et al	0.645	0.620	0.670	10.714	0.000
WPR	Huang et al	0.749	0.721	0.775	14.665	0.000
WPR	Tsai et al	0.527	0.496	0.558	1.724	0.085
WPR	Han et al	0.891	0.877	0.904	30.190	0.000
WPR	Tao et al	0.774	0.751	0.795	19.209	0.000
WPR		0.747	0.652	0.823	4.657	0.000
Overall		0.608	0.563	0.652	4.610	0.000

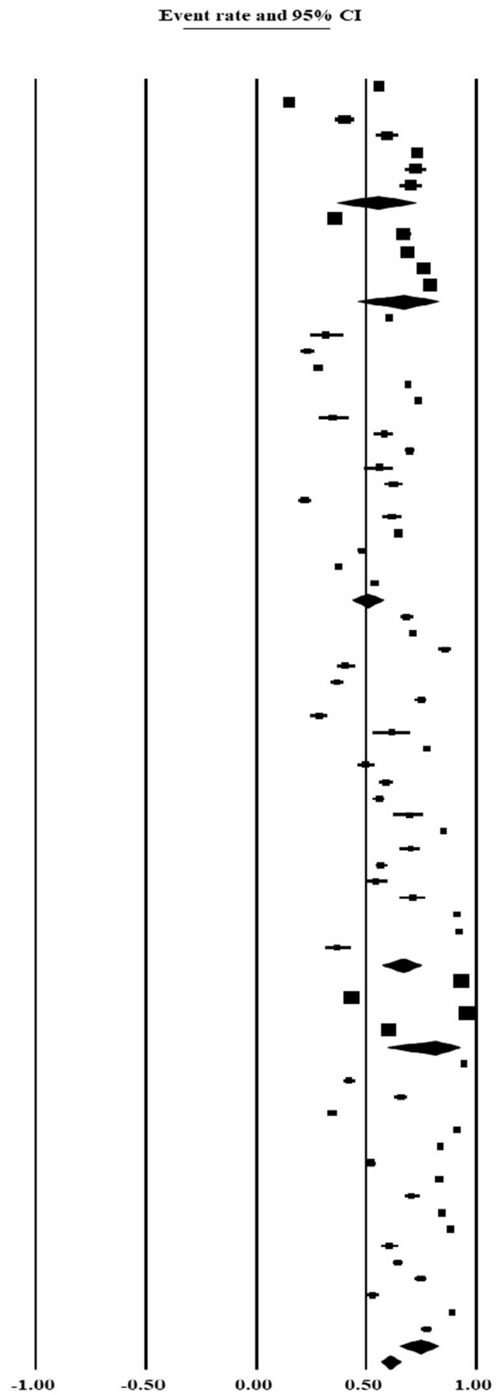

FIGURE 5
Forest plot shows the subgroup analysis of the pooled COVID-19 vaccine acceptance rate based on World Health Organization classification of the region 2022. ArR, African region; AmR, American region; EMR, Eastern Mediterranean Region; SEAR, South East Asian Region; WPR, Western Pacific Region; EuR, European Region.

Group by Country/region	Study name	Event rate	Lower limit	Upper limit	Z-Value	p-Value
Bangladesh	Hossain et al	0.429	0.404	0.454	-5.475	0.000
Bangladesh	Paul et al	0.605	0.590	0.620	13.467	0.000
Bangladesh		0.518	0.348	0.683	0.201	0.841
Botswana	Tlale et al	0.734	0.722	0.746	32.651	0.000
Botswana		0.734	0.722	0.746	32.651	0.000
Cameroon	Dinga et al	0.154	0.140	0.169	-30.819	0.000
Cameroon		0.154	0.140	0.169	-30.819	0.000
China	Wong et. al	0.422	0.394	0.450	-5.382	0.000
China	Wang et al	0.348	0.328	0.369	-13.531	0.000
China	Wang et al	0.913	0.900	0.924	30.057	0.000
China	Chen	0.838	0.825	0.850	34.227	0.000
China	Wang	0.522	0.500	0.544	1.995	0.046
China	Huang et al	0.844	0.833	0.855	39.829	0.000
China	Qin et al	0.885	0.869	0.899	27.020	0.000
China	Han et al	0.891	0.877	0.904	30.190	0.000
China	Tao et al	0.774	0.751	0.795	19.209	0.000
China		0.756	0.598	0.866	3.027	0.002
Czechia	Riad et al	0.702	0.653	0.747	7.456	0.000
Czechia		0.702	0.653	0.747	7.456	0.000
Egypt	Saied et al	0.540	0.519	0.561	3.691	0.000
Egypt		0.540	0.519	0.561	3.691	0.000
England	Bell et al	0.558	0.530	0.585	4.095	0.000
England		0.558	0.530	0.585	4.095	0.000
Ethiopia	Berihun et al	0.594	0.546	0.640	3.811	0.000
Ethiopia	Boche et al	0.727	0.676	0.773	7.803	0.000
Ethiopia		0.663	0.522	0.780	2.252	0.024
France	Vallée et al	0.713	0.652	0.767	6.337	0.000
France		0.713	0.652	0.767	6.337	0.000
Germany	Nohl et al	0.570	0.543	0.597	5.023	0.000
Germany	Holzmann-Littig et al	0.917	0.909	0.925	44.458	0.000
Germany		0.793	0.324	0.968	1.266	0.206
Indonesia	Harapan et al	0.933	0.918	0.945	24.275	0.000
Indonesia		0.933	0.918	0.945	24.275	0.000
Iran	Nakhostin-Ansari et al	0.690	0.676	0.703	25.109	0.000
Iran		0.690	0.676	0.703	25.109	0.000
Israel	Dror et al	0.750	0.724	0.775	15.863	0.000
Israel		0.750	0.724	0.775	15.863	0.000
Italy	Gerussi et al	0.408	0.369	0.448	-4.477	0.000
Italy	Palamenghi	0.590	0.559	0.620	5.672	0.000
Italy	Gallè et al	0.919	0.909	0.928	37.638	0.000
Italy		0.692	0.303	0.921	0.963	0.335
Japan	Yoda et al	0.657	0.628	0.684	10.233	0.000
Japan		0.657	0.628	0.684	10.233	0.000
Jordan	Sallam, et al\	0.284	0.265	0.303	-19.438	0.000
Jordan	El-Elimat et al	0.374	0.357	0.391	-13.877	0.000
Jordan		0.328	0.246	0.421	-3.510	0.000
Kuwait	Sallam et al	0.236	0.207	0.267	-13.851	0.000
Kuwait	Alibrahim and Awad	0.738	0.724	0.751	29.325	0.000
Kuwait		0.483	0.097	0.891	-0.062	0.951
Malaysia	Wong et al	0.945	0.930	0.957	22.072	0.000
Malaysia	Alwi et al	0.833	0.813	0.852	22.515	0.000
Malaysia	Mohamed et al	0.645	0.620	0.670	10.714	0.000
Malaysia		0.843	0.639	0.942	2.969	0.003
Malta	Gretch et al	0.618	0.529	0.699	2.592	0.010
Malta		0.618	0.529	0.699	2.592	0.010
Mexico	Lazarus et al	0.762	0.729	0.792	13.102	0.000
Mexico		0.762	0.729	0.792	13.102	0.000
Netherlands	Antwi-Berko et al	0.696	0.620	0.762	4.819	0.000
Netherlands		0.696	0.620	0.762	4.819	0.000
Nigeria	Mustapha et al	0.400	0.355	0.447	-4.167	0.000
Nigeria		0.400	0.355	0.447	-4.167	0.000
Poland	Feleszko et al	0.370	0.342	0.399	-8.390	0.000
Poland		0.370	0.342	0.399	-8.390	0.000
Qatar	Alabdulla	0.605	0.594	0.616	18.432	0.000
Qatar	Al-Mulla et al	0.626	0.581	0.669	5.357	0.000
Qatar		0.606	0.596	0.617	19.173	0.000
Republic of congo	Ditekemena	0.559	0.544	0.574	7.566	0.000
Republic of congo		0.559	0.544	0.574	7.566	0.000
Saudi Arabia	Sallam et al	0.318	0.249	0.396	-4.409	0.000
Saudi Arabia	Barry et al	0.700	0.676	0.723	15.098	0.000
Saudi Arabia	Almaghaslah et al	0.224	0.197	0.253	-15.209	0.000
Saudi Arabia	Yahia et al	0.618	0.576	0.658	5.386	0.000
Saudi Arabia	Elharake et al	0.649	0.643	0.655	45.050	0.000
Saudi Arabia	Alfageeh et al	0.480	0.459	0.501	-1.849	0.065
Saudi Arabia		0.496	0.374	0.620	-0.055	0.956
Scotland	Williams et al	0.775	0.756	0.793	23.189	0.000
Scotland		0.775	0.756	0.793	23.189	0.000
South Korea	Achangwa et al	0.708	0.673	0.740	10.730	0.000
South Korea		0.708	0.673	0.740	10.730	0.000
Sudan	Raja et al	0.558	0.491	0.623	1.705	0.088
Sudan		0.558	0.491	0.623	1.705	0.088
Taiwan	Huang et al	0.749	0.721	0.775	14.665	0.000
Taiwan	Tsai et al	0.527	0.496	0.558	1.724	0.085
Taiwan		0.646	0.410	0.827	1.218	0.223
Thailand	Sirikalyanpaiboon et al	0.956	0.938	0.969	16.765	0.000
Thailand		0.956	0.938	0.969	16.765	0.000
Tunisia	Khiari et al	0.350	0.287	0.419	-4.176	0.000
Tunisia		0.350	0.287	0.419	-4.176	0.000
Turkey	Kose et al	0.686	0.658	0.712	12.235	0.000
Turkey	Akarsu et al	0.497	0.462	0.533	-0.165	0.869
Turkey	İkiışık et al	0.547	0.497	0.596	1.839	0.066
Turkey	Ayhan et al	0.370	0.317	0.426	-4.451	0.000
Turkey		0.528	0.395	0.657	0.407	0.684
Uganda	Bongomin et al	0.701	0.648	0.749	6.945	0.000
Uganda		0.701	0.648	0.749	6.945	0.000
United Arab Emirates	Saddik et al	0.580	0.537	0.622	3.622	0.000
United Arab Emirates		0.580	0.537	0.622	3.622	0.000
United Kingdom	Freeman	0.717	0.704	0.729	29.946	0.000
United Kingdom	Williams, et al	0.860	0.828	0.887	14.460	0.000
United Kingdom	Dickerson et al	0.290	0.253	0.330	-9.398	0.000
United Kingdom	Roberts et al	0.850	0.839	0.860	41.710	0.000
United Kingdom		0.710	0.513	0.851	2.078	0.038
United States	Shekhar et al	0.360	0.345	0.375	-17.641	0.000
United States	Malik et al	0.670	0.634	0.705	8.632	0.000
United States	Reiter	0.690	0.669	0.710	16.574	0.000
United States	Khubchandani et al	0.790	0.771	0.808	23.386	0.000
United States		0.637	0.400	0.822	1.141	0.254
Vietnam	Nguyen et al	0.604	0.566	0.641	5.268	0.000
Vietnam		0.604	0.566	0.641	5.268	0.000
Overall		0.619	0.613	0.624	44.456	0.000

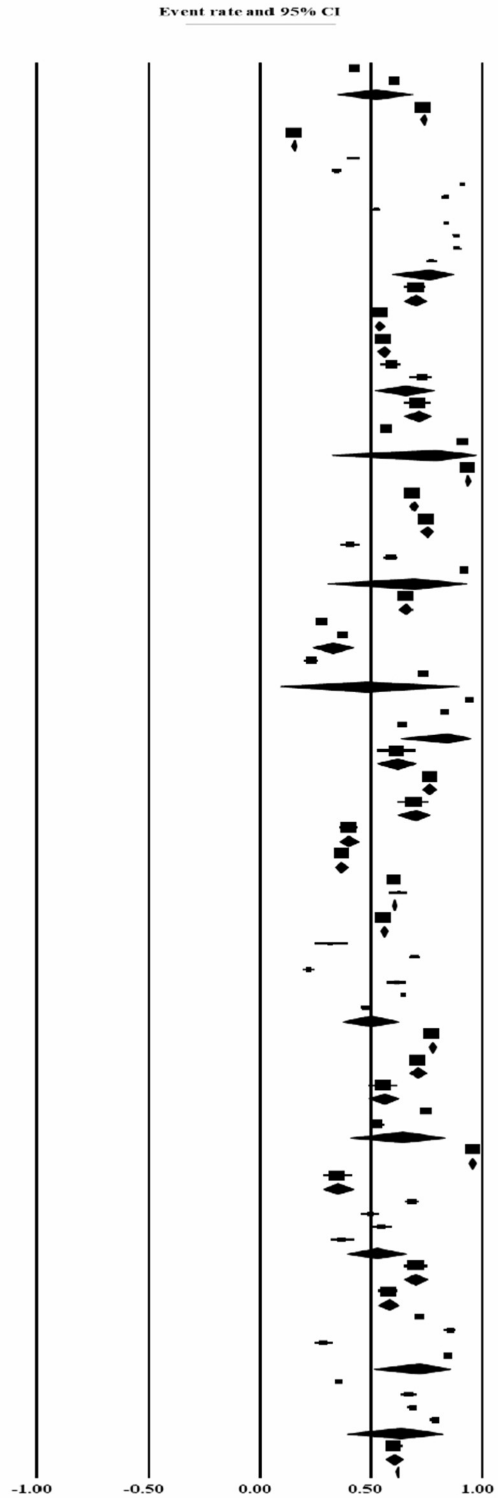

FIGURE 6
Forest plot shows the subgroup analysis of the pooled COVID-19 vaccine rate based on the country where the studies were conducted, 2022.

Group by Study participants	Study name	Event rate	Lower limit	Upper limit	Z-Value	p-Value
Child caregivers	Qin et al	0.885	0.869	0.899	27.020	0.000
Child caregivers		0.885	0.869	0.899	27.020	0.000
Healthcare workers	Shekhar et al	0.360	0.345	0.375	-17.641	0.000
Healthcare workers	Kose et al	0.686	0.658	0.712	12.235	0.000
Healthcare workers	Gretch et al	0.618	0.529	0.699	2.592	0.010
Healthcare workers	Sirikalyanpaiboon et al	0.956	0.938	0.969	16.765	0.000
Healthcare workers	Saddik et al	0.580	0.537	0.622	3.622	0.000
Healthcare workers	Barry et al	0.700	0.676	0.723	15.098	0.000
Healthcare workers	Boche et al	0.727	0.676	0.773	7.803	0.000
Healthcare workers	Nohl et al	0.570	0.543	0.597	5.023	0.000
Healthcare workers	Elharake et al	0.649	0.643	0.655	45.050	0.000
Healthcare workers	Holzmann-Littig et al	0.917	0.909	0.925	44.458	0.000
Healthcare workers		0.714	0.599	0.807	3.483	0.000
Patients	Gerussi et al	0.408	0.369	0.448	-4.477	0.000
Patients	Berihun et al	0.594	0.546	0.640	3.811	0.000
Patients	Khiari et al	0.350	0.287	0.419	-4.176	0.000
Patients	Vallée et al	0.713	0.652	0.767	6.337	0.000
Patients		0.518	0.368	0.666	0.234	0.815
Population	Malik et al	0.670	0.634	0.705	8.632	0.000
Population	Ditekemena	0.559	0.544	0.574	7.566	0.000
Population	Wong et al	0.945	0.930	0.957	22.072	0.000
Population	Wong et al	0.422	0.394	0.450	-5.382	0.000
Population	Yoda et al	0.657	0.628	0.684	10.233	0.000
Population	Freeman	0.717	0.704	0.729	29.946	0.000
Population	Williams, et al	0.860	0.828	0.887	14.460	0.000
Population	Alabdulla	0.605	0.594	0.616	18.432	0.000
Population	Reiter	0.690	0.669	0.710	16.574	0.000
Population	Wang et al	0.348	0.328	0.369	-13.531	0.000
Population	Sallam et al	0.318	0.249	0.396	-4.409	0.000
Population	Feleszko et al	0.370	0.342	0.399	-8.390	0.000
Population	Dinga et al	0.154	0.140	0.169	-30.819	0.000
Population	Wang et al	0.913	0.900	0.924	30.057	0.000
Population	Dror et al	0.750	0.724	0.775	15.863	0.000
Population	Dickerson et al	0.290	0.253	0.330	-9.398	0.000
Population	Lazarus et al	0.762	0.729	0.792	13.102	0.000
Population	Williams et al	0.775	0.756	0.793	23.189	0.000
Population	Sallam et al	0.236	0.207	0.267	-13.851	0.000
Population	Harapan et al	0.933	0.918	0.945	24.275	0.000
Population	Akarsu et al	0.497	0.462	0.533	-0.165	0.869
Population	Khubchandani et al	0.790	0.771	0.808	23.386	0.000
Population	Chen,	0.838	0.825	0.850	34.227	0.000
Population	Palamenghi	0.590	0.559	0.620	5.672	0.000
Population	Wang	0.522	0.500	0.544	1.995	0.046
Population	Sallam et al	0.284	0.265	0.303	-19.438	0.000
Population	Bell et al	0.558	0.530	0.585	4.095	0.000
Population	Alwi et al	0.833	0.813	0.852	22.515	0.000
Population	Achangwa et al	0.708	0.673	0.740	10.730	0.000
Population	Nakhostin-Ansari et al	0.690	0.676	0.703	25.109	0.000
Population	Hossain et al	0.429	0.404	0.454	-5.475	0.000
Population	Alibrahim and Awad	0.738	0.724	0.751	29.325	0.000
Population	Huang et al	0.844	0.833	0.855	39.829	0.000
Population	Antwi-Berko et al	0.696	0.620	0.762	4.819	0.000
Population	Mohamed et al	0.645	0.620	0.670	10.714	0.000
Population	Tlale et al	0.734	0.722	0.746	32.651	0.000
Population	Huang et ala	0.749	0.721	0.775	14.665	0.000
Population	Roberts et al	0.850	0.839	0.860	41.710	0.000
Population	Paul et al	0.605	0.590	0.620	13.467	0.000
Population	Bongomin et al	0.701	0.648	0.749	6.945	0.000
Population	Al-Mulla et al	0.626	0.581	0.669	5.357	0.000
Population	İkiışıket al	0.547	0.497	0.596	1.839	0.066
Population	Almaghaslah et al	0.224	0.197	0.253	-15.209	0.000
Population	Yahia et al	0.618	0.576	0.658	5.386	0.000
Population	Tsai et al	0.527	0.496	0.558	1.724	0.085
Population	Han et al	0.891	0.877	0.904	30.190	0.000
Population	Alfageeh et al	0.480	0.459	0.501	-1.849	0.065
Population	El-Elimat et al	0.374	0.357	0.391	-13.877	0.000
Population		0.639	0.584	0.691	4.790	0.000
PL Women	Nguyen et al	0.604	0.566	0.641	5.268	0.000
PL Women	Riad et al	0.702	0.653	0.747	7.456	0.000
PL Women	Tao et al	0.774	0.751	0.795	19.209	0.000
PL Women	Ayhan et al	0.370	0.317	0.426	-4.451	0.000
PL Women		0.622	0.450	0.768	1.398	0.162
Students	Mustapha et al	0.400	0.355	0.447	-4.167	0.000
Students	Raja et al	0.558	0.491	0.623	1.705	0.088
Students	Gallè et al	0.919	0.909	0.928	37.638	0.000
Students	Saied et al	0.540	0.519	0.561	3.691	0.000
Students		0.647	0.326	0.874	0.892	0.373
Overall		0.816	0.797	0.832	24.924	0.000

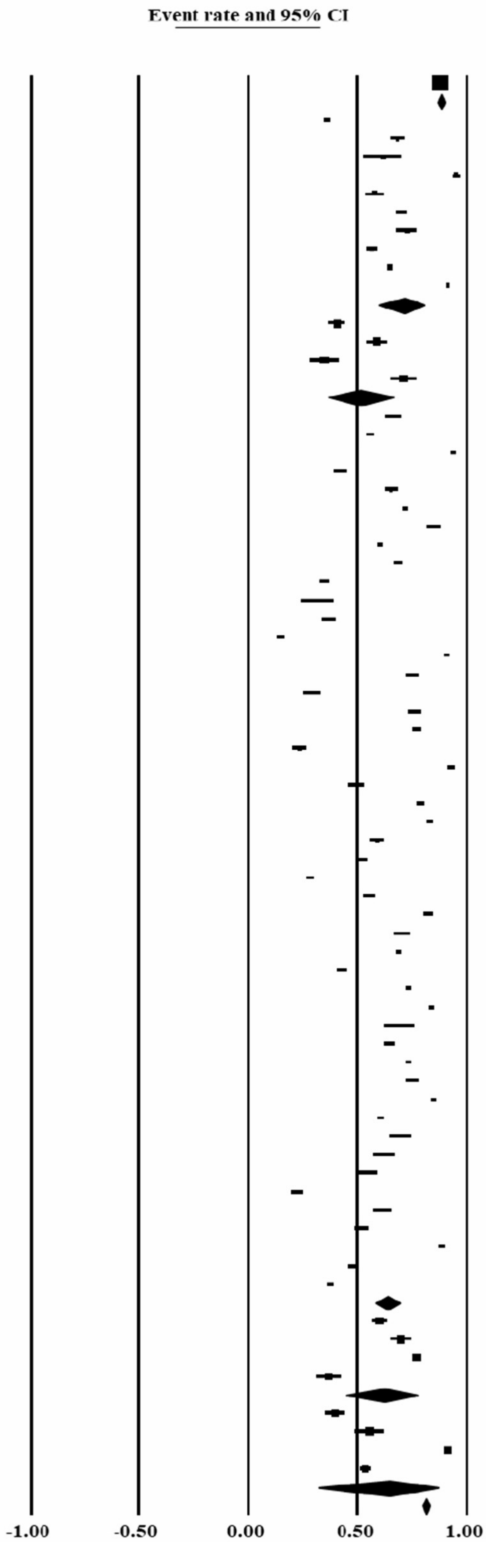

FIGURE 7
Forest plot shows the subgroup analysis of the pooled COVID-19 vaccine rate based on the study participants, 2022.

Group by Survey period	Study name	Statistics for each study: Event rate	Lower limit	Upper limit	Z-Value	p-Value
December 2020 to February 2021	Sallam et al	0.236	0.207	0.267	-13.851	0.000
December 2020 to February 2021	Sallam et al	0.284	0.265	0.303	-19.438	0.000
December 2020 to February 2021	Alwi et al	0.833	0.813	0.852	22.515	0.000
December 2020 to February 2021	Nakhostin-Ansari et al	0.690	0.676	0.703	25.109	0.000
December 2020 to February 2021	Hossain et al	0.429	0.404	0.454	-5.475	0.000
December 2020 to February 2021	Huang et al	0.844	0.833	0.855	39.829	0.000
December 2020 to February 2021	Khiari et al	0.350	0.287	0.419	-4.176	0.000
December 2020 to February 2021	Antwi-Berko et al	0.696	0.620	0.762	4.819	0.000
December 2020 to February 2021	Nguyen et al	0.604	0.566	0.641	5.268	0.000
December 2020 to February 2021	Mohamed et al	0.645	0.620	0.670	10.714	0.000
December 2020 to February 2021	Saddik et al	0.580	0.537	0.622	3.622	0.000
December 2020 to February 2021	Tlale et al	0.734	0.722	0.746	32.651	0.000
December 2020 to February 2021	Roberts et al	0.850	0.839	0.860	41.710	0.000
December 2020 to February 2021	Paul et al	0.605	0.590	0.620	13.467	0.000
December 2020 to February 2021	Nohl et al	0.570	0.543	0.597	5.023	0.000
December 2020 to February 2021	Al-Mulla et al	0.626	0.581	0.669	5.357	0.000
December 2020 to February 2021	İkiışık et al	0.547	0.497	0.596	1.839	0.066
December 2020 to February 2021	Almaghaslah et al	0.224	0.197	0.253	-15.209	0.000
December 2020 to February 2021	Yahia et al	0.618	0.576	0.658	5.386	0.000
December 2020 to February 2021	Elharake et al	0.649	0.643	0.655	45.050	0.000
December 2020 to February 2021	Vallée et al	0.713	0.652	0.767	6.337	0.000
December 2020 to February 2021	Alfageeh et al	0.480	0.459	0.501	-1.849	0.065
December 2020 to February 2021	Holzmann-Littig et al	0.917	0.909	0.925	44.458	0.000
December 2020 to February 2021	Galle et al	0.919	0.909	0.928	37.638	0.000
December 2020 to February 2021	Saied et al	0.540	0.519	0.561	3.691	0.000
December 2020 to February 2021	Ayhan et al	0.370	0.317	0.426	-4.451	0.000
December 2020 to February 2021		0.619	0.548	0.685	3.254	0.001
June to August 2020	Wong et al	0.422	0.394	0.450	-5.382	0.000
June to August 2020	Feleszko et al	0.370	0.342	0.399	-8.390	0.000
June to August 2020	Dinga et al	0.154	0.140	0.169	-30.819	0.000
June to August 2020	Lazarus et al	0.762	0.729	0.792	13.102	0.000
June to August 2020	Williams et al	0.775	0.756	0.793	23.189	0.000
June to August 2020	Akarsu et al	0.497	0.462	0.533	-0.165	0.869
June to August 2020	Khubchandani et al	0.790	0.771	0.808	23.386	0.000
June to August 2020	Chen	0.838	0.825	0.850	34.227	0.000
June to August 2020	Achangwa et al	0.708	0.673	0.740	10.730	0.000
June to August 2020		0.601	0.405	0.769	1.013	0.311
June to August 2021	Huang et al	0.749	0.721	0.775	14.665	0.000
June to August 2021	Raja et al	0.558	0.491	0.623	1.705	0.088
June to August 2021	Boche et al	0.727	0.676	0.773	7.803	0.000
June to August 2021		0.685	0.571	0.781	3.100	0.002
March to May 2020	Malik et al	0.670	0.634	0.705	8.632	0.000
March to May 2020	Wong et al	0.945	0.930	0.957	22.072	0.000
March to May 2020	Williams et al	0.860	0.828	0.887	14.460	0.000
March to May 2020	Reiter	0.690	0.669	0.710	16.574	0.000
March to May 2020	Sallam et ,al	0.318	0.249	0.396	-4.409	0.000
March to May 2020	Wang et al	0.913	0.900	0.924	30.057	0.000
March to May 2020	Dror et al	0.750	0.724	0.775	15.863	0.000
March to May 2020	Harapan et al	0.933	0.918	0.945	24.275	0.000
March to May 2020	Wang	0.522	0.500	0.544	1.995	0.046
March to May 2020	Bell et al	0.558	0.530	0.585	4.095	0.000
March to May 2020		0.765	0.647	0.853	4.016	0.000
March to May 2021	Mustapha et al	0.400	0.355	0.447	-4.167	0.000
March to May 2021	Berihun et al	0.594	0.546	0.640	3.811	0.000
March to May 2021	Alibrahim and Awad	0.738	0.724	0.751	29.325	0.000
March to May 2021	Sirikalyanpaiboon et al	0.956	0.938	0.969	16.765	0.000
March to May 2021	Bongomin et al	0.701	0.648	0.749	6.945	0.000
March to May 2021		0.726	0.556	0.849	2.545	0.011
September to November 2020	Shekhar et al	0.360	0.345	0.375	-17.641	0.000
September to November 2020	Ditekemena	0.559	0.544	0.574	7.566	0.000
September to November 2020	Kose et al	0.686	0.658	0.712	12.235	0.000
September to November 2020	Yoda et al	0.657	0.628	0.684	10.233	0.000
September to November 2020	Freeman	0.717	0.704	0.729	29.946	0.000
September to November 2020	Alabdulla	0.605	0.594	0.616	18.432	0.000
September to November 2020	Wang et al	0.348	0.328	0.369	-13.531	0.000
September to November 2020	Gerussi et al	0.408	0.369	0.448	-4.477	0.000
September to November 2020	Dickerson et al	0.290	0.253	0.330	-9.398	0.000
September to November 2020	Gretch et al	0.618	0.529	0.699	2.592	0.010
September to November 2020	Barry et al	0.700	0.676	0.723	15.098	0.000
September to November 2020	Tsai et al	0.527	0.496	0.558	1.724	0.085
September to November 2020	Han et al	0.891	0.877	0.904	30.190	0.000
September to November 2020	Tao et al	0.774	0.751	0.795	19.209	0.000
September to November 2020	El-Elimat et al	0.374	0.357	0.391	-13.877	0.000
September to November 2020		0.579	0.492	0.662	1.776	0.076
September to november 2021	Qin et al	0.885	0.869	0.899	27.020	0.000
September to november 2021	Riad et al	0.702	0.653	0.747	7.456	0.000
September to november 2021		0.810	0.573	0.931	2.458	0.014
Overall		0.645	0.603	0.685	6.508	0.000

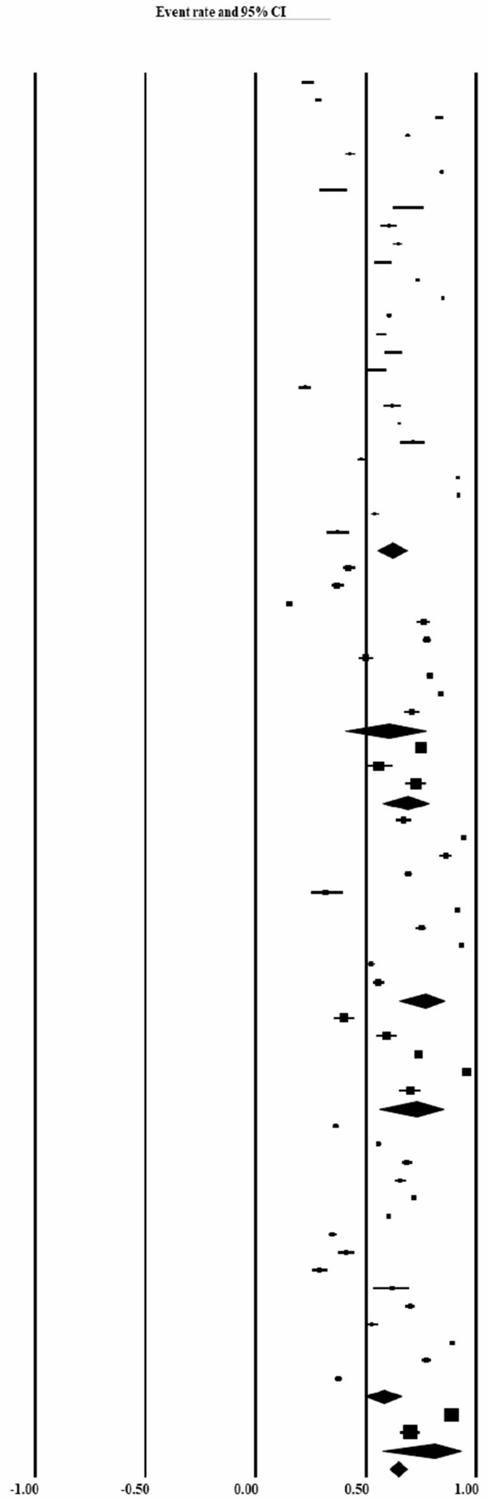

FIGURE 8
Shows the prevalence of the COVID-19 vaccine acceptance abased in the survey period, 2022.

TABLE 1 Results of sensitivity analysis for COVID-19 vaccine acceptance, 2022.

Criteria	Acceptance rate/prevalence	Heterogeneity	95% Confidence interval		P-value
			Upper limit	Lower limit	
After removing three articles with small sample size	65.2%		60.8	69.3	<0.001
After removing one article with small sample size	64.85		60.0	69.3	<0.001
After removing one article with low outcome	65.5%		61.5	69.4	<0.001
After removing four articles with high prevalence rate	62.0%		57.8	66.1	<0.001
After removing one article with low and four articles with high prevalence rate	65.8%		58.8	66.6	<0.001

the study participants or the survey period. The former study was mainly conducted in a specific study period, whereas the present study's findings depend on the studies conducted during COVID-19 pandemic.

The lowest prevalence of COVID-19 vaccine acceptance rate was reported in Cameroon [15.4% (95% CI: 14.0, 16.9], while the highest prevalence [95.6% (95% CI: 93.8, 96.9%] was reported in Thailand, followed by Indonesia [93.3% (95% CI: 91.8, 94.5%]. The variation may be due to the difference in sources of information and types of study participants. Because, the study conducted in Thailand involved healthcare workers, whereas the study conducted in Cameroon involved the general population.

Furthermore, the current study found a slight difference in the pooled prevalence of COVID-19 vaccine acceptance rate among the studies conducted in the United States [60.4% (95% CI 56.6, 64.1%)], United Arab Emirates [58.0% (95% CI 53.7, 62.2%)], Taiwan [64.6% (95% CI 41.0, 82.7%)], and Qatar [60.6% (95% CI 59.6, 61.7%)].

Similarly, there was slight difference in the prevalence of COVID-19 acceptance rate among the studies conducted in the United Kingdom [71% (95% CI: 51.3, 85.1%)], South Korea [70.8% (95% CI: 67.3, 74.0%)], Netherland [69.6% (95% CI: 62.0,76.2%)], Italy [69.2% (95% CI: 30.3, 92.1%)], Iran [69.0% (95% CI: 67.6, 70.3%)], France [71.3% (95% CI: 65.2, 76.7%)] and Czechia [70.2% (95% CI: 65.3, 74.7%)]. However, in some countries there was a lower prevalence, such as Cameroon and Jordan, which reported 15.4 and 32%, respectively. In general, the variation in the estimate of the vaccine acceptance rate may be due to the difference in the information and sociodemographic characteristics of the study participants (Supplementary File V).

Based on World Health Organization Region, the overall COVID-19 vaccine acceptance rate was 60.8% [95% CI: 56.3, 65.2%] that was slightly lower than our findings without subgroup analysis. The lowest COVID-19 vaccine acceptance rate was reported in the Eastern Mediterranean Region accounted for 60.8% [95% CI: 43.4, 57.2%], followed by the Western Pacific [74.7% CI: 65.2, 82.3%] and American region (66.4%: CI: 59.4, 82.3%).

However, the highest prevalence was reported in South East Asian Region, which accounted for 81.0% [95% CI: 59.9, 92.4%]. The variation in vaccine acceptance rate may be related to the level of risk perception, study participants involved, and access to information (Supplementary File VI).

Based on the survey period, the COVID-19 acceptance rate was 76.5, 60.1, 57.9, 61.9, 72.6, 68.5, and 81.0% for the articles conducted from March to May 2020, June to August 2020, September to November 2020, December 2020 to February 20211, March to May 2021, June to August 2021 and September to November 2021, respectively. This indicates that there is a decline in COVID-19 vaccine acceptance rate from March to November 2020. The current study is supported by various studies (country or region-specific studies), which reported a decline in willingness to accept COVID-19 vaccine (6, 13, 14).

Similarly, this finding was in line with the findings of another study, which reported a decline in the acceptance rate of the COVID-19 vaccine from more than 70.0% in March to <50% in October (82). However, there was an increasing in COVID-19 vaccine acceptance rate from December 2020 to November 2021. It could be related to an increase in awareness, a change in risk perception, and the round of vaccines given across the world. The variation in the vaccine acceptance rate based on the survey period is indicated in the figure below (Supplementary File VII).

In general, the current study found that there was a declining in COVID-19 vaccine acceptance rate in 2020 and increasing in 2021. However, the overall COVID-19-vaccine acceptance rate was 64.9%. This indicates that there is a need to improve community awareness in order to increase COVID-19-vaccine acceptance rate. The authors recommend the need to take appropriate actions to manage the COVID-19 pandemic. Thus, local and international government should take appropriate action in collaboration with non-governmental organizations and community members to build trust in the community and to ensure adequate vaccination coverage. Furthermore, transparent and effective communications are essential to reduce misinformation and vaccination hesitancy, build trust, and ensure adequate vaccination coverage (8). Additionally, novel decision models for vaccine selection need to be developed.

Implications of finding

The current study revealed that only about six out of ten study participants accepted the COVID-19 vaccine. This indicates that even if the COVID-19 vaccine is developed, the issue of accepting or taking the developed vaccine and managing the pandemic may be difficult. Not only for COVID-19, it must be used as input and considered to control other pandemics. These findings can be used as an input for concerned bodies, including health program planners, researchers, policymakers, and decision-makers, to take appropriate actions that can contribute to vaccine acceptance, ensure adequate vaccination coverage, and promote health.

Limitations

There was an unequal distribution of the studies conducted across the world. Furthermore, the acceptance rates of the COVID-19 vaccine in many countries of the world were not included because of the lack of studies that met the eligibility criteria. Similarly, as a result of variation in the unit of measurement/statistical analysis employed for data analysis, we could not able to determine the factors associated with COVID-19 acceptance rate. Furthermore, cross-sectional studies were included and causal relationships between the acceptance rate of the COVID-19 vaccine and the determinant factors cannot be established.

Conclusion

This review found a decline in the acceptance rate of the COVID-19 vaccine in 2020 and increasing acceptance in 2021. About 6 in 10 study participants accepted COVID-19 vaccine that needs critical attention to manage the COVID-19 pandemic. This finding indicated that even if the COVID-19 vaccine is developed, the issue of accepting or taking the developed vaccine and managing the pandemic will be difficult unless appropriate measures are taken when it is necessary. Furthermore, we recommend further studies, particularly on the determinants or factors that lead to hesitancy.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author/s.

Author contributions

DM conceived the idea and had a major role in the review, extraction, analysis of the data, writing, drafting, and editing of the manuscript. YD has contributed to data extraction, analysis, and editing. All authors read and approved the final version of the manuscript to be published and agreed on all aspects of this work.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.1044193/full#supplementary-material

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Diné teachings and public health students informing peers and relatives about vaccine education: Providing Diné (Navajo)-centered COVID-19 education materials using student health messengers

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Introduction/background: On 9 April 2021, the Centers for Disease Control and Prevention (CDC) reported that only 19. 9% of United States (US) adults were fully vaccinated against COVID-19. In that same week, the Navajo Nation (NN) reported that 37.4% of residents were fully vaccinated, making the NN a leader in the uptake of COVID-19 vaccines. Despite high vaccination rates, vaccine hesitancy exists within the NN. The Diné (Navajo) Teachings and Public Health Students Informing Peers and Relatives about Vaccine Education (RAVE) intervention was designed to utilize trusted health messengers as an effective means to address adults' vaccine concerns and hesitancy.

Methods: The research team used COVID-19 vaccine materials developed in a previous collaboration with non-Navajo tribal communities and publicly available materials. Diné Traditional Knowledge Holders (TKHs) were interviewed to develop and incorporate Diné-specific information on individual and collective health behaviors into the RAVE materials. These drafted health education materials were presented to NN community health representatives (CHRs) and Diné public health students using a consensus panel approach. NN residents who participated in the intervention completed a 16-element retrospective pretest.

Results: The adaptation and tailoring process of materials yielded 4 health education materials. The students recruited 46 adults for health education sessions. These participants then completed the retrospective pretest. Changes in the 16 elements were in the desired direction, although only six were significant: four related to attitudes and two concerned with vaccination intention. Participants were more likely to consider vaccination and to try to get vaccinated after the education session.

Discussion: Trusted messengers and culturally centered materials have been identified as effective means of health behavior education with Native American audiences. RAVE applied these intervention elements by (1) training Diné College public health students to leverage their cultural knowledge and social relationships (cultural and social capital) to recruit vaccine-hesitant adults and provide education; (2) building on previous understanding of Native American communities' vaccine concerns; and (3) integrating Diné perspectives on individual and collective health into the adaptation of materials designed for general audiences; this knowledge was gained from interviews with TKHs.

KEYWORDS

COVID-19 education, vaccine hesitancy, vaccine education, health messengers, Navajo

Introduction

American Indian/Alaskan Native (AI/AN) populations have been negatively impacted by the COVID-19 pandemic due to racial inequity, historical trauma, and health disparities resulting in an incidence of positive COVID-19 cases 3.5 times that of non-Hispanic whites (1). The Navajo Nation (NN) has the largest tribal enrollment at 332,129 and is the largest Native American reservation in the United States (US). The NN spans parts of Arizona, New Mexico, and Utah, where over 173,000 enrolled Diné citizens reside (2, 3). In May 2020, the NN surpassed both New York and New Jersey for the highest per-capita COVID-19 infection rate in the US with 2,304 positive cases per 100,000 residents, while the overall US rate was 636 positive cases per 100,000 residents (4). The increase in COVID-19 cases, and ultimately the highest rate of COVID-19-related mortality, is attributed to NN residents living in multigenerational homes, having limited access to running water and resources, and lacking social trust in external social systems (5–7). Although more NN residents were fully vaccinated at 37.4%, compared to 19.9% in the US adult population at the same time period, vaccine hesitancy was still evident, preventing some NN residents from receiving the vaccine (5, 8, 9). Vaccine uptake is critical in Native American populations as national data indicate that Native Americans have disproportionally high levels of pre-existing health conditions and have the highest rates of COVID-19-related mortality compared to other US populations (10, 11). Prior to the COVID-19 pandemic, Native Americans had higher vaccine rates than the general US populations, noted particularly for influenza and human papillomavirus infection (12, 13). Based on a review of social media discussions among NN residents, COVID-19 vaccine hesitancy is grounded in historical mistrust of the government (14, 15). This article describes the development of materials and the outcome of the vaccine safety education sessions developed for NN residents.

The Diné Teachings and Public Health Students Informing Peers and Relatives about Vaccine Education (RAVE) intervention were designed to integrate trust and culture to address adults' vaccine concerns and hesitancy. RAVE's objective was to increase NN adult residents' knowledge of the COVID-19 vaccines to encourage vaccination uptake. Undergraduate public health students at Diné College, a tribal college located on the NN, were identified as trusted messengers who could be trained to deliver and provide culturally centered, scientifically accurate vaccine-safety information to NN residents. These trusted health messengers used Diné-specific relationality and etiquette to talk to their peers and relatives who were hesitant about vaccination.

In addition to the Diné College public health students, RAVE engaged two NN community health representatives (CHRs) in the intervention development. CHRs, community health workers (CHWs), and lay health educators are a well-recognized workforce that helps reduce health disparities and improve health equity among underserved populations through direct home-based care and education (16). In NN, CHRs play a vital role as cultural mediators and are frontline public health workers, trusted by their communities. CHRs, CHWs, and lay health educators' duties were put on hold due to the COVID-19 pandemic and transitioned to crisis management focused on disaster response (17, 18).

Once trained in a classroom setting, Diné College public health students were able to deliver vaccine education to their peers and family members relying on their social and cultural obligation through *K'é*, a core cultural teaching referring to descent, clanship, and kinship, to inform and contribute to the relevance of necessary information (19, 20).

Methods

Developing education materials

The intervention team drew on the Theory of Planned Behavior (TPB) (21), COVID-19 vaccine education materials developed in a previous collaboration with non-Navajo tribal communities, and the Arizona Community Health Workers (AzCHOW) Association (22), as well as traditional Diné concepts of individual and collective health. The TPB posits that three core components, specifically attitudes, subjective norms, and perceived behavioral control, link beliefs to behaviors and thus shape an individual's behavioral intentions. Four Traditional Knowledge Holders (TKHs) were interviewed to understand COVID-19 and how vaccines fit into Diné views of maintaining wellness. The Navajo investigators on the research team reviewed the interview transcripts, identified the key concepts, and integrated the TKHs' Diné perspectives on individual and collective health into the adaptation of materials designed for RAVE's audiences. The in-depth analysis of the TKH interviews will be discussed in a forthcoming manuscript. Further adaptations were informed by health education materials from the Johns Hopkins Center for American Indian Health and the Navajo Department of Health (NDOH). The research team began developing the COVID-19 education materials using a free-to-use, online graphic-design tool called Canva^{tm}.

Consensus panels

The research team engaged in a consensus-based, decision-making method to review and modify vaccine education materials with CHRs and student health messengers. Consensus-based decision-making, or a consensus panel, involves the group to actively participate in making a decision or a plan in which all members are comfortable (23). This approach was used to leverage the collective knowledge of the CHRs and Diné College public health students to contribute to the comprehension and appeal of the COVID-19 education materials. Key foci of materials were to ensure the approach was culturally appropriate and addressed knowledge gaps about the COVID-19 vaccines, for example, the traditional perspectives of the pandemic and the difference between quarantine and isolation. The questions used in the consensus panels were based on criteria for language and content, format and organization, and imagery and colors.

The draft COVID-19-education materials were presented to CHRs in the first consensus panel. After the first consensus panel feedback, the research team began revising the materials. Once materials were complete, a second consensus panel was conducted with Diné College public health students to further refine the materials. Once the CHRs and public health students approved the final revisions and provided any final remarks, the materials were saved as final electronic PDF files or printed.

Health messenger training

A total of 16 Diné College students were enrolled in a special topics course and were trained using the aforementioned culturally centered materials to become health messengers providing vaccine safety education. Based on the aforementioned work in non-Navajo tribal communities, Native Americans described being motivated to get vaccinated to keep their families healthy; this commitment to family wellbeing was incorporated into the vaccine safety materials. In addition, students were provided with extensive information on the technology of vaccine development, clinical trials, and vaccine myths propagating on social media.

Students gained confidence in delivering materials through motivational interviewing (24). Once student health messengers were trained, they were tasked to recruit between 5 and 10 peers and/or relatives to whom they would deliver and discuss the vaccine-education materials. Eligibility for recruitment included individuals who have not received the COVID-19 vaccine, aged 18 years and older, have been identified as any race and gender, and have resided or worked on the NN. Once student health messengers identified their potential participants, they scheduled a one-on-one or group session either in-person or virtually through Zoom^{tm}. At the beginning of each session, health messengers read and answered questions related to the Human Subject consent form and secured informed consent for participation *via* electronic or hard copy signatures.

Retrospective pretest

To determine the effectiveness of the intervention, student health messengers administered a retrospective pretest to participants receiving the health message. The questionnaire asked participants to report their attitudes, perceived behavioral control, subjective norms, and intent to receive a COVID-19 vaccine after the education session, and then report their views before the session through the retrospective pretest. Data were collated in Microsoft Excel and chi-square tests were performed using OpenEpi.com (25) which makes basic data analysis available *via* the Internet to users who might otherwise not have access to statistical software. After each student health messenger session, the retrospective pretest was administered *via* hard copy or electronically through SurveyMonkey^{tm}. As guided by the TPB, the retrospective pretest (26) sought to evaluate shifts in attitudes and intention to get vaccinated as well as influences, such as perceived behavioral controls and subjective norms. The retrospective pretest was used in place

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of a traditional pretest/posttest to reduce subjects' burden as only one administration is required and minimizes bias since participants often overestimate their knowledge of a topic in a classic pretest/posttest design (26).

Results

Consensus panel

Two CHRs and 13 public health students participated in the material development consensus panel, of which over 75% of consensus panel members identified as Diné and women. A total of three 1-h-long consensus panels were conducted with the CHRs and student health messengers, 1 for the CHRs, and 2 for the student health messengers. CHRs and student health messengers provided feedback on the health education materials in the following areas: language and content, format and organization, and images and colors. The feedback provided include clarifying wording or using less scientific terms, adding borders for better organization, making images Navajo-specific, and/or validating the information on the education materials. Additional feedback can be seen in Supplementary Table 1 (consensus panel results).

Final health education materials

A total of four education materials were created as follows: COVID-19 Vaccines, COVID-19 FAQs and Myths, Quarantine vs. Isolation, and Traditional Knowledge of COVID-19. The final version of the education materials can be seen in Supplementary Table 2 (COVID-19 health education materials).

Evaluation of participant education

A total of 46 individuals completed the retrospective pretest to assess changes in attitudes, perceived behavioral control, subjective norms, and intent to receive the vaccine. Possible answers used either a binary scale, "A Great Deal/Not at All," or one of the two four-point, Likert-type scales: "Strongly Agree" to "Strongly Disagree" or "Very Likely" to "Very Unlikely." Questions with four possible answers were collapsed into the binary outcome for analysis. No participant demographics were collected and not all participants answered every question, so total responses ranged from 43 to 46. All responses indicated a change in the desired direction, including five questions where the desired direction would be a negative change from pretest to posttest.

Four of the nine attitude questions and two of the three intent questions demonstrated a statistically significant change. The single perceived-behavioral-control and three subjective-norm questions were approached but they did not attain significance. Statistically significant changes occurred with increases in the number of participants who believed that getting the COVID-19 vaccine was a good idea (56.5%), that the vaccine would prevent COVID-19 (66.3%), and that the vaccines would protect the community (53.3%); fewer believed that the research conducted on the vaccines was insufficient (−22.5%). Willingness to consider getting the COVID-19 vaccine (42.9%) and intent to get the vaccine (77.3%) both significantly increased, demonstrating that using students trained as health messengers is effective in changing attitudes and intents surrounding vaccination status in individuals with which they are familiar (refer to Supplementary Table 3). The questionnaire asked participants to report their change in attitudes, perceived behavior control, subjective norms, and intent to receive the vaccine by health messaging recipients.

Discussion

The RAVE intervention illustrated that undergraduate public health students who have social and cultural capital in a community can be effective health messengers. Social capital refers to the non-financial resources available through social networks, most notably support gained through the interpersonal connections and norms of trust and reciprocity on which networks depend (27). Cultural capital is obtained from resources based on shared values, behavioral norms, and culture-specific knowledge acquired by group learning occurring through shared experiences and histories as well as cultural knowledge, stories, and activities (28). This relational asset has received limited attention in health promotion literature but has been discussed in reference to nursing education as a means to enhance the quality of care and engage older adults in volunteerism (28–30). RAVE demonstrates these assets can contribute to initiating an atmosphere of trust, credibility, and caring. *K'é* embodies social and cultural capital within the Diné relational environment. A core element of *K'é* is honoring individual and familial relationships to people and ultimately all living things, thus guiding positive behaviors and interactions of Diné people with relatives (31, 32). *K'é* supported Diné public health students' ability to establish an earnest social connection, allowing them to recruit individuals who were distrustful of the healthcare system and gain consent from these individuals to hear about vaccine safety. As the information was being delivered by a "relative," the health message was accepted as credible and the intention of the messenger was interpreted as sincere, grounded in the messenger's legitimate concern for the participant's health (31, 32).

Although *K'é* is a distinctively Diné concept, RAVE demonstrates that significant attitudinal and intentional shifts in health behaviors can occur when both the message and the messenger share social and cultural capital with the recipient. Health promotion efforts have documented that trust and empathy are enhanced with the ethnic concordance of providers and patients (33) and the ethnic and socio-economic concordance of community health workers and community members (34). RAVE demonstrated that trust and empathy can be enhanced when the message is culturally centered and shaped by the messengers themselves. Although not directly documented in RAVE's evaluation, participants may have been particularly receptive to these predominantly young adults aspiring to contribute to the public health workforce of the NN. Indigenous people have long identified future generations as the path to build tribal capacity and self-determination (35). Using an academic-course setting can be effective in training students, the majority of whom were members of the community, as trusted messengers to deliver health education to peers and family. By doing so, attitudes and intentions toward the uptake of health practices can be changed in targeted populations who might otherwise be resistant to those practices. RAVE suggests that undergraduate students are an underutilized public health resource in Indigenous communities and perhaps in other underserved communities striving toward health equity.

Limitations/strengths

The limitations of RAVE were the small number of student participants and the lack of peers and family members who were recruited. At least 20 students were initially enrolled in the course, but a few withdrew because they had other time commitments or felt it would be too challenging to recruit participants. Of the 16 students who remained in the class, only 12 were able to recruit peers and family members because many of the individuals they knew had already been vaccinated. The strength of RAVE was the long-term partnership between Diné College and Northern Arizona University through the NIH-NIGMS supported mechanism, the Navajo Native American Research Center for Health (NARCH) Partnership. The senior and junior investigators, staff, and students of the Navajo NARCH bring a diversity of experience, skills, and passion to design, implement, and evaluate innovative strategies to achieve health equity for the Diné people.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by Northern Arizona University Institutional Review Board, Diné College Institutional Review Board, Navajo Nation Human Research Review Board. The patients/participants provided their written informed consent to participate in this study.

Author contributions

MT: manuscript preparation, writing—original draft preparation, and writing—review and editing. CB, SG, CK, CD, and NT-S: writing—review and editing. MB: supervision. All authors have read and agreed to the published version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.1046634/full#supplementary-material

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Investigation on the hesitancy of COVID-19 vaccination among liver transplant recipients: A cross-sectional study in China

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Objectives: The hospitalization and mortality rate from COVID-19 appears to be higher in liver transplant recipients when compared with general populations. Vaccination is an effective strategy to reduce the risk during the COVID-19 pandemic. We aimed to evaluate COVID-19 vaccine hesitancy in liver transplant recipients.

Methods: In April 2022, we conducted an online-based survey through WeChat platform to investigate the vaccination hesitancy among liver transplant recipients followed at Shanghai Renji Hospital and further explore possible influencing factors. Survey items included multiple choice, Likert-type rating scale and open-ended answers. Participants were classified as no hesitancy group and hesitancy group. Using univariate analysis, ROC curve analysis and multiple logistic regression to evaluate associations between baseline characteristics and COVID-19 vaccine hesitancy.

Results: 449 liver transplant recipients participated in the survey with 299 (66.6%) of them being categorized as vaccine hesitancy. In no hesitancy group, 73 (48.7%) recipients had completed vaccination, while 77 (51.3%) were not yet but intended to be vaccinated. In contrast, 195 (65.2%) recipients in hesitancy group were hesitant to get vaccinated, while the remaining 104 (34.8%) refused. The most common side effect was injection arm pain ($n = 9$, 12.3%). The common reasons for vaccine willingness was trusted in the effectiveness of the vaccine and fear of contracting COVID-19. The most common reason for vaccination hesitancy is fear of side effects, and the most effective improvement was the support from the attending physician. Factors associated with vaccine hesitancy include female sex, influenza vaccination status, awareness of the importance and safety of vaccine, attitudes of doctors and others toward vaccine, medical worker source information of vaccine, relative/friend with medical background, total score of VHS (Vaccine Hesitancy Scale), accessibility of vaccine.

Conclusion: For liver transplant recipients, COVID-19 vaccine is an important preventive measure. Identifying the factors influencing COVID-19 vaccine hesitancy is therefore critical to developing a promotion plan. Our study shows that more comprehensive vaccine knowledge popularization and relevant medical workers' training can effectively improve the acceptance of COVID-19 vaccine in this population.

KEYWORDS

COVID-19, prevention, vaccine survey, vaccine hesitancy, vaccine acceptance, liver transplantation

Introduction

In December 2019, COVID-19 has caused a pandemic in many countries around the world. In March 2022, Omicron, a mutated COVID-19 virus, began to spread in China, especially Shanghai, causing a major blow to economy, medical system, and social life. Compared with the previously detected COVID-19 virus, this variant is more infectious and poses a serious threat to the health of vulnerable populations (e.g., the elderly, hematology patients, solid organ transplant recipients). Solid organ transplant recipients (e.g., liver) appear to be more susceptible to COVID-19 and have higher rates of hospitalization and mortality compared with other populations due to large immunosuppressants after surgery and potential comorbidities (1, 2). The mortality rate among solid organ transplant recipients infected with COVID-19 has been reported between 13 and 30% (1). Safe and effective vaccines are essential to reduce the risk of COVID-19, protect vulnerable populations, and prevent the pandemic. Currently, more than 280 COVID-19 vaccines are in development, and many of them have entered the Chinese healthcare system, such as Sinovac and Sinopharm (3, 4).

At the end of March 2021, the National Health Commission of the People's Republic of China released the first edition of COVID-19 vaccine vaccination technical guideline to further popularize and promote vaccination, but it lacked detailed description of solid organ transplant recipients (4). While some other guidelines [e.g., AISF (5), EASL (6), and AASLD (7)] strongly recommend that liver transplant recipients should be vaccinated against COVID-19. However, one of the major obstacles to promote COVID-19 vaccination is vaccine hesitancy (8). According to the World Health Organization (WHO), vaccination hesitancy means the delay in acceptance or reluctance of vaccination despite availability of vaccination services, which has been recognized as one of the 10 threats to global health due to the declining vaccination rates (9).

According to several online questionnaires, solid organ transplant recipients' vaccine hesitancy about COVID-19 was mainly attributed to concerns about its side effects, potential comorbidities, and doctors' negative advice (10, 11). Several secondary factors were also associated with vaccine hesitancy, including type of graft, main source of vaccine information, education level, influenza vaccination experience and willingness, perceptions of the importance of COVID-19 vaccines, risk perception and trust, and religious and moral beliefs (8). Other unreported factors may also be involved, such as the surprising speed of COVID-19 vaccine development, the relatively lack of efficacy and safety data in solid organ transplant recipients (6, 12–14), and the spread and amplification of negative information about vaccines by some organization or individual (15).

Current surveys of COVID-19 vaccine hesitancy have focused on health workers, students, patients with chronic diseases, the elderly, and children, and have rarely included solid organ transplant recipients. We reviewed the literature and found small number of reports on the willingness of liver transplant recipients to be vaccinated against COVID-19 (11). It has reported that solid organ transplant recipients are generally associated with low willingness to get vaccinated against COVID-19. However, the majority of these subjects were kidney transplant recipients (10). So far, there has been no related investigation about immunosuppressed people after liver transplantation in China. To fill this gap, we conducted such a survey to identify factors influencing vaccine hesitancy among liver transplant recipients in China and to promote vaccine promotion.

Materials and methods

Study design and sample

An anonymous, self-designed, and structured online questionnaire was conducted in Chinese liver transplant recipients aged 18 years and above, from 26 April to 10 May 2022. The questionnaire was made available through WeChat platform, released by the department of Liver Surgery, Renji Hospital Shanghai Jiao Tong University. A web link collector generated the survey QR code through which participants could access the survey and send their answers. Inclusion criteria included: adult recipients (age ≥18 years old) who were followed up after liver transplantation in our hospital. Exclusion criteria included: pre-transplant vaccination against COVID-19, missing or illogical questionnaire information, loss of follow-up. Ethical approval was granted by the

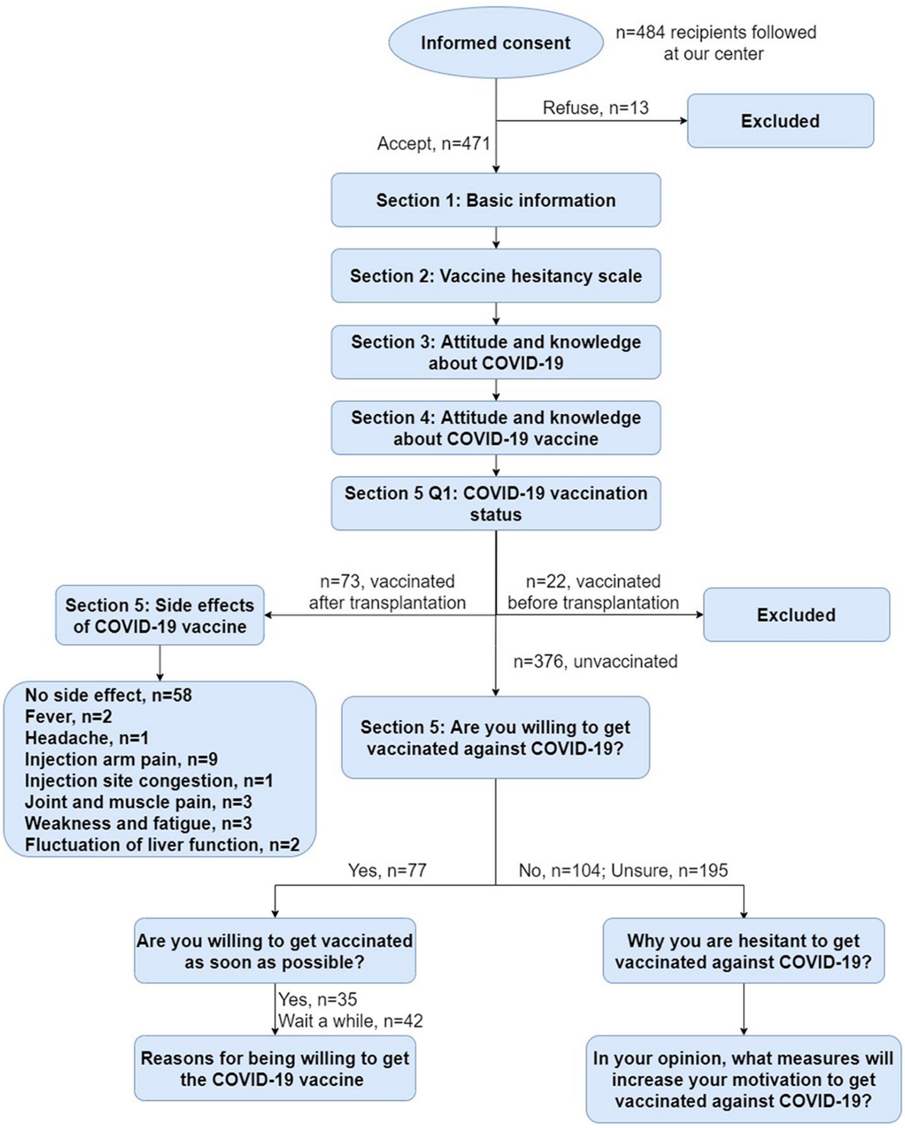

FIGURE 1
The flow chart for the five sections of the questionnaire.

Ethics Committee of Renji Hospital Shanghai Jiaotong University (No. KY2022-138-B). Participants in this study were voluntary, and an informed consent was placed at the top of the questionnaire. Patients who give consent to inform will access to the subsequent questionnaire. Completion of the anonymous survey did not result in any benefit or financial compensation for the recipients. The confidentiality of all data was guaranteed (ClinicalTrials.gov Identifier: NCT05532592). Participants were classified as no hesitancy group (NHG) and hesitancy group (HG) to accept COVID-19 vaccination. COVID-19 vaccines were totally free in China and offered independently of the questionnaire responses.

Survey items

Our follow-up questionnaire comprised five sections (Figure 1). For details of the questionnaire items, please refer to the corresponding table or the supplementary materials we have uploaded. The first section includes demographic data, health state, transplantation and medication, chronic diseases and allergy history, influenza vaccination. The second section is a scale (VHS) to quantify vaccination hesitancy among liver transplant recipients. The third section is about the attitudes and perceptions of the participants toward COVID-19. The fourth section investigates the knowledge of the participants about COVID-19 vaccines. The final section confirms their vaccination status and evaluates their vaccine acceptance or hesitancy.

Vaccine Hesitancy Scale (VHS) was developed by the WHO SAGE Working Group on Vaccine Hesitancy that was widely used in different countries and settings (16–18). VHS comprised 10 items about adult attitudes toward vaccination and each item was scored 10–50 and summed to calculate a total score, with higher score indicating greater hesitancy. In this study, we used the 10 items of the VHS that are measured on a five-point Likert-type rating scale ranging from "strongly agree" to "strongly disagree." No changes were made to the wording of the items. We administered questions in a random order to mitigate any order effect. We reversed three items in the scoring of the scale so that higher scores indicated more hesitancy on all items. The survey items are available at: https://doi.org/10.6084/m9.figshare.13207145

Statistical analysis

Statistical analysis was performed using IBM SPSS 23.0. Categorical variables were presented as number (percentage), and quantitative variables were presented as mean ± standard deviation. Chi-square test was used for univariate analysis of categorical variables. Student's *t*-test were used for quantitative variables. Mann-Whitney *U*-test were used for ranking variables. Variables with $p < 0.1$ in the univariate analysis were included in multiple logistic regression analysis, to assess factors associated with vaccination hesitancy. Odds ratio and 95% confidence intervals were calculated. The Hosmer–Lemeshow test and Omnibus test were performed for the model fit estimation. ROC curve analysis was used to calculate the cutoff point of VHS results. The level of statistical significance was set at $p < 0.05$.

Results

Demographic data and sample characteristics

Overall, 484 recipients from follow-up list participated in the online survey between 26 April and 10 May 2022. A total of 471 valid questionnaires were obtained. The response rate was 97.3%. Among these participants, 22 recipients received COVID-19 vaccine before transplantation, so we excluded them. Finally, 449 recipients met the criteria for inclusion in this study.

Based on the WHO definition of vaccine hesitancy mentioned above, we considered that there was no vaccine hesitancy in recipients who got vaccine after transplantation or were willing to be vaccinated. Therefore, we classified them into the no hesitancy group (NHG). Accordingly, recipients who were uncertain or rejective, were identified as vaccine hesitancy, and we categorize them into the hesitancy group (HG).

Subsequently, a total of 150 recipients were enrolled in the NHG (Vaccinated/Willing to be vaccinated), including 73 (48.7%) recipients vaccinated after liver transplantation and 77 (51.3%) who were currently unvaccinated but willing to be vaccinated. And there were 299 recipients in the HG (Unwilling or uncertain of vaccination), including 195 (65.2%) who were uncertain and 104 (34.8%) who refused vaccination.

Of the 449 recipients, male was the majority (n = 308, 68.6%), compared with 141 female (31.4%). Mean (±standard deviation) age was 54.56 (±10.69) years old, with most recipients located in the 45–60 age range. The primary etiology of transplantation was mainly hepatitis B (because only one case was hepatitis C) (n = 193, 43%), followed by autoimmune liver disease (n = 119, 26.5%), liver tumor (n = 60, 13.4%), and others (n = 77, 17.1%). Most recipients reported to have exceeded 12 months after transplantation, with a mean time of 64.67 months. All respondent recipients were adhering to their immunosuppressive therapy and most of them had regular follow-up biopsy (n = 366, 81.5%). Other related information and significant difference between the two groups are shown in Table 1.

Vaccine hesitancy scale

Vaccine hesitancy scale scores of the two groups were displayed in Table 2. Mann-Whitney *U*-test for each item score and Student's *t*-test for the total score showed significant differences and HG scored significantly higher than NHG, suggesting that HG had a significantly higher quantification of vaccine hesitancy on the scale.

Then we conducted ROC curve analysis for NHG and HG, and NHG and participants refusing vaccination, to calculate the cutoff point of VHS results (Figure 2). The results of the ROC curve analysis are shown in Table 3. The cutoff point between NHG and HG was 215 (p < 0.001), with the sensitivity 71.2%, and the specificity 58.7%. While the cutoff point between NHG and participants refusing vaccination was also 215 (p < 0.001), with the sensitivity 87.5%, and the specificity 58.7%.

Attitude toward COVID-19

Attitudes and perceptions of COVID-19 were almost identical between the two groups and significant differences only existed in two items (Table 4). We can see that NHG participants learn about COVID-19 more thoroughly [yes vs. no:

TABLE 1 Demographic data and sample characteristics of participants.

	Variables	Total participants (*n*, %)	Vaccination status		*p*-Value*
			Vaccinated/willing to be vaccinated (*n*, %)	Unwilling or uncertain of vaccination (*n*, %)	
	Total (*n*)	449	150	299	
Sex	Male	308 (68.6)	115 (76.7)	193 (64.5)	0.009*
	Female	141 (31.4)	35 (23.3)	106 (35.5)	
Age (years)	>18 and ≤30	10 (2.2)	2 (1.3)	8 (2.7)	0.49
	>30 and ≤45	71 (15.8)	26 (17.3)	45 (15.1)	
	>45 and ≤60	248 (55.2)	87 (58)	161 (53.8)	
	>60	120 (26.7)	35 (23.3)	85 (28.4)	
	Age (mean ± standard deviation)	54.56 ± 10.694	54.85 ± 10.61	54.41 ± 10.751	0.682
Nationality	Han	434 (96.7)	145 (96.7)	289 (96.7)	0.995
	Others	15 (3.3)	5 (3.3)	10 (3.3)	
Marital status	Married	401 (89.3)	135 (90)	266 (89)	0.737
	Single/divorced/widowed	48 (10.7)	15 (10)	33 (11)	
Occupation	Enterprise workers	135 (30.1)	50 (33.3)	85 (28.4)	0.042*
	Farmer	35 (7.8)	10 (6.7)	25 (8.4)	
	Government officers	36 (8)	15 (10)	21 (7)	
	Retired/vacation#	182 (40.5)	47 (31.3)	135 (45.2)	
	Student	8 (1.8)	3 (2)	5 (1.7)	
	Other vocations#	53 (11.8)	25 (16.7)	28 (9.4)	
Living situation	Live alone	41 (9.1)	15 (10)	26 (8.7)	0.651
	With family	408 (90.9)	135 (90)	273 (91.3)	
Residence	Urban	365 (81.3)	119 (79.3)	246 (82.3)	0.451
	Rural	84 (18.7)	31 (20.7)	53 (17.7)	
Education level	High school or below	222 (49.4)	72 (48)	150 (50.2)	0.665
	College or above	227 (50.6)	78 (52)	149 (49.8)	
Monthly income per capita (RMB)	>20,000	57 (12.7)	22 (14.7)	35 (11.7)	0.313
	10,000–20,000	94 (20.9)	37 (24.7)	57 (19.1)	
	5,000–10,000	170 (37.9)	54 (36)	116 (38.8)	
	<5,000	128 (28.5)	37 (24.7)	91 (30.4)	
Have relative/friend with medical background	Yes	173 (38.5)	49 (32.7)	124 (41.5)	0.071
	No	276 (61.5)	101 (67.3)	175 (58.5)	
Self-assessment of health	I'm healthy	206 (45.9)	80 (53.3)	126 (42.1)	0.025*

(Continued)

TABLE 1 (Continued)

		Variables	Total participants (*n*, %)	Vaccination status		*p*-Value*
				Vaccinated/willing to be vaccinated (*n*, %)	Unwilling or uncertain of vaccination (*n*, %)	
		Uncertain or unhealthy	243 (54.1)	70 (46.7)	173 (57.9)	
Causes of transplantation		Hepatitis B or C#	193 (43)	79 (52.7)	114 (38.1)	0.019*
		Autoimmune liver disease (including PBC/PSC)#	119 (26.5)	29 (19.3)	90 (30.1)	
		Liver tumor	60 (13.4)	17 (11.3)	43 (14.4)	
		Others	77 (17.1)	25 (16.7)	52 (17.4)	
Post-transplantation time		≤3 months	9 (2)	3 (2)	6 (2)	0.177
		>3 and ≤6 months	14 (3.1)	1 (0.7)	13 (4.3)	
		>6 and ≤12 months	36 (8)	11 (7.3)	25 (8.4)	
		>12 months	390 (86.9)	135 (90)	255 (85.3)	
		Time (mean ± standard deviation)	64.67 ± 54.147	66.42 ± 54.328	63.79 ± 54.126	0.627
Type of immunosuppressant used[a]		1	184 (41)	70 (46.7)	114 (38.1)	0.104
		2	202 (45)	65 (43.3)	137 (45.8)	
		≥3	63 (14)	15 (10)	48 (16.1)	
Immunological rejection by biopsy		Yes	73 (16.3)	24 (16)	49 (16.4)	0.755
		No	293 (65.3)	101 (67.3)	192 (64.2)	
		Uncertain due to no biopsy	83 (18.5)	25 (16.7)	58 (19.4)	
Treatment of primary disease		Cure	399 (88.9)	143 (95.3)	256 (85.6)	0.002*
	Not healed	50 (11.1)	7 (4.7)	43 (14.4)		
Chronic disease	Endocrine diseases	Yes	147 (32.7)	49 (32.7)	98 (32.8)	0.981
		No	302 (67.3)	101 (67.3)	201 (67.2)	
	Chronic respiratory diseases	Yes	30 (6.7)	11 (7.3)	19 (6.4)	0.695
		No	419 (93.3)	139 (92.7)	280 (93.6)	
	Cardiovascular and cerebrovascular diseases	Yes	137 (30.5)	54 (36)	83 (27.8)	0.074
		No	312 (69.5)	96 (64)	216 (72.2)	
	Chronic nephrosis	Yes	39 (8.7)	16 (10.7)	23 (7.7)	0.291
		No	410 (91.3)	134 (89.3)	276 (92.3)	

(Continued)

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TABLE 1 (Continued)

Variables			Total participants (*n*, %)	Vaccination status: Vaccinated/willing to be vaccinated (*n*, %)	Vaccination status: Unwilling or uncertain of vaccination (*n*, %)	*p*-Value*
	Chronic liver diseases	Yes	55 (12.2)	15 (10)	40 (13.4)	0.303
		No	394 (87.8)	135 (90)	259 (86.6)	
	Immune system diseases	Yes	4 (0.9)	0 (0)	3 (1)	0.537
		No	445 (99.1)	150 (100)	296 (99)	
	Tumor	Yes	14 (3.1)	2 (1.3)	12 (4)	0.21
		No	435 (96.9)	148 (98.7)	287 (96)	
	Others	Yes	177 (39.4)	57 (38)	120 (40.1)	0.663
		No	272 (60.6)	93 (62)	179 (59.9)	
HBV+ now		Yes	91 (20.3)	23 (15.3)	68 (22.7)	0.065
		No	358 (79.7)	127 (84.7)	231 (77.3)	
Drug allergy history		Yes	72 (16)	16 (10.7)	56 (18.7)	0.028*
		No	377 (84)	134 (89.3)	243 (81.3)	
Food allergy history		Yes	19 (4.2)	2 (1.3)	17 (5.7)	0.031*
		No	430 (95.8)	148 (98.7)	282 (94.3)	
Vaccine allergy history		Yes	8 (1.8)	5 (3.3)	3 (1)	0.167
		No	441 (98.2)	145 (96.7)	296 (99)	
Delay or refuse vaccinations except for illnesses or allergies		Yes	101 (22.5)	21 (14)	80 (26.8)	0.002*
		No	348 (77.5)	129 (86)	219 (73.2)	
Influenza vaccination during last year (2021–2022)		Yes	16 (3.6)	15 (10)	1 (0.3)	0.001*
		No	433 (96.4)	135 (90)	298 (99.7)	
Intention toward influenza vaccination for the current season		Yes	31 (6.9)	24 (16)	7 (2.3)	0.001*
		No	418 (93.1)	126 (84)	292 (97.7)	
Other vaccines after transplantation (except for influenza and COVID-19)		Yes	33 (7.3)	14 (9.3)	19 (6.4)	0.254
		No	416 (92.7)	136 (90.7)	280 (93.6)	

[a]Immunosuppressants including: tachlimus, mycophenolate mofetil, mycophenolate sodi, prednisone, rapamycin, cyclosporine.
*p-values <0.05 are marked with an asterisk.
#Subgroups with differences in univariate analysis.

TABLE 2 Vaccine hesitancy scale result.

Items	Vaccination status		p-Value*
	Vaccinated/willing to be vaccinated (mean ± standard deviation)	Unwilling or uncertain of vaccination (mean ± standard deviation)	
Vaccines are important for my health	17.87 ± 10.781	27.32 ± 13.837	0.001*
Vaccines are effective	18.07 ± 10.146	26.45 ± 13.291	0.001*
Being vaccinated is important for the health of others in my community.	15.67 ± 9.653	21.1 ± 12.815	0.001*
All routine vaccinations recommended by the CDC are beneficial	18.07 ± 10.911	22.27 ± 12.458	0.001*
New vaccines carry more risks than older vaccines.	26.6 ± 14.601	29.26 ± 13.138	0.047*
The information I receive about vaccines from the CDC is reliable and trustworthy.	19 ± 10.666	24.01 ± 12.149	0.001*
Getting vaccines is a good way to protect me from disease.	16.67 ± 10.144	22.24 ± 12.638	0.001*
Generally, I do what my doctor or healthcare provider recommends about vaccines for me.	14.8 ± 10.148	17.79 ± 11.577	0.002*
I am concerned about serious adverse effects of vaccines.	32.2 ± 14.346	39.36 ± 13.334	0.001*
I do not need vaccines for diseases that are not common anymore.	28 ± 15.801	32.21 ± 13.968	0.006*
Total score	207.93 ± 75.559	262.04 ± 78.091	0.001*

*p-values <0.05 are marked with an asterisk.

51 (34%) vs. 66 (22.1%); $p = 0.007$], and their occupational risk of COVID-19 was relatively higher [high vs. low risk: 63 (42%) vs. 94 (31.4%); $p = 0.027$].

Knowledge about COVID-19 vaccine

In this section, when comparing COVID-19 vaccine hesitancy or not, there were apparent differences between the two groups, including: awareness of the first edition of COVID-19 vaccine vaccination technical guideline, awareness of the side effects and precautions of COVID-19 vaccine, the main source of information on COVID-19 vaccine, safety of COVID-19 vaccine, efficacy of COVID-19 vaccine, whether vaccination can help control the epidemic and promote the health of society, COVID-19 vaccine will lead to the recurrence of the primary disease, COVID-19 vaccine is not safe for post-transplantation, COVID-19 vaccine is inconvenient for post-transplantation, safety of COVID-19 vaccine in post-transplantation, efficacy of COVID-19 vaccine in post-transplantation, COVID-19 vaccine is important for liver transplant patients, have actively sought advice about COVID-19 vaccine, surgery doctor's attitude toward COVID-19 vaccine, family and friends' attitudes toward COVID-19 vaccine. Detailed information is shown in Table 5. These differences are in line with our expectations. Overall, recipients in NHG were more knowledgeable about the COVID-19 vaccine, had more trust in the vaccine, and received more support. We will continue our analysis as followings.

Vaccination status

(1) Recipients vaccinated after surgery: side effects

We analyzed common vaccine-related side effects in post-transplantation vaccinated COVID-19 recipients (n = 73), including fever, headache, tinnitus, light-headed, injection arm pain, injection site congestion, numbness of the arm, joint and muscle pain, weakness and fatigue, sore throat, nausea/vomiting, diarrhea, skin rash, anaphylaxis, edema, hypertensive attack, heart-related side effects, fluctuation of liver function, other side effects (Figure 3). These symptoms were self-reported by participants and not diagnosed by medical institutions. It was found that the incidence of side effects in our study was 20.55%, and there was no symptom serious or requiring medical attention. The most common side effect was injection arm pain, followed by joint and muscle pain, weakness and fatigue, fever, fluctuation of liver function, injection site congestion and headache.

(2) Unvaccinated but willing to be vaccinated: reasons for willing to get vaccinated

We then surveyed participants who were willing to be vaccinated (Figure 4). Half of the participants (n = 35, 45.45%) were willing to get vaccinated as soon as possible, while the other half (n = 42, 54.55%) wanted to wait a while. As for the reasons for willing to get vaccinated, the highest proportion were "vaccination is an effective measure to prevent disease (n = 62, 80.52%)" and "worry about getting COVID-19 (n = 62, 80.52%)."

(3) Unvaccinated but hesitant or refusing to be vaccinated: reasons for vaccination hesitancy and management

The main reasons for vaccination hesitancy were analyzed from the data of the 299 participants in HG (Figure 5). The results showed that among these participants who were unsure to be vaccinated (n = 195, 65.22%), the most common reason was "side effects and safety of vaccine (n = 139, 71.28%)," followed by "vaccine conflicts with current medication (n = 117, 60.00%)," "vaccine has an impact on existing chronic diseases (n = 103, 52.82%)" and "vaccine affect liver function (n = 91, 46.67%)." The main reasons for the participants unwilling to be vaccinated (n = 104, 34.78%) were also the same with different order.

Measures to improve COVID-19 vaccine hesitancy were consistent, with the overwhelming majority of HG recipients opting for the support of their attending physician (Figure 6).

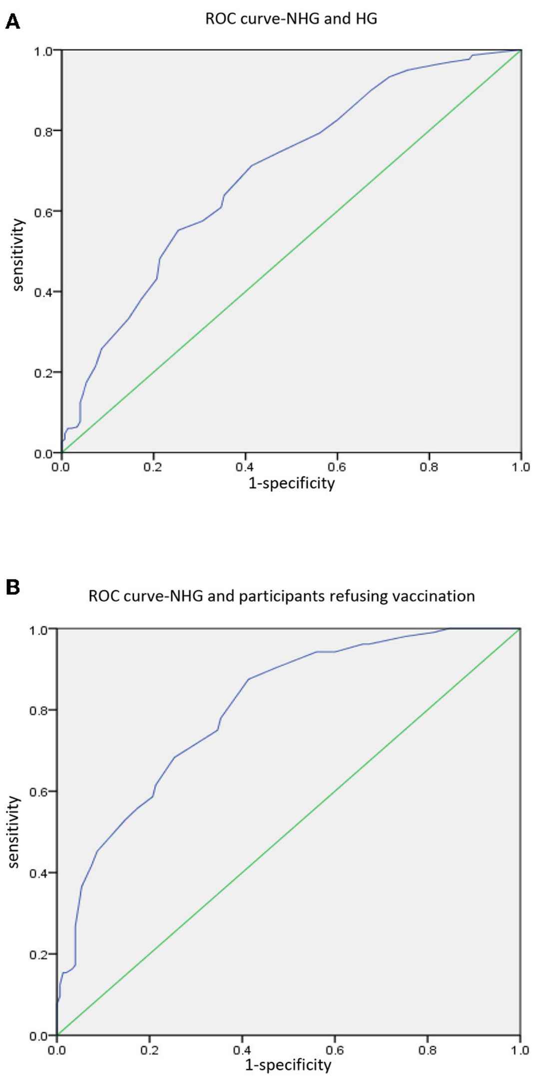

FIGURE 2
ROC curve analysis. **(A)** Analysis between NHG and HG. **(B)** Analysis between NHG and participants refusing vaccination.

Logistics regression results: Predictors for vaccine hesitancy

For the above items with statistical results $p < 0.1$, they were included in multiple logistic regression analysis to further explore their correlation with vaccine hesitancy. In the logistic regression analysis result as showed in Figure 7, factors positively associated with vaccination hesitancy are followings: female recipients (OR = 2.483, 95% CI = 1.159–5.319), had relative/friend with medical background (OR = 2.060, 95% CI = 1.050–4.038), refused to get influenza vaccination during last year (2021–2022) (OR = 20.630, 95% CI = 1.304–326.499), had no intention toward influenza vaccination for the current season (OR = 6.954, 95% CI = 1.874–25.811), total score of VHS (OR = 1.005, 95% CI = 1.000–1.010), the main source of information on COVID-19 vaccine was medical worker (OR = 9.676, 95% CI = 1.083–86.448), COVID-19 vaccination is

TABLE 3 ROC curve analysis results of vaccine hesitancy scale.

	AUC	95% CI	*p*-Value*	Cutoff point	Sensitivity	Specificity
ROC curve analysis for NHG and HG	0.696	0.644–0.747	0.001*	215	71.2%	58.7%
ROC curve analysis for NHG and participants refusing vaccination	0.802	0.749–0.856	0.001*	215	87.5%	58.7%

AUC, area under the curve; 95% CI, 95% confidence interval; NHG, no hesitancy group; NH, hesitancy group.
*p-values <0.05 are marked with an asterisk.

TABLE 4 Results of attitude toward COVID-19.

		Variables	Total participants (*n*, %)	Vaccination status		*p*-Value*
				Vaccinated/willing to be vaccinated (*n*, %)	Unwilling or uncertain of vaccination (*n*, %)	
		Total (*n*)	449	150	299	
Know COVID-19[a]		Yes	117 (26.1)	51 (34)	66 (22.1)	0.007*
		Uncertain or no	332 (73.9)	99 (66)	233 (77.9)	
Have you ever had COVID-19		Yes	5 (1.1)	4 (2.7)	1 (0.3)	0.081
		No	444 (98.9)	146 (97.3)	298 (99.7)	
Are you worried about getting COVID-19 (first or again)		Yes	399 (88.9)	130 (86.7)	269 (90)	0.294
		No	50 (11.1)	20 (13.3)	30 (10)	
Do you have any friends or family members who have had COVID-19		Yes	45 (10)	14 (9.3)	31 (10.4)	0.731
		No	404 (90)	136 (90.7)	268 (89.6)	
Occupational risk of COVID-19		High	157 (35)	63 (42)	94 (31.4)	0.027*
		Low	292 (65)	87 (58)	205 (68.6)	
Risk of COVID-19 infection in patients after liver transplantation		Higher	276 (61.5)	97 (64.7)	179 (59.9)	0.342
		General or lower	74 (16.5)	26 (17.3)	48 (16.1)	
		Uncertain	99 (22)	27 (18)	72 (24.1)	
Impact of COVID-19 on the health of patients after liver transplantation		More serious	343 (76.4)	119 (79.3)	224 (74.9)	0.484
		General or less	32 (7.1)	8 (5.3)	24 (8)	
		Uncertain	74 (16.5)	23 (15.3)	51 (17.1)	
What worries you as a liver transplant patient about the current COVID-19 pandemic	Infection leads to recurrence of the disease or interfere with recovery	Yes	376 (83.7)	121 (80.7)	255 (85.3)	0.211
		No	73 (16.3)	29 (19.3)	44 (14.7)	
	The symptoms and consequences of COVID-19 are more serious	Yes	291 (64.8)	103 (68.7)	188 (62.9)	0.226
		No	158 (35.2)	47 (31.3)	111 (37.1)	
	Hospital or community control leads to drug dispensing difficulties	Yes	275 (61.2)	91 (60.7)	184 (61.5)	0.858
		No	174 (38.8)	59 (39.3)	115 (38.5)	
	Affect access to health care	Yes	267 (59.5)	85 (56.7)	182 (60.9)	0.392
		No	182 (40.5)	65 (43.3)	117 (39.1)	
	Increase the cost of treatment	Yes	144 (32.1)	40 (26.7)	104 (34.8)	0.082
		No	305 (67.9)	110 (73.3)	195 (65.2)	
	Other worries	Yes	30 (6.7)	9 (6)	21 (7)	0.682
		No	419 (93.3)	141 (94)	278 (93)	

[a]Know COVID-19: have some knowledge of the prevention measures, symptoms, prognosis and treatment of COVID-19.
*p-values <0.05 are marked with an asterisk.

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TABLE 5 Results of knowledgement about COVID-19 vaccine.

		Variables	Total participants (*n*, %)	Vaccination status		*p*-Value*
				Vaccinated/willing to be vaccinated (*n*, %)	Unwilling or uncertain of vaccination (*n*, %)	
		Total (*n*)	449	150	299	
Know the first edition of COVID-19 vaccine vaccination technical guideline		Yes	121 (26.9)	52 (34.7)	69 (23.1)	0.009*
		No	328 (73.1)	98 (65.3)	230 (76.9)	
Know the side effects and precautions of COVID-19 vaccine		Yes	133 (29.6)	56 (37.3)	77 (25.8)	0.011*
		No	316 (70.4)	94 (62.7)	222 (74.2)	
The main source of information on COVID-19 vaccine		Social media platforms#	214 (47.7)	83 (55.3)	131 (43.8)	0.012*
		TV programs and news releases	94 (20.9)	28 (18.7)	66 (22.1)	
		Family, friends or community	93 (20.7)	33 (22)	60 (20.1)	
		Medical worker#	31 (6.9)	4 (2.7)	27 (9)	
		Others	17 (3.8)	2 (1.3)	15 (5)	
Safety of COVID-19 vaccine		Safe	117 (26.1)	62 (41.3)	55 (18.4)	0.001*
		Not safe or uncertain	332 (73.9)	88 (58.7)	244 (81.6)	
Efficacy of COVID-19 vaccine		Yes	210 (46.8)	90 (60)	120 (40.1)	0.001*
		No or uncertain	239 (53.2)	60 (40)	179 (59.9)	
Vaccination helps control the epidemic and the health of society		Agree	289 (64.4)	115 (76.7)	174 (58.2)	0.001*
		Disagree/uncertain	160 (35.6)	35 (23.3)	125 (41.8)	
Availability of COVID-19 vaccine		Convenient	422 (94)	143 (95.3)	279 (93.3)	0.395
		Inconvenient	27 (6)	7 (4.7)	20 (6.7)	
As a liver transplant patient, what are your main concerns about getting the COVID-19 vaccine	Affect recovery after liver transplantation	Yes	227 (50.6)	71 (47.3)	156 (52.2)	0.333
		No	222 (49.4)	79 (52.7)	143 (47.8)	
	Lead to the recurrence of the primary disease	Yes	189 (42.1)	49 (32.7)	140 (46.8)	0.004*
		No	260 (57.9)	101 (67.3)	159 (53.2)	
	Affect post-transplant medication	Yes	223 (49.7)	68 (45.3)	155 (51.8)	0.193
		No	226 (50.3)	82 (54.7)	144 (48.2)	
	More serious side effects	Yes	321 (71.5)	101 (67.3)	220 (73.6)	0.167
		No	128 (28.5)	49 (32.7)	79 (26.4)	
	Not safe for post-transplantation	Yes	258 (57.5)	64 (42.7)	194 (64.9)	0.001*
		No	191 (42.5)	86 (57.3)	105 (35.1)	

(Continued)

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TABLE 5 (Continued)

Variables		Total participants (n, %)	Vaccination status		p-Value*
			Vaccinated/willing to be vaccinated (n, %)	Unwilling or uncertain of vaccination (n, %)	
Doubtful validity for post-transplantation	Yes	192 (42.8)	55 (36.7)	137 (45.8)	0.064
	No	257 (57.2)	95 (63.3)	162 (54.2)	
Inconvenient for post-transplantation	Yes	195 (43.4)	38 (25.3)	157 (52.5)	0.001*
	No	254 (56.6)	112 (74.7)	142 (47.5)	
Other concerns	Yes	13 (2.9)	5 (3.3)	8 (2.7)	0.925
	No	436 (97.1)	145 (96.7)	291 (97.3)	
Safety of COVID-19 vaccine in post-transplantation	Safe	55 (12.2)	49 (32.7)	6 (2)	0.001*
	Not safe or uncertain	394 (87.8)	101 (67.3)	293 (98)	
Efficacy of COVID-19 vaccine in post-transplantation	Yes	75 (16.7)	51 (34)	24 (8)	0.001*
	No or uncertain	374 (83.3)	99 (66)	275 (92)	
COVID-19 vaccine is important for liver transplant patients	Agree	159 (35.4)	97 (64.7)	62 (20.7)	0.001*
	Disagree/uncertain	290 (64.6)	53 (35.3)	237 (79.3)	
Have actively sought advice about COVID-19 vaccine	Yes	318 (70.8)	121 (80.7)	197 (65.9)	0.001*
	No	131 (29.2)	29 (19.3)	102 (34.1)	
Surgery doctor's attitude toward COVID-19 vaccine	Support	100 (22.3)	65 (43.3)	35 (11.7)	0.001*
	Neutral or rejective	349 (77.7)	85 (56.7)	264 (88.3)	
Family and friends' attitudes toward COVID-19 vaccine	Support	203 (45.2)	98 (65.3)	105 (35.1)	0.001*
	Neutral or rejective	246 (54.8)	52 (34.7)	194 (64.9)	
Family members have got COVID-19 vaccine	Yes	438 (97.6)	149 (99.3)	289 (96.7)	0.159
	No	11 (2.4)	1 (0.7)	10 (3.3)	

*p-values <0.05 are marked with an asterisk.
#Subgroups with differences in univariate analysis.

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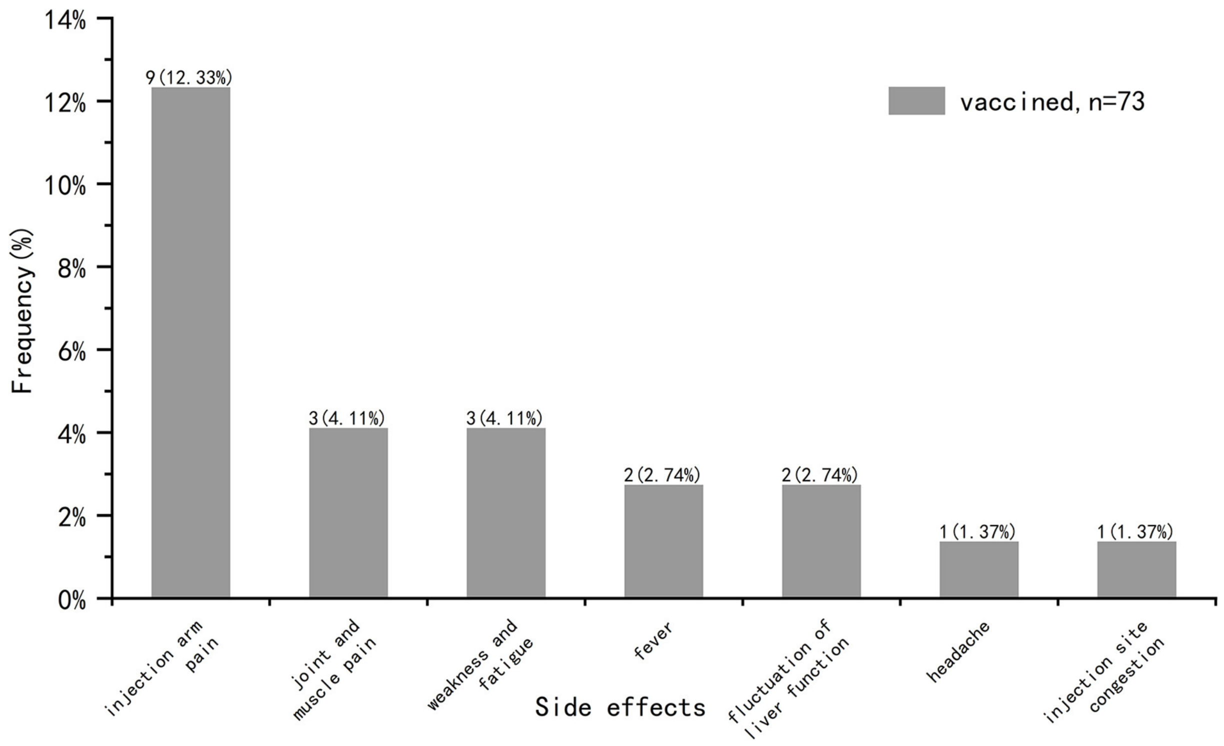

FIGURE 3
COVID-19 vaccine related side effects in vaccinated participants.

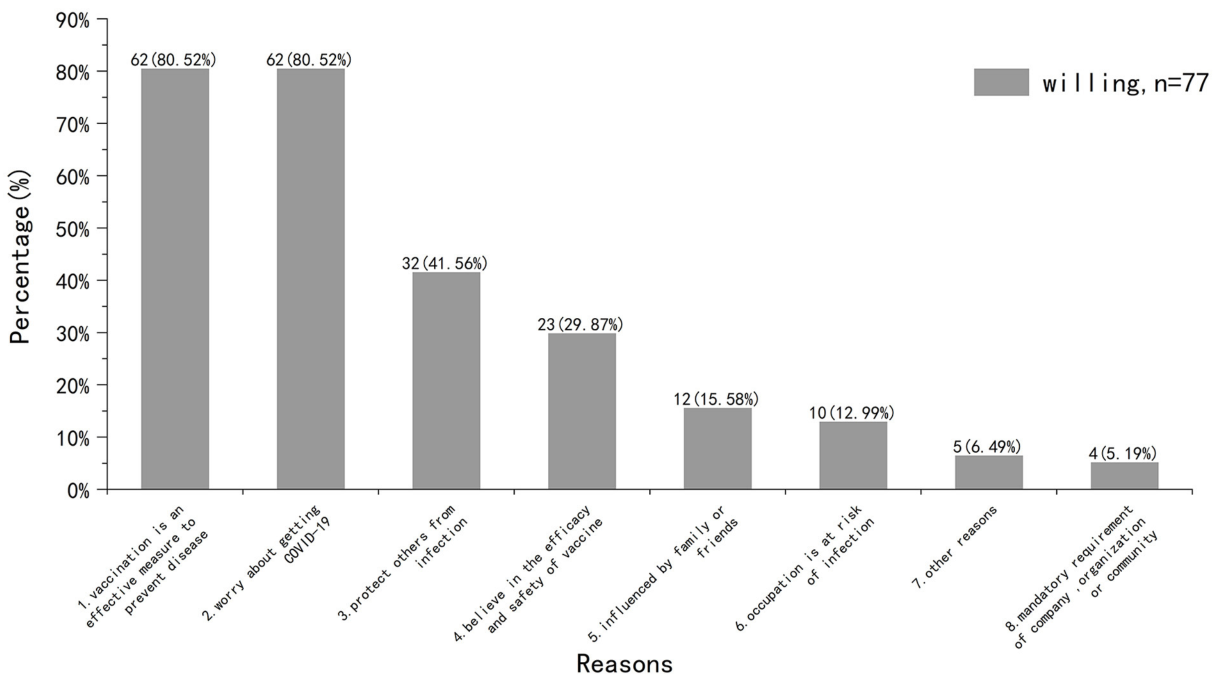

FIGURE 4
Reasons for willing to get vaccinated.

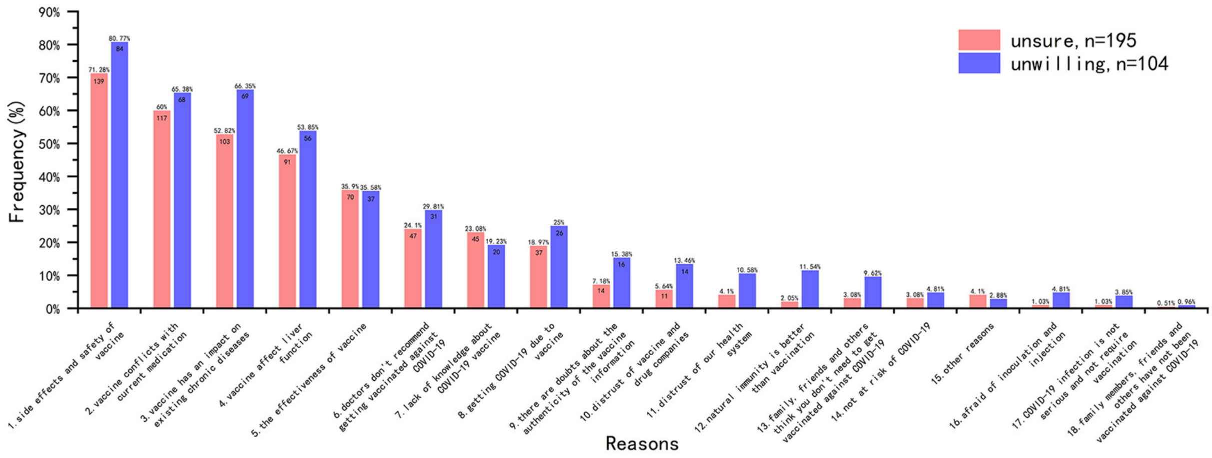

FIGURE 5
Reasons for vaccination hesitancy.

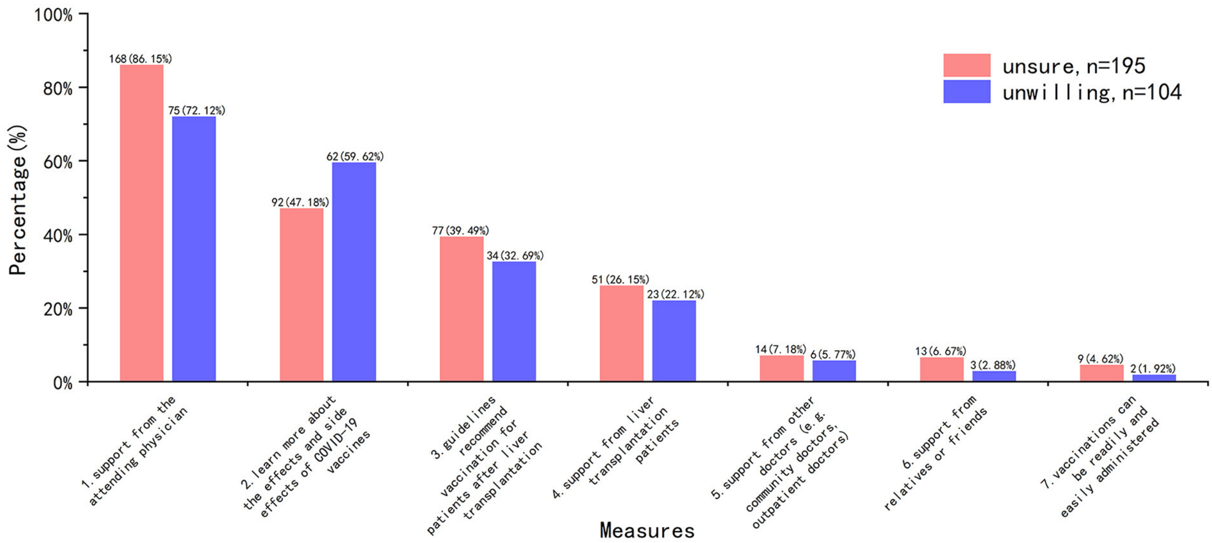

FIGURE 6
Measures to improve COVID-19 vaccine hesitancy.

inconvenient for post-transplantation (OR = 2.599, 95% CI = 1.339–5.043), distrusted the safety of COVID-19 vaccine in post-transplantation (OR = 4.772, 95% CI = 1.429–15.941), not perceived the importance of COVID-19 vaccine for liver transplant patients (OR = 3.067, 95% CI = 1.528–6.157), surgery doctor did not recommend COVID-19 vaccination (OR = 3.893, 95% CI = 1.805–8.396), family or friends believed they should not get COVID-19 vaccine (OR = 2.055, 95% CI = 1.096–3.852).

Discussion

Coronavirus is derived from the Latin word "corona" meaning "crown"(19). It causes a range of human respiratory tract infections varying from mild cold to severe respiratory distress syndrome (20). The present coronavirus disease 2019 (COVID-19) is an emerging global health threat. It is known to be acquired from a zoonotic source and typically spreads through contact and droplet transmission (21). It started from

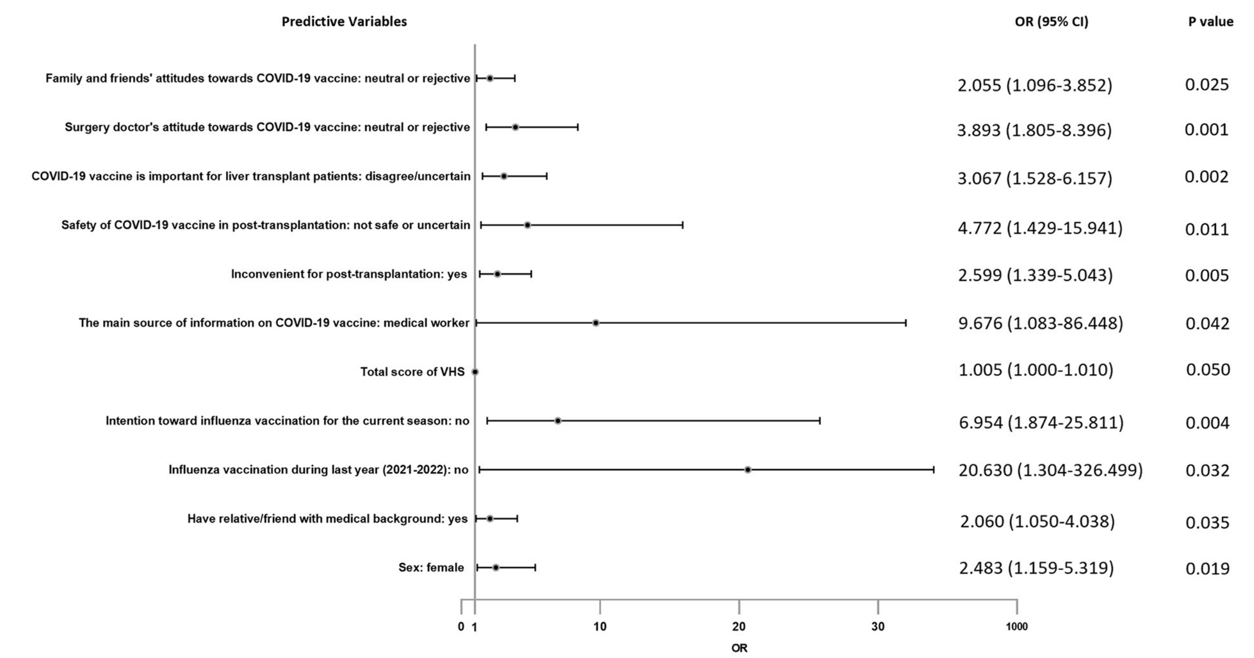

FIGURE 7
Forest plot of predictors for vaccine hesitancy.

Wuhan city of China at the end of December 2019 and since then spread rapidly around the world, creating a pandemic.

Nowadays, COVID-19 vaccination is considered to be the most appropriate measure to prevent COVID-19 infection, reduce the severity caused by COVID-19 infection and control COVID-19 pandemic. So far, the Chinese government and communities have made great efforts to promote the nationwide vaccination against COVID-19, including but not limited to publishing the first edition guideline of COVID-19 vaccine vaccination (4), popularization of COVID-19 vaccine on social networks and other platforms, completely free COVID-19 vaccine and even certain material rewards to encourage vaccination. A global survey of COVID-19 vaccines has revealed that Chinese residents have the highest acceptance (90%) (22). So far, China has made remarkable progress against COVID-19 compared to other regions, keeping the morbidity and mortality to a minimum, in which vaccines play an essential role.

However, while China's COVID-19 vaccine guideline recommends vaccination for immunocompromised people, including liver transplant recipients, there is no detailed description or data on the efficacy and safety of the vaccine in this population. As a result, liver transplant recipients are often hesitant to respond to government calls.

During routine follow-up after liver transplantation, we learned that some recipients had been vaccinated against COVID-19, while most were on the sidelines. Therefore, we hope to explore the common causes and influencing factors of vaccine hesitancy among liver transplant recipients through this survey. A previous survey among Chinese solid organ transplant recipients showed insufficient vaccination rate and willingness, most commonly due to fear of comorbidities (10). Associated factors included type of transplantation organ, the main source of vaccine information, education level, influenza vaccination intention, influenza vaccination status in the previous season, and perception of the importance of vaccines.

Unfortunately, the majority of study involved kidney transplant recipients, but only very few liver transplant recipients. Due to the differences in surgical methods, post-operative immunosuppressive usage, and many other aspects, it may be difficult to directly apply the information of kidney transplant recipients to liver transplant recipients. There are also differences in time and social environment: this study started in June 2021, when the epidemic situation in China was relatively stable, the time of COVID-19 vaccines introduction in China was relatively short, and there was a lack of information on the use COVID-19 vaccines in immunosuppressed population. Our study was carried out in May 2022, when China was facing a severe epidemic, especially in Shanghai, a medical and economic hub, where the omicron variant was rampant, and the safety and effectiveness of COVID-19 vaccine in transplant recipients were confirmed (12, 13).

Our results are partly in line with expectations and explain their vaccine hesitancy. In our study, there were 150 participants (33.4%) who were willing or completed vaccination after transplantation, and 299 participants (66.6%) with vaccine hesitancy who were unwilling or uncertain about vaccination. Although there was still a gap between this result and that of normal adults in China (60.4–82.3%) (23–26) or liver transplant recipients in Italy (85.3%) (11), we believe there had been a significant improvement compared to previous survey (10). Due to the limited literature on adult liver transplant recipients, it is difficult to compare our outcome with other regions or countries.

Among participants who had completed COVID-19 vaccination ($n = 73$), the incidence of side effects was 20.55% and the most common reported symptom was pain at the injection arm. This was in line with the results reported by Boyarsky et al. (27) and Erol et al. (28). Among participants who were willing to be vaccinated ($n = 77$), about half of them ($n = 35$, 45.45%) wanted to be vaccinated as soon as possible, while the rest ($n = 42$, 54.55%) wanted to wait a while. Previous study attributed this delay to distrust in the efficacy and safety of the vaccine (11). We believe that the higher proportion of delayed vaccination in our study may be due to the severity of the epidemic in China during the investigation period, the high risk of COVID-19 transmission and the closed-loop management measures in some areas. Also, we consider the main reasons for COVID-19 vaccine willingness mentioned above are related to this situation.

Why did participants hesitate to get the COVID-19 vaccine? We investigated major factors of vaccine hesitancy in HG. Concerns about vaccine safety and side effects were the most common reason among participants who were unsure or refused to receive the vaccine. Several other reasons that were relatively common (close to 50% or above) included "vaccine has an impact on existing chronic diseases," "vaccine conflicts with current medication" and "vaccine affect liver function," which were about fear of comorbidities or the impact on graft. This result is highly similar to that of Costantino et al. (11) and Ou et al. (29), suggesting that side effects, transplant organ, and comorbidities are the main factors that cause vaccine hesitancy in related population.

When we asked what improvements were needed in HG to increase their willingness to get COVID-19 vaccine, a noticeable finding was that "support from the attending physician" topped significantly the other choices ($n = 243$, 81.27%), while only 6.69% HG participants reported "support from other doctors" was helpful. However, we noted that 88.3% ($n = 264$) of the HG participants reported that their surgery doctors had "neutral or rejective" attitude, but only 26.09% ($n = 78$) of them had vaccine hesitancy due to "doctors don't recommend getting vaccinated against COVID-19." Therefore, it was not difficult to assume that most attending physician's response to the recipient's post-transplantation vaccination was equivocal. Recipients trust their attending physician, and doctors' "hesitancy" will contribute to their "vaccine hesitancy." Aslam et al. (30) reported that experience with influenza and zoster vaccines in solid organ transplant population can be applied to COVID-19 vaccine. In fact, some liver associations or organizations have published guidelines or recommendations on COVID-19 vaccination for liver transplant recipients (5–7). These literatures suggest that transplant recipients are at a higher risk of poor prognosis, and COVID-19 vaccine is recommended early after transplantation. In addition, some studies have reported good safety in liver transplant and other solid organ transplant recipients after receiving COVID-19 vaccine (12, 13). Even though efficacy may be insufficient (low antibody levels), this is not a reason to deny preventative protection. However, according to our survey, even attending physicians, let alone other non-transplant physicians, have limited knowledge about COVID-19 vaccine. Therefore, in order to effectively improve the willingness of transplant recipients to COVID-19 vaccine, it is necessary to strengthen the training of doctors, especially attending doctors, or publish relevant popular science articles on the basis of hospitals/departments.

We assessed factors associated with vaccine hesitancy in terms of four sections mentioned above. In the initial univariate analysis (Chi-square test), many significant differences were found between NHG and HG. After multiple logistic regression analysis and excluding confounding factors, our results showed that some factors were related to vaccine hesitancy independently. It is surprising that women are more likely to be reluctant to get vaccinated. Similar studies rarely yield differences between the sexes. We have two hypotheses for this: women think more about pain, side effects or other vaccine-related factors; our study was not a random sample, which may be due to sampling bias. We were shocked that the main source of vaccine information from medical workers was a contributing factor to vaccine hesitancy. This result was in stark contrast to several previous studies (10). Subsequently, we conducted a one-to-one telephone follow-up of these HG participants ($n = 27$) and learned that all the suggestions given by medical workers were uncertain or opposed. Therefore, the essence of this phenomenon was medical workers had limited COVID-19 vaccine knowledge, and we speculated that "have relative/friend with medical background contributing to vaccine hesitancy" was also related to this. Earnshaw et al. (31) highlighted doctors as the most trusted source of information about COVID-19. Doctor's advice greatly influences patient's behavior. So that was why a neutral or negative recommendation from their surgery doctor would cause obvious vaccine hesitancy. Of course, neutral/negative advice from family and friends also played a role. Consistent with studies conducted by Gan et al. (23) and Alfageeh et al. (32), people without influenza vaccination during last year (2021–2022) were more hesitant to be vaccinated. Similarly, people with negative intention toward influenza vaccination for the current season were more likely to have vaccine hesitancy. Garcia et al. and Di Gennaro et al. (33, 34) came to the same conclusion. Our survey indicated that people who denied the importance and safety of vaccines for liver transplant recipients had more hesitancy. They believe that vaccination might be harmful to them and would not protect them from COVID-19. It suggested that improving patients' knowledge of vaccine will help to increase the vaccine willingness. As for "inconvenient for post-transplantation," it is easy to understand that the nationwide containment management has caused a lot of inconvenience, including medical activity.

Vaccine hesitancy scale is an effective tool for investigating vaccine hesitancy in adults. In our study, Student's *t*-test, ROC curve analysis and logistics regression all proved that participants with higher total score were more hesitant to get vaccinated. As mentioned above, we conducted ROC curve analysis twice among different populations, and the cutoff points obtained were all 215. This result is similar to general population survey conducted by Akel et al. (16). In this regard, we believe that VHS can be used as a tool for mass screening during follow-up of liver transplant recipients to identify potential recipients with COVID-19 vaccine hesitancy and give them appropriate relative advice.

Of course, there are many limitations in our results, which may cause some bias. First, the participants were not randomly sampled. Instead, we gave questionnaires based on WeChat platform to liver transplant recipients in follow-up and they voluntarily chose to participate or not. This may lead to selection bias and exclude some potential participants who had difficulty answering questionnaires online (such as the elderly, visual impairment, cognitive impairment, non-use of Internet/WeChat, etc.). Secondly, there were many items in our questionnaire (about 60 questions). Even if the respondents who agreed to participate in the survey were expected to fill in the questionnaire carefully and truthfully before the survey, there was still the possibility of being impatient or even filling in the questionnaire carelessly. Thirdly, compared with some other studies, our sample size was still insufficient. These defects should be avoided as much as possible in future studies.

Conclusion

This is the first study to investigate the attitudes and hesitancy of liver transplant recipients toward vaccination after the introduction of COVID-19 vaccine in China. In summary, the continued hesitancy of liver transplant recipients to the COVID-19 vaccine is a hindrance to preventing the spread of COVID-19 in immunosuppressed population and controlling the epidemic. It is important to identify the factors that influence vaccine hesitancy in liver transplant recipients in order to establish appropriate improvements in doctor-patient communication. Our results listed possible related reasons and factors, highlighted the importance of more comprehensive vaccine health education, and emphasized the critical role of all health workers, including transplant physicians, in promoting vaccination. We hope our results will play a role in promoting vaccination campaigns for liver transplant recipients.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of Renji Hospital Shanghai Jiao Tong University (No. KY2022-138-B). The patients/participants provided their written informed consent to participate in this study.

Author contributions

Conceived and designed the experiments and administrated the project: YP, YQ, and QX. Performed the data analysis: YP, SG, XZ, and CX. Validated the data: YP and XZ. Supervised the project: YQ, JZ, and QX. Wrote the paper: YP. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Effectiveness of the BBV-152 and AZD1222 vaccines among adult patients hospitalized in tertiary hospitals in Odisha with symptomatic respiratory diseases: A test-negative case–control study

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Two vaccines, namely BBV-152 (COVAXIN®) and AZD1222 (COVISHIELD™), were deployed against SARS-CoV-2 in India from January 16, 2021. Frontline health care workers were vaccinated first, followed by the adult population. However, limited data on vaccine effectiveness are available for the population of India. Therefore, we aimed to evaluate the effectiveness of two doses of each of these two common vaccines against COVID-19 infection among hospitalized patients with pulmonary conditions. We adopted a test-negative case–control design and recruited a sample of adults who were admitted to one of six tertiary care hospitals in Odisha. All participants were hospitalized patients with COVID-19-like pulmonary signs and symptoms. Participants who tested positive for SARS CoV-2 *via* RT-PCR were treated as cases, and those who tested negative were treated as controls. Logistic regression, adjusted for participants' age, sex, and number of comorbidities, was used to calculate the effectiveness of the two vaccines, using the formula: 100*(1 − adjusted odds ratio). Between March and July of 2021, data were collected from 1,614 eligible adults (864 cases and 750 controls). Among all participants, 9.7% had received two doses of one of the two COVID-19 vaccines. Vaccine effectiveness was 74.0% (50.5%–86.0%) for two doses of BBV-152 and 79.0% (65.4%–87.2%) for two doses of AZD1222. Thus, two doses of either BBV-152 or AZD1222 nCoV-19 vaccine were found to be substantially effective in protecting against COVID-19-related infection.

KEYWORDS

BBV-152, AZD1222, COVAXIN, COVISHIELD, vaccine effectiveness

1. Introduction

The rapid spread of the COVID-19 pandemic elicited worldwide efforts in health care to address an urgent and essential need for effective therapeutic strategies against SARS-CoV-2. Considerable mortality and morbidity have been caused by the COVID-19 pandemic (1), which has provided a subtle reminder to the world that emerging infectious diseases can endanger lives, disrupt societies, and damage economies. Vaccines are among the most reliable and cost-effective public health interventions, reducing morbidity as well as mortality worldwide (2). Sputnik V was the first COVID-19 vaccine, developed and registered by Russia; it was followed by the Pfizer and Moderna vaccines, which were put to emergency use by the FDA of the USA (3, 4). Population studies on the effectiveness of these vaccines have been conducted in several countries (5, 6), where they have been found to be effective in providing protection against severe disease (7).

Two vaccines, AZD1222 (COVISHIELD) and BBV-152 (COVAXIN), were approved by the Indian government on 3rd January, 2021 for use in a vaccination drive. The AZD1222 vaccine was created by the University of Oxford; it employs a replication-deficient chimpanzee viral vector, based on a weakened form of an adenovirus (common cold virus) that infects chimpanzees, and carries the genetic code for the SARS-CoV-2 virus spike protein. The BBV-152 vaccine, which was developed by Bharat Biotech, is a liquid vaccine that contains whole virion inactivated SARS-CoV-2 virus. These two vaccines were initially administered to health care workers and then gradually provided to the general population, where they were observed to be effective in prevention of symptomatic COVID-19 (8). In conjunction with the continuation of the vaccination program, the effectiveness of these vaccines among the broader Indian population should be evaluated in real-world scenarios.

Vaccine effectiveness has been described as reduction in the risk of infection with or adverse effects of a disease (9). The efficacy of a vaccine under controlled conditions differs greatly from its efficacy real-world settings; hence, studies of vaccine effectiveness are essential (10) to identify the generalizability of a vaccine's effects among not only the vulnerable, but also the entire general population. Mass vaccination strategies are essential in halting the pandemic, but data on the effectiveness of vaccines are crucial in guiding future policy decisions and fostering public trust. Hence, we conducted a study based on a test-negative case–control design to evaluate separately the effectiveness of two doses of the AZD1222 or BBV-152 vaccine among hospitalized patients with COVID-19-like pulmonary diseases, with or without SARS-CoV-2 infection, which was tested by means of reverse transcription polymerase chain reaction (RT-PCR).

2. Methodology

2.1. Study design and participants

This study was based on a test-negative case–control design, and the participants were patients who were admitted to tertiary care hospitals in four cities in Odisha, namely Bhubaneswar, Puri, Rourkela, and Bolangir. Studies using the test-negative case–control design have been found to be sufficiently powerful to estimate the effectiveness of vaccines against various respiratory diseases; such studies have also been found to exhibit a high level of agreement with the findings of randomized controlled studies (11–13). As per the "Evaluation of COVID-19 vaccine effectiveness" guidelines, a set of recommendations for vaccine efficacy studies published by the World Health Organization (14), the participants recruited for this study were hospitalized patients with signs and symptoms of pulmonary diseases similar to those of SARS-CoV-2, such as sore throat, cough, bronchitis, breathlessness, pneumonia accompanied by fever, headache, or body aches.

2.2. Case definition

Patients having symptomatic pulmonary disease and positive confirmation of SARS-CoV-2 infection *via* RT-PCR were regarded as "cases" (test-positive). In contrast, "controls" (test-negative) were those patients who had signs and symptoms of pulmonary disease but tested negative *via* RT-PCR for SARS-CoV-2 infection.

2.3. Inclusion and exclusion criteria

Individuals were included in the study if they were eligible to receive any of the vaccines (aged ≥18 years) during the study period, were able to provide informed consent, and were admitted to the health care facility with symptomatic respiratory illness. Between March 2021 and July 2021, 16,827 patients were admitted across the six tertiary hospitals in Odisha. Twelve thousand and sixty-five patients were excluded due to having no signs and symptoms of respiratory disease or clinical diagnosis report. Of the remaining 4,762 patients, 1,954 individuals were excluded due to being under 18 years of age. Any participants exhibiting clinical symptoms of the disease of interest (here COVID-19) within 2 weeks before vaccination cannot participate in a vaccine efficacy study (14); for this reason and on the basis of other exclusion criteria, such as readmission or not meeting the case criteria, another 1,194 individuals were excluded from the final sample. Following these exclusions, 1,614 individuals formed the final sample for the study, with 864 being cases and 750 being controls.

2.4. Sample size

The formula used for sample size calculation was:

$$N1 = (z/d)^2 \, [1/A\,(1 - A) + 1/C_2\,(1 - P_2)]$$

Based on a minimum of one control per case, a specified precision of ± 10%, and a type I error rate of 0.05, and assuming vaccine effectiveness of 50% and coverage of 50%, the required sample size was calculated to be:

Cases: 828 & Controls: 828

Although we identified sufficient cases, as per the case definition, the hospital setting did not quite provide sufficient eligible controls to achieve the specified sample size.

2.5. Data collection

Data were collected in the same way for both cases and controls. Clinical data for each individual were obtained from the patient records (both electronic and print) of the relevant hospital. A range of data were collected from the records, including name, age, gender, ethnicity, phone number, place, occupation, presence of comorbidities (asthma, hypertension, diabetes, chronic renal diseases, chronic obstructive pulmonary diseases, cardiovascular diseases, sickle cell anemia, rheumatoid diseases, etc.), COVID-19 testing data, symptoms, oxygen requirements during admission, and outcome. Vaccination data for each patient in the study were obtained by checking their vaccination certificate and hospital records. In cases of unavailability of this data, the patient or their caregiver was contacted for this information. To avoid observer bias, a deidentified dataset was constructed for data analysis and provided to researchers other than those who were involved in data collection.

2.6. Statistical analysis

Descriptive statistics on vaccination status are presented in the form of frequencies (*n*, %); continuous variables (age, years of education) are summarized in terms of mean (±standard deviation) and/or median with interquartile range (IQR). For the purpose of COVID-19 vaccine effectiveness studies, an individual is considered to be potentially protected as a result of their vaccination only once 14 days have elapsed since their first dose and 7–14 days have elapsed since their second dose, if applicable (14). In accordance with these guidelines, participants were categorized into three groups based on the number of days that had passed since their second vaccine dose ("<14 days," "14–28 days," or "more than 28 days") as a measure of their vaccine coverage status (see Table 1). Vaccine effectiveness was calculated in terms of odds ratio (OR) using the formula: 100*(1-OR), and is reported along with a 95% confidence interval.

Logistic regression, using both adjusted and unadjusted methods, was used to compare the proportion of individuals testing positive among those who had received two doses of either vaccine to the proportion among those who had not been vaccinated. Data from the same sample of unvaccinated participants were entered into the comparison for each vaccine. Observations were entered into the regression model only for participants for whom the number of doses received, vaccine received (BBV-152 or AZD1222), and RT-PCR test result had all been recorded. The effectiveness of each vaccine was analyzed separately. Potential confounders and biases, such as age, gender, and number of comorbidities that might influence vaccine effectiveness, were adjusted for in the analysis.

The statistical software package STATA (v. 16.0; StataCorp LLC, Texas, USA) was used for data cleaning and statistical analyses. A *p*-value of <0.05 was taken as the threshold for significance.

3. Results

The median age of participants with confirmed SARS-CoV-2 infection was found to be 50 years, with an IQR of 40–60 years. Among these, 72.8% were men and more than one-third of them fell into the 45–60 age bracket (Table 2). The median age among the controls was 45 years (IQR: 30–59 years), of whom 68.1% were men and nearly one-fourth of them fell into the same age bracket as the cases (45–60 years). The majority of both cases (62.6%) and controls (56.8%) were residents of rural Odisha. Among participants who were diagnosed with COVID-19 infection, 5.9% were health care workers. The prevalence of comorbidities was lower among the control group (23.0%) than among those who were diagnosed with COVID-19 (63.0%).

At the time at which this study was conducted, 9.7% of the study population (157 out of 1,614) had been vaccinated with two doses of either of the vaccines. Among these, 59 had received two doses of BBV-152 and the other 98 patients had received two doses of AZD1222. However, data on both date of vaccination and details of hospitalization were available for only 44 (74.6%) and 83 (84.7%) of the participants in the BBV-152 and AZD1222 groups, respectively.

Among the 44 participants who had received two doses of BBV-151, 26 (59.1%) were admitted to the hospital within 2 weeks of receiving their second dose; another 5 (11.3%) were admitted within 2–4 weeks, and 13 (29.6%) >4 weeks later. Of patients who had received both doses of AZD1222, 28 (28.6%) were considered to be cases and 70 (71.4%) controls, as per their RT-PCR results. Among the 24 cases for whom the dates of second vaccine dose and hospitalization were both available, 12 (50.0%) were hospitalized with respiratory distress within 2 weeks of their second dose, while a smaller number were admitted beyond this period [7 (29.2%) were hospitalized within

TABLE 1 Vaccination status among cases and controls.

Vaccine type	Number of doses	Days from vaccination to enrollment in study	Cases	Controls	Total
			n (%)	*n* (%)	*n* (%)
COVAXIN (BBV-152)	Double dose	<14 days	4 (26.7)	22 (75.9)	26 (59.1)
		14–28 days	3 (20.0)	2 (6.9)	5 (11.3)
		>28 days	8 (53.3)	5 (17.2)	13 (29.6)
COVISHIELD (AZD1222)	Double dose	<14 days	12 (50.0)	31 (52.5)	43 (51.8)
		14–28 days	7 (29.2)	4 (6.8)	11 (13.3)
		>28 days	5 (20.8)	24 (40.7)	29 (34.9)

14–28 days, and 5 (20.8%) were admitted at least 4 weeks after receiving their second dose].

The effectiveness of each of the two vaccines, AZD1222 and BBV-152, is presented in Table 3. Unadjusted vaccine effectiveness for a double dose of AZD1222 was calculated to be 70.2% (53.1%—81.0%), and for BBV-152, unadjusted effectiveness was 65.0% (38.9%—80.0%). Adjusted vaccine effectiveness was calculated to be 79.0% (65.4%—87.2%) and 74.0% (50.5%—86.0%) for a double dose of AZD1222 and BBV-152, respectively.

4. Discussion

The vaccine effectiveness of two doses of AZD1222 or BBV-152 was tested among adults (>18 years) with a range of comorbid conditions. Two doses of AZD1222 were found to have 79% effectiveness, while the effectiveness of the BBV-152 vaccine was 74.0%. These findings indicate that the effectiveness of the AZD1222 and BBV-152 vaccines in averting COVID-19 infection among hospitalized adults in Odisha with respiratory symptoms is generally high.

The adjusted vaccine effectiveness of two doses of BBV-152 observed in our study was 74.0% (95% CI: 50.5%—86.0%), which is close to the efficacy of the vaccine against symptomatic COVID-19 disease observed during its phase 3 clinical trials, namely 77.8% (95% CI: 65.2%—86.4%) (15). Furthermore, the vaccine effectiveness of two doses of AZD1222 against symptomatic COVID-19 was found to be 79.0% (95% CI: 65.4%—87.2%), which is higher than the efficacy of the same vaccine (70.4%) as evaluated based on a pooled analysis of four randomized, double-blind controlled trials (16). Thus, the results for both the vaccines were similar to those attained in their phase 3 clinical trials.

The effectiveness of the AZD1222 and BBV-152 vaccines has been calculated in many studies. A study among HCWs in the armed forces of India vaccinated with the AZD1222 vaccine reported a 91%—94% reduction in risk of breakthrough cases of COVID-19 (17). Hospitalization was found to be reduced by about 88% due to vaccination in a cohort study conducted in Scotland (16, 18). Various other studies have shown a 60%—70% reduction in breakthrough infections of vaccinated individuals (7, 16, 19), which supports the findings of our study.

This study has several strengths of its own. First, a suitable level of power was achieved through recruitment of a sample of scientifically calculated size that included all adult age groups in the community, recruited since the beginning of the vaccination program among the general population. The evidence generated on vaccine effectiveness is highly generalizable due to the variability of the sample characteristics (i.e., data were collected from various cities and hospitals without restricting the sample to specific populations or communities). Adjusting for various covariates in the regression model somewhat reduced the risk of bias attributable to vaccination status or COVID-19 infection rates.

The limitations of the study are attributable to its observational nature, meaning that its results must be interpreted with caution. Erroneous handling of RT-PCR samples tested in various labs might have resulted in false reports, which may have produced some degree of error in the vaccine effectiveness observed in the study in an unknown direction. Additionally, this was a hospital-based study, and the majority of mild cases occurring during the second wave of the pandemic did not result in hospital admissions, which might have caused discrepancy in the observed effectiveness of both the vaccines. Furthermore, non-uniformity of hospital admission policies with respect to patients' clinical condition might have exerted an effect on the vaccine effectiveness observed. Finally, differences in time course between vaccinated and unvaccinated individuals, occurring due to various factors, may have created biases; these potential confounders can better be assessed and interpreted with the help of a large cohort study.

5. Conclusion

In conclusion, the study findings will aid formulation of a strategy to develop maximum utilization of the AZD1222 and

TABLE 2 Baseline characteristics across cases ($n = 864$) and controls ($n = 750$).

Characteristics	Cases *n* (%)	Controls *n* (%)	Total
Age (years): median (IQR)	50 (40–60)	45 (30–59)	47.5 (35–60)
Age (years): mean ± SD	50.0 ± 14.1	45.2 ± 17.0	47.8 ± 15.7
Age group (in years) ($n = 1,614$)			
18–29	52 (6.0)	174 (23.2)	226 (14.0)
30–44	254 (29.4)	198 (26.4)	452 (28.0)
45–59	331 (38.3)	192 (25.6)	523 (32.4)
60 and above	227 (26.3)	186 (24.8)	413 (25.6)
Gender ($n = 1,614$)			
Male	629 (72.8)	511 (68.1)	1,140 (70.6)
Female	235 (27.2)	239 (31.9)	474 (29.4)
Area of residence ($n = 1,614$)			
Rural	541 (62.6)	426 (56.8)	967 (59.9)
Urban	323 (37.4)	324 (43.2)	647 (40.1)
Caste ($n = 1,614$)			
General	471 (54.5)	409 (54.5)	880 (54.5)
OBC	252 (29.2)	260 (34.7)	512 (31.5)
SC	74 (8.6)	22 (3.0)	96 (6.2)
ST	67 (7.7)	59 (7.8)	126 (7.8)
Education ($n = 1,614$)			
Years of schooling	11.4 ± 3.7	11.7 ± 3.7	11.5 ± 3.7
Occupation ($n = 1,614$)			
Health care workers	23 (2.6)	26 (3.5)	49 (3.1)
Front line workers	28 (3.3)	31 (4.1)	59 (3.6)
Others	813 (94.1)	693 (92.4)	1,506 (93.3)
Number of comorbidities ($n = 1,614$)			
0	320 (37.0)	580 (77.3)	900 (55.7)
1	379 (43.9)	103 (13.7)	482 (29.9)
2	132 (15.3)	49 (6.6)	181 (11.2)
3 or more	33 (3.8)	18 (2.4)	51 (3.2)

TABLE 3 Vaccine effectiveness (VE) for double doses of the BBV-152 and AZD1222 vaccines.

Vaccination status	COVISHIELD (AZD1222)				COVAXIN (BBV-152)			
	Cases	Controls	VE (95% CI)	Adj. VE* (95% CI)	Cases	Controls	VE (95% CI)	Adj. VE* (95% CI)
Unvaccinated	713 (57.3)	532 (42.7)	Ref.	Ref.	713 (57.3)	532 (42.7)	Ref.	Ref.
Double dose	28 (28.6)	70 (71.4)	70.2% (53.1%−81.0%)	79.0% (65.4%−87.2%)	19 (32.2)	40 (67.8)	65.0% (38.9%−80.0%)	74.0% (50.5%−86.0%)

*Adjusted for age, sex, and number of comorbidities.

BBV-152 vaccines in public health practice. The findings provide assurance on the advantages of deploying these vaccines, and on the necessity of administering two doses, particularly among populations where the incidence of SARS-CoV-2 infection remains high.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Institutional Ethical Committee of ICMR—Regional Medical Research Centre, Bhubaneswar. The patients/participants provided their written informed consent to participate in this study.

Author contributions

SP designed the study and critically reviewed the manuscript. DB, SK, PM, CR, AS, RM, SM, AM, and CD performed coordination, data collection, and management. JSK, SKP, SK, SG, and MP carried out the data analysis. MP wrote the manuscript. All authors read and approved the final manuscript.

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Conflict of interest

RM was employed by Employee's State Insurance Corporation (ESIC) Hospital.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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SARS-CoV-2 delta (B.1.617.2) spike protein adjuvanted with Alum-3M-052 enhances antibody production and neutralization ability

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Background: Optimizing adjuvant is one of the critical methods to improve the vaccine. 3M-052, a novel TLR7/8 agonist which was designed for slow dissemination at the injection site, has a potential as adjuvant, but its performance as a vaccine adjuvant for SARS-CoV-2 (B.1.617.2) spike protein has not been studied. The present study aimed to evaluate the effect of Alum-3M-052 as an adjuvant to improve mice serum antibody titers and pseudovirus neutralization efficiency.

Method: Female Balb/c mice were immunized 3 times at day 0, 7 and 21 intramuscularly with SARS-CoV-2 (B.1.617.2) spike protein and adjuvant (Alum or Alum-3M-052). Mice serum was collected weekly since day 7. Antibody titers of mice serum anti-SARS-CoV-2 (B.1.617.2) IgG and IgM were detected by ELISA. Inhibition rates of mice serum blocking SARS-CoV-2 (B.1.617.2) spike protein binding to ACE2 were detected by SARS-CoV-2 (B.1.617.2) Inhibitor Screening Kit. Neutralization efficiencies of mice serum against both SARS-CoV-2 (BA.2.12.1) pseudovirus and SARS-CoV-2 (B.1.617.2) pseudovirus were detected by pseudovirus neutralizing assay.

Result: Serum of mice immunized by SARS-CoV-2 (B.1.617.2) spike protein adjuvanted with Alum-3M-052 had highest antibody titers and higher neutralization efficiency against both SARS-CoV-2 (BA.2.12.1) pseudovirus and SARS-CoV-2 (B.1.617.2) pseudovirus. Besides, neutralization efficiency of anti-SARS-CoV-2 (B.1.617.2) spike protein antibody against SARS-CoV-2 (BA.2.12.1) pseudovirus was lower than that of SARS-CoV-2 (B.1.617.2) pseudovirus.

Conclusion: Alum-3M-052 rapidly increased the titer of anti-SARS-CoV-2 (B.1.617.2) spike protein neutralizing antibodies and enhanced the neutralization ability against pseudoviruses and variants. This study provided evidence for the application of Alum-3M-052 as an adjuvant in COVID-19 vaccines production.

KEYWORDS

adjuvant, 3M-052, spike protein, antibody, SARS-CoV-2 (B.1.617.2)

Introduction

After the first identification in Indian in December 2020, SARS-CoV-2 (B.1.617.2), one of Delta variants, spreads throughout about 175 countries rapidly (https://cov-lineages.org/global_report_B.1.617.2.html). Just 1 year later, the emergence of the Omicron once again refreshed scientists' understanding of SARS-CoV-2 transmission rate: past 1 million of new daily COVID-19 case at the end of 2021, according to Reuters. SARS-CoV-2 and its variants invade lung cells by binding to angiotensin-converting enzyme 2 (ACE2) *via* the receptor binding domain (RBD) of the virus spike protein (1). Antibodies aganist SARS-CoV-2 spike protein can effectively prevent the transmission of SARS-CoV-2 and its variants by inhibiting virus invading lung cells (2). Therefore, vaccines are one of the most effective ways to prevent the circulation of SARS-CoV-2 and its variants.

The Delta variants (B.1.617.2) has 23 mutations compared with the Alpha strains (3). New mutations enhanced the binding ability of the spike protein to the human ACE2, which thus makes the B.1.617.2 strain more contagious (3). The Delta variants were remarkably less sensitive to both serum neutralizing antibodies from recovered patients and vaccine-elicited antibodies, compared with the wild type bearing D614G (4). Despite the high vaccination rates and high prevalence of SARS-CoV-2 infection, the Delta variants still keep increasing virus replication fitness and reducing sensitivity to neutralizing antibodies (5). More troublesome is Omicron variant (especially BA.2.12.1). Liu et al. reported that mutations of Omicron variant at 452 (L452R and L452Q) of BA.2.12.1 might be one of the key drivers of neutralization resistance (6). As a result, similar to B.1.617.2, BA.2.12.1 variant can also evade immunity from the past infections and current vaccines (7). Hence, it is urgent matter to improve protective power of vaccines.

Adjuvants, as a critical component of vaccines, induce high titer and long-lasting antibody response (8). TLR agonists, one of the common vaccine adjuvants, recognize pathogens through pathogen-specific molecular patterns (PAMPs) to induce antimicrobial and inflammatory responses that affect innate and adaptive immunity (9, 10). It has been reported that TLRs agonists like imidazoquinolines imiquimod (R-837, TLR7 agonist) and resiquimod (R-848, TLR7/8 agonist) can active the TLR7/8 receptors on dendritic cell, and induce TH1 type of adaptive immune response (11). However, one of the limitations of resiquimod and other similar TLR7/8 agonists as vaccines is they are distributed rapidly throughout the body after injection, leading to systemic cytokines induction (12). 3M-052 is a novel TRL7/8 agonist. Due to its lipid-modified physical properties, 3M-052 stay at vaccination site and enhance the local TH1 immune response without inducing systemic cytokine production (13). Moreover, alum have been used clinically as adjuvant for more than half a century, which is believed to contributes to the uniform distribution of adsorbed antigens (14). Recently, Alum-3m-052 showed stronger virus neutralization ability in HIV-1 vaccination studies (9). Hence, we speculated that Alum-3M-052 has potential as an adjuvant.

Here, we used Alum-3M-052 as an adjuvant to immunize mice with SARS-CoV-2 (B.1.617.2) spike protein to evaluate the improvement of serum antibody titers and virus neutralization ability. We found Alum-3M-052 significantly enhanced antibody titers and higher neutralization efficiency against both SARS-CoV-2 (BA.2.12.1) pseudovirus and SARS-CoV-2 (B.1.617.2) pseudovirus.

Our research will provide data support for the clinical application of 3M-052 as a novel SARS-CoV-2 vaccine adjuvant.

Materials and methods

Mice vaccination

For each group, female Balb/c mice (6–8 weeks of age, $n = 4$) were immunized 3 times at day 0, 7 and 21 intramuscularly. Spike protein (Sino Biological, Beijing, China) was dissolved in PBS at the final concentration of 0.1 µg/µl. Alum-3M-052 was a mixture that contained 50 µl 2% aluminum hydroxide gel adjuvant (InvivoGen, France) and 2 µg 3M-052 (MedChemExpress, NJ, USA) in 50 ul PBS. For vaccine test group, 50 µl spike protein solution and 50 µl Alum-3M-052 were mixed at 150 rpm for 30 min by a shaker (Kylin-Bell, Jiangsu, China) at 4°C. For vaccine control group, 50 µl spike protein solution and 50 µl 2% aluminum hydroxide gel adjuvant were mixed at 150 rpm for 30 min by a shaker at 4°C. For negative control group, 50 µl PBS and 50 µl 2% aluminum hydroxide gel adjuvant were mixed at 150 rpm for 30 min by a shaker at 4°C. The blood samples were collected 1 week following each immunization.

ELISA for anti-SARS-CoV-2 (B.1.617.2) IgG/IgM titer detection

ELISA plates (R&D, MN, USA) were coated with 2.5 µg/ml SARS-CoV-2 (B.1.617.2) spike protein (spike protein was diluted in PBS) and incubated at 4°C overnight. The plates were washed 3 times by wash buffer (R&D, MN, USA). Then, the plates were incubated with diluted serum samples for 1 *h* at 37°C and washed 3 times by wash buffer. The plates were incubated with diluted AP-conjugated goat Anti-mouse IgG (Yeasen, Shanghai, China) (1:500) for 1 *h* at 37°C. Then the plates were washed 3 times by wash buffer and developed with pNPP (Sigma, Darmstadt, Germany). Reactions were stopped with 3M NaOH (Sigma, Darmstadt, Germany). The optical density was determined at 450 nm. According to the above method, IgM was detected by AP-conjugated Goat Anti-mouse IgM (Abcam, Cambridge, UK) as the secondary antibody.

Inhibition rates of mice serum blocking SARS-CoV-2 (B.1.617.2) spike protein binding to ACE2

We used the SARS-CoV-2 (B.1.617.2) Inhibitor Screening Kit (Spike RBD) (ACRO, Beijing, China) to detect inhibition rates of mice serum blocking SARS-CoV-2 (B.1.617.2) spike protein binding to ACE2. Positive control, negative control and 50-fold diluted mice serum were added to micro-plates coated with ACE2 protein, respectively. After 1 *h* incubation at 37°C, micro-plates were washed 3 times. Then, 100 μl of substrate solution was added in each well of micro-plates and the micro-plates were incubated at 37°C for 20 *min*. Finally, 50 μl of stop solution was added in each well and the absorbance (OD) was measured at 450 nm.

$$\text{Inhibition rate} = (OD_{\text{sample}} - OD_{\text{negative control}}) / (OD_{\text{positive control}} - OD_{\text{negative control}}) \times 100\%.$$

Pseudovirus neutralizing assay

HEK-293T cells were seeded (5×10^6) in a 100 mm dish and were co-transfected with 12 μg Plove-luciferase-EGFP plasmid, 6 μg psPAX2 plasmid and 2 μg spike protein variant (B.1.617.2 or BA.2.12.1) plasmid using Lipofectamine 3000 (Invitrogen, CA, USA) according to the manufacturer's instructions. After 8 *h* post-transfection, the medium was replaced with new culture medium. Two kinds of pseudotyped viruses were collected and filtered through 0.45 μm filter after 48 *h* transfection. RNA of pseudoviruses were extracted using MiniBEST Viral RNA/DNA Extraction Kit Ver.5.0 (TaKaRa, Otsu, Japan). Reverse transcription was conducted according to the protocol of HiScript® III All-in-one RT SuperMix Perfect kit (Vazyme, NJ, USA). RT-PCR was performed by TransLv Lentivirus qPCR Titration Kit (TransGen, Beijing, China).

To assess the neutralization of SARS-CoV-2 (B.1.617.2 or BA.2.12.1) infection, the 293T cells (1.2×10^4/100 μL/well) were seeded in a flat-bottom culture 96-well plates and incubated overnight. Subsequent virus (~2×10^4 RLU) was mix with 6 serial three-fold dilutions (50-folds as initial dilution) of mice serum in a 96-well plate. The mixture was incubated at 37°C for 1h and then transferred to the flat-bottom culture 96-well plates with seeded 293T cells. 6 virus control well (containing cells with virus) and 6 background control well (only containing cells) were also added in each 96-well plate. After 8 *h* incubation, the medium was replaced by fresh culture medium. Luciferase substrate was added to the 96-well plate (60 μL/well) after another 48 h incubation. The luminescence signal was detected by TECAN Infinite 5 min later.

Statistical analysis

Statistical analysis was perform using the GraphPad Prism 8.0. Comparisons among three groups were performed with one-way ANOVA test followed by Tukey's multiple comparison test or Brown-Forsythe test. Comparisons between two groups were performed with unpaired Student's *t*-test. A *p*-value of <0.05 was considered statistically significant. $^{*}p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$.

Result

SARS-CoV-2 (B.1.617.2) with adjuvant Alum-3M-052 induced robust specific IgG antibody responses in mice.

We compared the ELISA results of three groups to evaluate the promoting effect of adjuvants in antibody production (Supplementary data 1). Absorbance values of serum (diluted from 25 to 204800 times) collected at day 14 and day 28 were significantly higher in vaccine test group compared with other two groups (Figure 1A). Absorbance values of serum in vaccine control group were increased in vaccine control group at day 28, which were remarkably higher than that in vaccine negative group (Figure 1A). Moreover, at day 14, the ED_{50} of IgG antibody of vaccine test group was significantly higher than that of vaccine control group (Figure 1B). At day 28, the ED_{50} of vaccine test group reached 59,055, which was remarkably higher than the other two groups (Figure 1B). ED_{50} was increased in vaccine control group at day 28, but there was no significant difference compared with vaccine negative group (Figure 1B). These results suggested that the adjuvant Alum-3M-052 increased IgG antibody productions.

SARS-CoV-2 (B.1.617.2) with adjuvant Alum-3M-052 induced IgM antibody responses in mice

Next, we compared IgM antibodies titers in three groups (Supplementary data 2). The IgM absorbance values of the vaccine test group were lower than those of the vaccine control group in day 7 and day 14, but there was no statistical difference. The absorbance values of vaccine control group decreased in day 28 (Figure 2). In vaccine test group, the titers of IgM antibodies were more stable than those in vaccine control group.

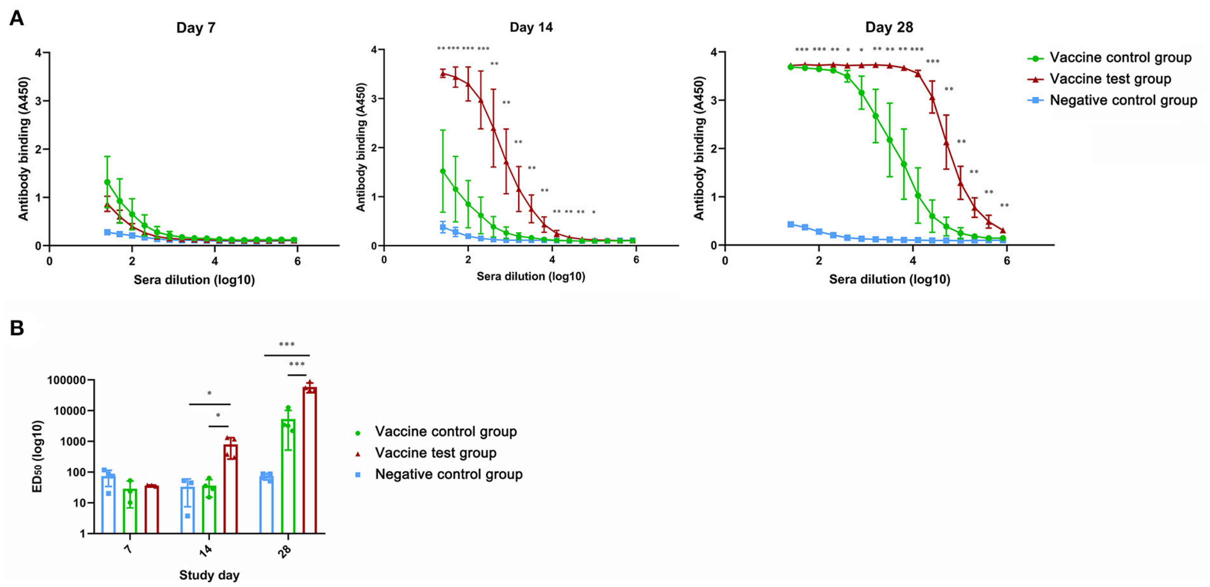

FIGURE 1
Anti-spike protein (B.1.617.2) IgG antibody titers in mice serum of three groups. **(A)** Anti-spike protein (B.1.617.2) IgG antibody titers in mice serum of three groups at day 7, 14, and 28. **(B)** Comparisons of ED_{50} titers of mice serum Anti-spike protein (B.1.617.2) IgG antibody in three groups at day 28 (Vaccine test group, $n = 4$; Vaccine control group, $n = 4$; Negative control group, $n = 4$; $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$ $p < 0.05$ was considered statistically significant.).

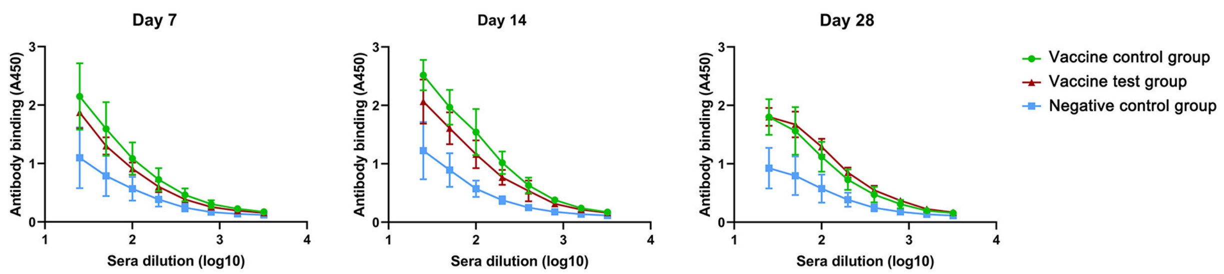

FIGURE 2
Anti-spike protein (B.1.617.2) IgM antibody titers in mice serum of three groups at day 7, 14, and 28 (Vaccine test group, $n = 4$; Vaccine control group, $n = 4$; Negative control group, $n = 4$.).

SARS-CoV-2 (B.1.617.2) with adjuvant Alum-3M-052 promoted neutralizing antibodies productions in mice

To further investigate effect of serum neutralizing antibodies on inhibiting the binding of the of SARS-CoV-2 (B.1.617.2) spike protein to ACE2, we performed an ACE2 competitive binding assay (Figure 3A) (Supplementary data 3). At day 28, the inhibition rate of serum antibodies in the vaccine test group was 86.22%, which was significantly higher than that of other two groups (Figure 3B). Additionally, in vaccine control group, the inhibition efficiency was 23.95%, which was significantly higher than that of the negative control group (Figure 3B). At day 7 and day 14, all the inhibition rates were low in three groups, and there was no significant statistical difference (Figure 3B). Therefore, Alum-3M-052 significantly improved the inhibition efficiency of serum neutralizing antibodies on the binding of SARS-CoV-2 (B.1.617.2) spike protein to ACE2.

SARS-CoV-2 (B.1.617.2) with adjuvant Alum-3M-052 induce higher pseudovirus neutralizing antibodies in mice

We also compared the pseudovirus neutralizing activity against SARS-CoV-2 (B.1.617.2) in three groups by pseudovirus neutralization assay for SARS-CoV-2 (B.1.617.2) (Supplementary data 4). At day 28, the neutralization efficiency of vaccine test group reached 99% at 50-fold dilution, which was significantly higher than the other two groups (Figure 4A).

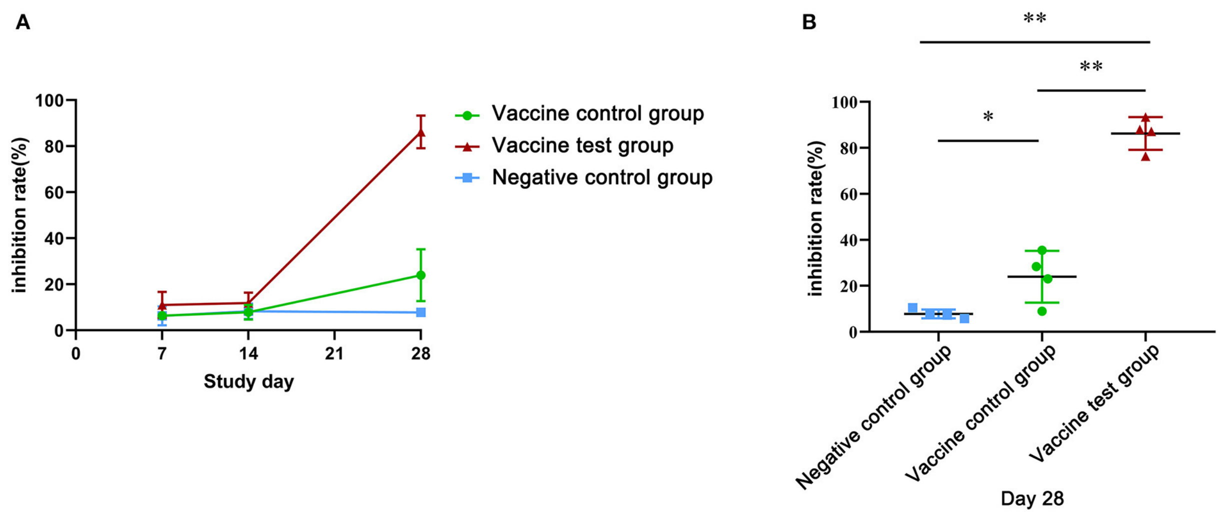

FIGURE 3
Inhibition rates of neutralizing antibodies blocked the SARS-CoV-2 (B.1.617.2) spike protein binding to ACE2. **(A)** Inhibition rates of mice serum neutralizing antibodies in three groups at day 7, 14, and 28. **(B)** The comparison of inhibition rates of neutralizing antibodies in the three groups on day 28 (Vaccine test group, $n = 4$; Vaccine control group, $n = 4$; Negative control group, $n = 4$; $^{*}p < 0.05$; $^{**}p < 0.01$; $p < 0.05$ was considered statistically significant.).

The neutralization efficiency of vaccine control group was significantly higher than that in negative control group (Figure 4A). At day 7 and day 14, there were no significant differences in neutralization efficiency among three groups (Figure 4A). Moreover, the mean ED_{50} of vaccine test group was 882 at day 28, while the mean ED_{50} of vaccine control group was less than 57 (Supplementary data 4). Results suggested that Alum-3M-052 improved the neutralizing efficiency against SARS-CoV-2 (B.1.617.2) pseudovirus.

Furthermore, we compared the neutralization efficiency of against SARS-CoV-2 (BA.2.12.1) pseudovirus in three groups. At day 28, the neutralization efficiency of vaccine test group reached 93% at 50-fold dilution, which was significantly higher compared with the other two groups (Figure 4B). Notably, the neutralization efficiency of vaccine control group was higher than the control group, but there was no statistical difference (Figure 4B). The mean ED_{50} of vaccine test group against SARS-CoV-2 (BA.2.12.1) subvariants was 454, which lower than that in SARS-CoV-2 (B.1.617.2) (Figure 4C). Results suggested that alum-3M-052 promoted the production of neutralizing antibodies against SARS-CoV-2 (B.1.617.2), and these neutralizing antibodies also had strong neutralizing efficiency against SARS-CoV-2 (BA.2.12.1).

Discussion

Vaccine adjuvant works as one of the critical components of vaccines and induces high titer and long-lasting antibody response (8, 9). Small molecule TLR7/8-specific agonists have demonstrated potential as adjuvants, since they activate DCs and monocytes and thus enhance both humoral and cellular immune response (15, 16). Compared with resiquimod and imiquimod that distributed rapidly throughout the body after injection, 3M-052, a novel lipid-modified TRL7/8 agonist, stay at vaccination site and improve the potency of neutralizing antibodies (9). It was reported that Alum-3M-052 induces durable HIV-1 envelope-specific plasma cells and humoral immunity in nonhuman primate (10). What is more, Alum-3M-052 significantly improve titers of anti-SARS-CoV-2 RBD trimer protein antibody and thus prevent SARS-CoV-2 from infecting the lungs (17). Here, we immunized mice with SARS-CoV-2 (B.1.617.2) spike protein adjuvanted with Alum-3M-052. We found that Alum-3M-052 not only significantly increased the titers of anti-SARS-CoV-2 (B.1.617.2) spike protein neutralizing antibody in mice serum, but also dramatically improved the neutralization ability of serum antibodies to SARS-CoV-2 (B.1.617.2) pseudovirus and SARS-CoV-2 (BA.2.12.1) pseudovirus.

Serum neutralizing antibodies block the entry of SARS-CoV-2 virus into lung cells (7). In our study, Alum-3M-052 rapidly increased titers of anti-SARS-CoV-2 (B.1.617.2) spike protein antibody in mice serum and significantly increased the neutralization ability against SARS-CoV-2 (B.1.617.2) pseudovirus. The binding of the spike protein with host ACE2 receptor is the initial step of SARS-CoV-2 virus entry, and inhibition of this step is critical for preventing virus invasion (1). We noticed that neutralizing antibody titers in mice serum of the vaccine test group increased significantly at day7 after the second boost, but the neutralizing antibody was not enough to inhibit the binding of SARS-CoV-2 (B.1.617.2) spike protein to ACE2 protein, nor to prevent pseudoviruses invade target cells.

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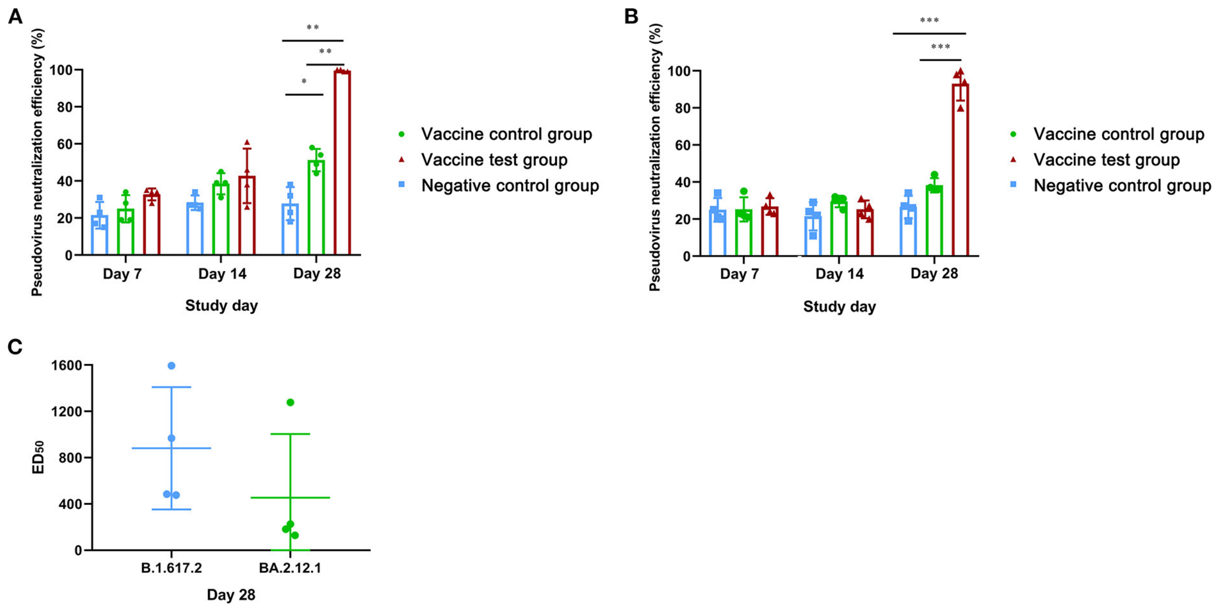

FIGURE 4
Neutralization efficiencies of mice serum neutralizing antibodies against pseudovirus of SARS-CoV-2 (B.1.617.2) and SARS-CoV-2 (BA.2.12.1). **(A)** Neutralization efficiencies of mice serum neutralizing antibodies against SARS-CoV-2 (B.1.617.2) pseudovirus in three groups at day 7, 14, and 28. **(B)** Neutralization efficiencies of mice serum neutralizing antibodies against SARS-CoV-2 (BA.2.12.1) pseudovirus at day 7, 14, and 28. **(C)** The comparison of ED_{50} of neutralization efficiencies between SARS-CoV-2 (B.1.617.2) pseudovirus and SARS-CoV-2 (BA.2.12.1) pseudovirus in vaccine test group on day 28 (Vaccine test group, $n = 4$; Vaccine control group, $n = 4$; Negative control group, $n = 4$; $^*p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$; p <0.05 was considered statistically significant.).

Results indicated that not only antibody titer but also its binding quality is important for protection, especially when SARS-CoV-2 variants, which present higher affinity for ACE2. This partly explained why recovered patients and vaccinated patients are also at risk of coronavirus reinfection.

SARS-CoV-2 (BA.2.12.1) have exhibited poor susceptibility to neutralizing antibodies in sera of recovered patients and vaccinated populations (18). There are differences in protective efficacies of the SARS-CoV-2 vaccines against different mutant strains (19, 20). We found relatively high antibody titers provide effective protection against mutant strains in different degrees of range. We found that at day 7 after the third boost with SARS-CoV-2 (B.1.617.2) spike protein, neutralizing ability of mice serum against the SARS-CoV-2 (BA.2.12.1) pseudovirus was strong. This suggested that Alum-3M-052, as a vaccine adjuvant, has a potential to improve vaccine protection against new mutant variants.

Besides, based on the fact that higher IgG antibody titers and more stable IgM antibody titers in vaccine test group, we speculated Alum-3M-052 may improve antigen presentation of maturation of the immune response. This need to be confirmed in the further study. We will investigate the persistence, safety and immune mechanism of Alum-3M-052.

In conclusion, Alum-3M-052 not only rapidly increased the titer of anti-SARS-CoV-2 (B.1.617.2) spike protein neutralizing antibodies, but also enhanced the neutralization ability against pseudoviruses and variants. Our study provided a basis for the application of 3M-052 as an adjuvant in COVID-19 vaccine development.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author/s.

Ethics statement

The animal study was reviewed and approved by Guangzhou Medical University Animal Care and Use Committee.

Author contributions

MY and QQ designed the research and revised the language of the paper. HH and ZZ analyzed the data and wrote the draft. XX, ZL, and XZ collected the research data. All authors read and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.976686/full#supplementary-material

SUPPLEMENTARY DATA 1
Data of mice serum IgG antibody titers against spike protein (B.1.617.2).

SUPPLEMENTARY DATA 2
Data of mice serum IgM antibody titers against spike protein (B.1.617.2).

SUPPLEMENTARY DATA 3
Data of inhibition rates of mice serum neutralizing antibody against SARS-CoV-2 spike protein (B.1.617.2).

SUPPLEMENTARY DATA 4
Data of neutralization efficiencies of mice serum neutralizing antibodies against pseudovirus of SARS-CoV-2 (B.1.617.2) and SARS-CoV-2 (BA.2.12.1).

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Anti-SARS-CoV-2 spike IgG following injection of the third dose vaccine: A systematic review with meta-analysis of heterologous versus homologous vaccination

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Background: The mass vaccination is a key strategy to prevent and control the coronavirus disease 2019 (COVID-19) pandemic. Today, several different types of vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have been developed worldwide. These vaccines are usually administered in a two-dose schedule, and the third dose is currently being administered in most countries. This study aimed to systematically review and meta-analyze the immunogenicity of heterologous vs. homologous vaccination after administration of the third dose of COVID-19 vaccines.

Methods: Electronic databases and websites including Scopus, PubMed, Web of Science, and Google scholar were searched for relevant randomized clinical trial (RCT) studies. After applying the inclusion and exclusion criteria, a total of three RCTs were included in the study. These RCTs were included 2,613 healthy adults (18 years or older and without a history of laboratory-confirmed COVID-19) with 15 heterologous and five homologous prime-boost vaccination regimens. Anti-SARS-CoV-2-spike IgG levels at day 28 after administration of the third dose, were compared between the heterologous and homologous regimens.

Results: The highest antibody responses had been reported for the homologous vaccination regimen of m1273/m1273/m1273 (Moderna), followed by the heterologous regimen of BNT/BNT/m1273. In addition, the immunogenicity of viral vector and inactivated vaccines was remarkably enhanced when they had been boosted by a heterologous vaccine, especially mRNA vaccines.

Conclusion: This systematic review suggests that mRNA vaccines in a homologous regimen induce strong antibody responses to SARS-CoV-2 compared to other vaccine platforms. In contrast, viral vector and inactivated vaccines show a satisfactory immunogenicity in a heterologous regimen, especially in combination with mRNA vaccines.

KEYWORDS

SARS-CoV-2, COVID-19 vaccine third dose, heterologous vaccination, homologous vaccination, anti-SARS-CoV-2 antibody

1. Introduction

In 2019, a new coronavirus strain known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in China and quickly spread around the world. Coronavirus disease 2019 (COVID-19), the disease caused by SARS-CoV-2, has had substantial detrimental health and economic impacts on different countries. As of March 2022, more than 508 million people have been infected, and more than 6 million people have died due to COVID-19 (1).

Although many efforts have been made to eradicate or control the disease up to now, SARS-CoV-2 spread is still rising in many world regions. One of the strategies that are believed to be effective, at least in controlling and managing the COVID-19 pandemic, is the mass vaccination of world people. Several companies around the world have developed vaccines against SARS-CoV-2 using various platforms (including ribonucleic acid, non-replicating viral vector, whole inactivated virus, and protein subunit), of which 10 have been licensed for emergency use by the World Health Organization (WHO), including BNT162b2, mRNA-1273, ChAdOx1 nCoV-19, Ad26.COV2.S, Covishield, CoronaVac, BBIBP-CorV, Covaxin, NVX-CoV2373, and Novavax (2, 3). These vaccines are usually injected in a two-dose schedule with a minimum interval of 4 weeks (4).

Although the injection of two doses of these vaccines has significantly prevented mortality and hospitalization due to COVID-19 (5, 6), there is evidence of waning immunity over time (7–10). Therefore, to maintain immunity against COVID-19, the injection of a third dose vaccine (booster dose) is being performed in most countries (11, 12). Studies have shown that injection of the third dose of COVID-19 vaccine (whether homologous or heterologous) can significantly increase the level of anti-spike protein IgG, anti-receptor binding domain (RBD), as well as neutralizing antibodies (even against new variants such as delta and omicron) that might be finally resulted in overcoming the COVID-19 pandemic and associated burnout and pressure on healthcare systems (13–15). Serum levels of these antibodies are directly correlated to the protection against COVID-19. In a study by Munro et al., injection of m1273 (Moderna) vaccine to the individuals who had previously received two doses of BNT (Pfizer) or ChAd (AstraZeneca) vaccines could increase anti-spike protein IgG up to 11.5 and 32.3 times, respectively, compared to control group (receiver of MenACWY, quadrivalent meningococcal conjugate vaccine) (14).

At the beginning of COVID-19 vaccination, due to the shortage of vaccine and delay of supply, and also due to a rare but dangerous complication of blood clotting after receiving the first dose of ChAd vaccine, some countries inevitably used a heterologous vaccine in the second dose (16, 17). Interestingly, heterologous vaccination (i.e., administration of different vaccines in prime-boost schedules) not only had no unbearable adverse events in vaccinees but also was more immunogenic than homologous vaccination (i.e., administration of same vaccines in prime-boost schedules) (18–20). This issue has been well reviewed and discussed in three meta-analysis papers published so far (16, 21, 22). However, no systematic review with meta-analysis paper has been yet published about the immunogenicity of heterologous vs. homologous vaccination after injection of the third dose of COVID-19 vaccines. Therefore, in this systematic review study, all articles published as of February 2022 investigating the immunogenicity of heterologous vs. homologous vaccination after injections of the third dose of COVID-19 vaccines have been reviewed and analyzed. In this study, anti-spike IgG level was used as a criterion to compare immunogenicity between the heterologous and homologous vaccination regimens. Of note, in order to directly compare immunogenicity among the studies, we converted, if necessary, anti-spike IgG levels to the international standard unit of binding antibody units (BAU) per milliliter (BAU/mL) by using the conversion factors mentioned in each study.

2. Methods

This study is a systematic review and meta-analysis assessing the immunogenicity of heterologous vs. homologous vaccination regimens after the third dose of COVID-19 vaccines in healthy adults (18 years or older and without a history of laboratory-confirmed COVID-19) based on RCT studies published within the last 2 years. This study was conducted

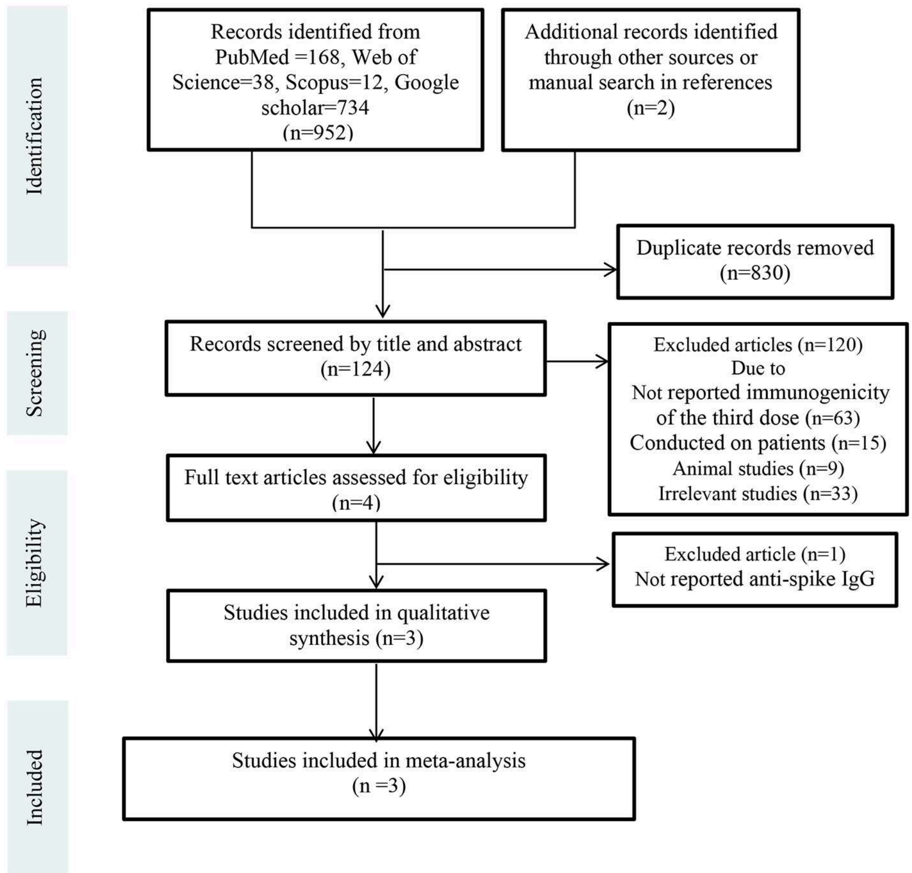

FIGURE 1
PRISMA flow diagram.

under the Guideline of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist (23). The study question was: in the people who received the third dose of COVID-19 vaccines (P), if heterologous vaccine (I) compared with homologous vaccine (C) induces more antibody responses (O).

2.1. Search strategy

Two separate authors (F.A. and S.A.J.) conducted the online search from electronic databases and websites including Scopus, PubMed, Web of Science, and Google scholar from January 01, 2019, to February 2022. Additionally, we manually screened references or citations of each article. The search terms used in these databases were COVID-19 vaccination, SARS-CoV-2, homologous booster vaccination, heterologous booster vaccination, heterologous prime-boost COVID-19 vaccination, homologous prime-boost COVID-19 vaccination. After the primary search and identification of related studies, we removed duplicate studies. Then, articles were screened by titles and abstracts and irrelevant studies were excluded. Subsequently, full-text versions of the remaining articles (13, 14, 24, 25) were independently assessed for eligibility by two researchers (F.A. and S.A.J.). The third researcher (M.S.M.) monitored the selection accuracy of eligible studies in all steps. These steps are shown in PRISMA Flow Diagram (Figure 1).

2.2. Inclusion and exclusion criteria

We included all randomized clinical trials investigating immunogenicity of the third dose of COVID-19 vaccines. The exclusion criteria were as follows: studies conducting on patients, studies with no comparison arm, studies not reporting anti-spike IgG, animal studies, review articles, and editorials.

2.3. Quality assessment

The quality of eligible studies was evaluated using the Jadad scale (26). This scale is a good procedure for quality

TABLE 1 Quality assessment of studies included to meta-analysis.

	Atmar et al. (13)	Munro et al. (14)	Clemens et al. (24)
Random sequence generation (selection bias)	No	Yes	Yes
Allocation concealment (selection bias)	No	Yes	Yes
Blinding (performance bias and detection bias)	No	Yes	Yes
Incomplete outcome data (attrition bias)	Yes	Yes	Yes
Selective reporting (reporting bias)	No	No	No
Other bias	No	No	No

assessment of clinical trials studies. The full text of each study was evaluated by two independent authors (F.A. and S.A.J.). Any disagreements were resolved by discussion with the third author (M.S.M.). Finally, data from unbiased studies entered the meta-analysis (Table 1).

2.4. Data extraction

M.S.M and F.A extracted the data. The concentration of anti-spike IgG at day 28 after injection of the third dose, was selected as a criterion to compare immunogenicity between heterologous vs. homologous COVID-19 vaccination regimens. Of note, to directly compare immunogenicity among the studies, we converted, if necessary, anti-spike IgG levels to the international standard unit of binding antibody units (BAU) per milliliter (BAU/mL) by using the conversion factors mentioned in each study. Before analysis, these data were log-transformed (Log10).

The other main variables that were extracted from the studies were: first author's name, publication year, sample size, mean age and gender of participants, type of vaccination regimens (heterologous or homologous), and type of vaccines [m1273=mRNA-1273 vaccine (Moderna), BNT=BNT162b2 vaccine (Pfizer–BioNTech), Ad26=Ad26.COV2.S (Johnson & Johnson's Janssen), ChAd=ChAdOx1 (Oxford–AstraZeneca), NVX=NVX-CoV2373 (Novavax), SARS-CoV-2 Vaccine Vero Cell (Sinopharm)].

2.5. Statistical analysis

Forest plot was created using Comprehensive Meta-Analysis (CMA) software version 3. The forest plot represents the point and overall effect size with 95% confidence interval (CI) of standardized mean differences (SMD) of anti-spike IgG levels between heterologous and homologous vaccination regimens using random effect model. I^2 statistic was used as a measure of heterogeneity among the studies. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Study selection and characteristics of the studies included

Totally 954 records were retrieved from electronic databases and websites. After removing duplicates ($n = 830$), 124 studies were screened by title and abstract. Of these, 120 records were excluded due to not reported immunogenicity of the third dose ($n = 63$), conducted on patients ($n = 15$), animal studies ($n = 9$), and other reasons ($n = 33$). Four articles were assessed for eligibility by full-text. One article was excluded because it had not reported anti-spike IgG level. Finally, three RCTs were included in the meta-analysis (13, 14, 24). Figure 1 shows the details of the PRISMA flow diagram.

Totally, 4,876 healthy adults (18 years or older and without a history of laboratory-confirmed COVID-19) had been enrolled in these three trials. Of them, 2,613 had received the third dose of different types of COVID-19 vaccines and their data were included in this meta-analysis. The mean age of participants was 58.2 years, and nearly 53% of them was female ($n = 1,394$). Table 2 shows the main characteristics of the included studies, as well as the serum levels of anti-spike IgG at day 28 after administration of the third dose of COVID-19 vaccine for 15 heterologous and five homologous vaccination regimens.

3.2. Anti-SARS-CoV-2-spike IgG

Three studies had reported anti-spike IgG levels at day 28 following the injection of third dose of different regimens of heterologous and homologous COVID-19 vaccination (13, 14, 24). The results revealed that the highest anti-spike IgG levels belonged to homologous vaccination regimen of m1273/m1273/m1273 (Moderna), followed by heterologous regimen of BNT/BNT/m1273. In addition, the immunogenicity of viral vector and inactivated vaccines was remarkably increased if they had been boosted by a heterologous vaccine, especially mRNA vaccines (Table 2).

Figure 2 represents forest plot of standardized mean differences (SMD) of anti-spike IgG concentrations between

TABLE 2 Characteristics of the studies included in meta-analysis.

References	Type of primary series vaccines	Type of third dose vaccines	*N*	Mean/median age (year)	Gender (Female) (n)	Homologous	Heterologous
						Anti-spike IgG concentration (BAU/mL) (CI 95%)	
Munro et al. (14)	BNT/BNT	BNT	96	62.6	61	3,413 (3,025, 3,850)	-
	BNT/BNT	NVX	101	62.1	65	-	1,361 (1,129, 1,641)
	BNT/BNT	chAd	97	61.9	57	-	1,682 (1,466, 1,929)
	BNT/BNT	Ad26	87	62	60	-	2,140 (1,815, 2,522)
	BNT/BNT	m1273	91	63	63	-	4,231 (2,232, 5,136)
	ChAd/ChAd	ChAd	99	63.7	54	308 (258, 367)	-
	ChAd/ChAd	NVX	95	63.5	61	-	874 (730, 1,046)
	ChAd/ChAd	Ad26	98	65	4	-	691 (582, 820)
	ChAd/ChAd	m1273	96	63.8	48	-	3,898 (3,303, 4,600)
	ChAd/ChAd	BNT	93	65.1	50	-	2,571 (2,220, 2,977)
Atmar et al. (13)	Ad26/Ad26	Ad26	50	50	14	369 (291, 476)	-
	Ad26/Ad26	BNT	52	48	14	-	2,277 (1,833, 2,828)
	Ad26/Ad26	m1273	53	57	14	-	2,986 (2,478, 3,598)
	BNT/BNT	BNT	49	50	18	3,164 (2,646, 3,779)	-
	BNT/BNT	Ad26	50	50	15	-	2,600 (2,086, 3,240)
	BNT/BNT	m1273	50	55	17	-	5,231 (4,274, 6,404)
	m1273/m1273	m1273	51	53	16	6,224 (5,282, 7,333)	-
	m1273/m1273	Ad26	49	50	17	-	4,560 (3,544, 5,867)
	m1273/m1273	BNT	51	54	17	-	5,273 (4,567, 6,088)
Clemens et al. (24)	CoronaVac/CoronaVac	CoronaVac	281	58	165	312 (274, 356)	-
	CoronaVac/CoronaVac	Ad26	295	59	181	-	2,173 (1,989, 2,374)
	CoronaVac/CoronaVac	BNT	333	61	204	-	4,349 (3,971, 4,763)
	CoronaVac/ CoronaVac	ChAd	296	60	179	-	2,162 (1,907, 2,452)

heterologous and homologous vaccination regimens, grouped by type of vaccines. As shown in this figure, SMD is negative when homologous vaccination regimens belong to mRNA platforms (m1273 and BNT; SMD = −0.36 BAU/mL, 95% CI −0.85–0.13; random effect model, I^2 = 93%). This means that mRNA vaccines can induce strong antibody responses when administered in homologous regimens. On the other hand, SMD is positive for heterologous regimens of viral vector (ChAd and Ad26, SMD = 2.07 BAU/mL, 95% CI 1.50–2.65; random effect model, I^2 = 96%) and inactivated vaccines (CoronaVac, SMD = 2.71 BAU/mL, 95% CI 1.92–3.50; random effect model, I^2 = 96%). This means that to obtain a better immunogenicity, viral vector and inactivated vaccines should be boosted at the third dose by a heterologous vaccine, especially mRNA platforms.

In this study, the publication bias was assessed visually by a funnel plot (Figure 3) and "trim and fill" method (27). The results indicated that under the random effects model the point estimate and 95% CI for the combined studies is 1.05 (0.30–1.80). Using Trim and Fill these values are unchanged. So, there was no publication bias.

4. Discussion

In this systematic review, a comprehensive review has been done on the immunogenicity of different types of heterologous and homologous COVID-19 vaccination regimens after injection of the third dose to provide scientific evidence to improve vaccination strategies. To this end, based on the inclusion and exclusion criteria, a total of three randomized clinical trials conducted on 2,613 healthy people (older than 18 years and without a history of laboratory-confirmed

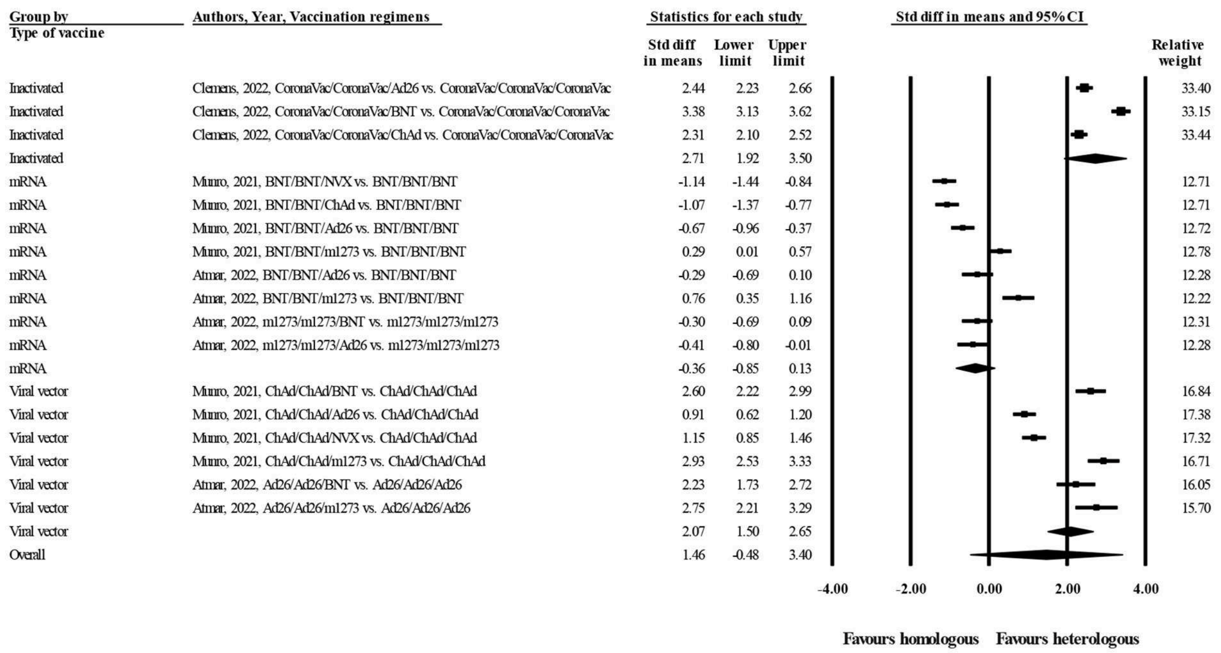

FIGURE 2
Forest plot of log-transformed concentrations of anti-spike IgG at day 28 after administration of the third dose of COVID-19 vaccines (heterologous vs. homologous vaccination; grouped by type of vaccines).

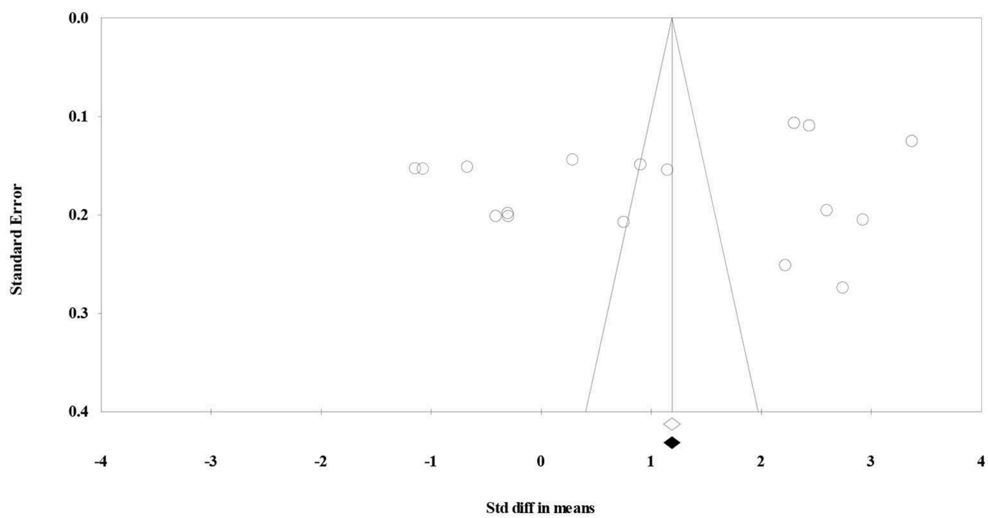

FIGURE 3
Funnel plot to assess publication bias.

COVID-19) were included in the meta-analysis. Our study shows that a significant antibody response against SARS-CoV-2 obtains in a homologous and heterologous vaccination regimen of mRNA vaccines (m1273/m1273/m1273, followed by BNT/BNT/m1273). On the other hand, in case of viral vector and inactivated vaccines, the antibody titers are lower in homologous vaccination regimens compared with heterologous regimens. Interestingly, the immunogenicity of these types of vaccines remarkably enhances when they are administered in a heterologous regimen, especially with a third dose of mRNA vaccines. These findings suggest that mRNA vaccines in a homologous regimen induce strong antibody responses to SARS-CoV-2 compared with other vaccine platforms. In contrast, other vaccine platforms show a satisfactory immunogenicity in a heterologous regimen, especially in combination with mRNA vaccines.

Studies have shown that both humoral and cellular immune responses are important in protecting people from COVID-19 hospitalization and death (28–31). It has been reported that serum levels of anti-spike and anti-RBD antibodies are predictors of immune protection from symptomatic SARS-CoV-2 infection (32, 33), and that neutralizing antibody levels are also correlated to protection from symptomatic infection with SARS-CoV-2 variants of concern, including delta (34) and Omicron (24). Although homologous regimens of a three-dose of mRNA vaccines (m1273 or BNT) generate higher titers of neutralizing antibodies to SARS-CoV-2 D614G pseudovirus (13), delta (B.1.617.2), and omicron variants (B.1.1.529) (24) compared with homologous regimens of adenoviral vectored vaccine (ChAd or Ad26), evidence shows that there is a little difference in initial protection, and server disease or death from SARS-CoV-2 infection after mRNA or adenoviral vector vaccination (28, 35). This may highlight the important role of T cell responses in protective immunity against COVID-19; because viral vector vaccines are somewhat more potent in inducing CD4+ and CD8+ T cell responses against SARS-CoV-2 than mRNA platforms (36). T cell responses also support the generation and maintenance of high-affinity antibodies to SARS-CoV-2.

Based on the discussion mentioned above, it can be concluded that to induce a robust and sustained immunity against SARS-CoV-2, a vaccine should elicit both humoral and cellular immune responses. This may be attained by a heterologous vaccination regimen. For instance, in a study by Atmar et al., it has been reported that injection of an mRNA (m1273 or BNT) vaccine as a third dose to the individuals who had previously received a two-dose of Ad26 platforms, could induce both high titers of neutralizing antibodies and spike-specific Th1 responses in comparison to those receiving a three-dose homologous regimen of Ad26 (13). For this reason, the results of our study should be interpreted with caution, meaning that although a three-dose homologous regimen of mRNA vaccines can induce higher titers of antibody responses than other vaccine platforms, this necessarily does not mean that homologous regimen of mRNA platform is the best choice for COVID-9 vaccination. mRNA vaccines can be a suitable choice as a third dose for those people who have previously received a two-dose of viral vector or inactivated vaccines.

In a similar systematic review and meta-analysis published recently, Cheng et al. have studied the effect of different combinations of homologous and heterologous vaccination regimens on increasing the levels of neutralization and anti-RBD antibodies after the third dose of COVID-19 vaccines (37). In accord with the results of our study, they have reported that the use of mRNA vaccines as a third dose in adults who had previously received two doses of viral vector or inactivated vaccines, can significantly increase antibody responses. In other words, for inactivated and viral vector vaccines, heterologous vaccination regimens are more immunogenic than homologous regimens.

There are some differences between our study and Cheng et al. study (37) that should be mentioned. First, in our study, only RCT studies have been entered into meta-analysis, whereas in Cheng study, RCT as well as observational and non-randomized studies have been included. Second, in our study, anti-spike IgG level has been compared between heterologous and homologous vaccination regimens, whereas in Cheng et al. study, this antibody has not been studied. Third, in Cheng et al. study, all data related to the neutralization and anti-RBD antibodies levels from the original papers, regardless of the measurement day (days 14 or 28 after booster injection) have been entered into meta-analysis, whereas in our study, to control the effect of time variable on the antibody levels, only those studies have been included in the meta-analysis that anti-spike IgG concentrations were measured at day 28 after injection of the third dose. Fourth, in Cheng et al. study, the differences in concentration of neutralization and anti-RBD antibodies before and after injection of third dose of heterologous and homologous vaccination regimens, have been shown in separate forest plots, whereas in our study the differences in anti-spike antibody level among heterologous and homologous vaccination regimens have been shown in one forest plot. This can facilitate transmission of the study message to readers.

There are also some limitations to our study. First of all, there was a substantial heterogeneity (>0.95%) among the studies included that should be taken into account when interpreting the results. The reason for this high heterogeneity may be due to this fact that immune responses to vaccines are affected by many different factors, such as age, sex, race, genetics, lifestyle, nutrition status, body mass index, exercise, and type of vaccine (38). Although in this study, we performed subgroup analysis based on the type of vaccine, however, heterogeneity was still high, probably due to the above-mentioned factors. It seems that this high heterogeneity is inevitable in meta-analysis of vaccine studies, as also seen in Cheng et al. study (37). Second, due to the low number of studies, we could not perform subgroup analysis based on other variables (for example, age, sex, and race). Third, we only searched in English databases, hence the relevant studies that published in other languages may be omitted from our meta-analysis.

5. Conclusion

This systematic review suggests that mRNA vaccines in a homologous regimen induce strong antibody responses to SARS-CoV-2 compared to other vaccine platforms. In contrast, viral vector and inactivated vaccine platforms show a satisfactory immunogenicity in a heterologous regimen, especially in combination with mRNA vaccines.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The Research Ethics Committee of Sabzevar University of Medical Sciences approved the study protocol (Approval ID: IR.MEDSAB.REC.1401.024).

Author contributions

M-SM: study concept and design. FA, SJ, and M-SM: acquisition of data. FA: analysis, interpretation of data, and statistical analysis. ES and MS: drafting of the manuscript. M-SM and SJ: critical revision of the manuscript for important intellectual content. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Understanding COVID-19 vaccine hesitancy: A cross-sectional study in Malang District, Indonesia

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Introduction: Vaccine hesitancy could undermine efforts to reduce incidence of coronavirus disease 2019 (COVID-19). Understanding COVID-19 vaccine hesitancy is crucial to tailoring strategies to increase vaccination acceptance. This study aims to investigate the prevalence of and the reasons for COVID-19 vaccine hesitancy in Malang District, Indonesia.

Methods: Data come from a cross-sectional study among individuals aged 17-85 years old (N = 3,014). Multivariate ordered logistic regression was used to identify factors associated with postponing or refusing COVID-19 vaccines. The Oxford COVID-19 vaccine hesitancy scale was used to measure vaccine hesitancy. A wide range of reasons for hesitancy, including coronavirus vaccine confidence and complacency, vaccination knowledge, trust and attitude in health workers and health providers, coronavirus conspiracy, anger reaction and need for chaos, populist views, lifestyle, and religious influence, was examined.

Results and discussion: The results show that 60.2% of the respondents were hesitant to receive the COVID-19 vaccine. Low confidence and complacency beliefs about the vaccine (OR = 1.229, 95% CI = 1.195–1.264) and more general sources of mistrust within the community, particularly regarding health providers (OR = 1.064, 95% CI = 1.026–1.102) and vaccine developers (OR = 1.054, 95% CI = 1.027–1.082), are associated with higher levels of COVID-19 vaccine hesitancy. Vaccine hesitancy is also associated with anger reactions (OR = 1.019, 95% CI = 0.998–1.040), need for chaos (OR = 1.044, 95% CI = 1.022–1.067), and populist views (OR = 1.028, 95% CI = 1.00–1.056). The findings were adjusted for socio-demographic factors, including age, sex, education, marital status, working status, type of family, household income, religious beliefs, and residency. The results suggest the need for an effective health promotion program to improve community knowledge of the COVID-19 vaccine, while effective strategies to tackle "infodemics" are needed to address hesitancy during a new vaccine introduction program.

KEYWORDS

vaccine hesitancy, coronavirus, confidence and complacency beliefs, cross-sectional study, rural Indonesia

Introduction

The coronavirus disease 2019 (COVID-19) pandemic continues to evolve and impact communities around the world, including in Indonesia. Since the first case was reported in December 2019, as of April 1, 2022, the pandemic has caused more than 6 million infectious disease cases and 155,164 deaths in Indonesia. The COVID-19 vaccine is a vital pillar in recovery from the pandemic (1), yet its full potential will be realized only if we can overcome vaccine hesitancy. According to the World Health Organization (WHO), vaccine hesitancy is a delay, disapproval or refusal of vaccinations notwithstanding the availability of vaccination services (2).

Vaccine hesitancy is a crucial problem that must be addressed given the increasing frequency of vaccine concerns and the requirement to immediately maintain high vaccination coverage across the country in order to reduce the effects of the current coronavirus pandemic. Potential disease epidemics caused by vaccine hesitancy would result in unnecessary pain and death for a large portion of the population as well as a waste of limited local health department resources. The COVID-19 vaccine is considered one of the most effective ways to protect individual health, secure the most vulnerable groups, restore social and economic life, and perhaps attain population health and safety through immunity (3). However, high levels of uptake are necessary for COVID-19 vaccinations to be effective. Vaccine hesitancy may thus lead to significant risks for the hesitant individual as well as the wider community.

Vaccine hesitancy has multifactorial and complex causes that entail a variety of interventions at the individual, medical, community, and healthcare system levels (4). These multifactorial causes, however, are frequently viewed through the lens of complacency, lack of confidence, and low convenience (5). Complacency occurs when the perceived risks of vaccine-preventable diseases are low, so vaccination is not considered necessary. A person's decision to accept or reject a vaccine can be viewed as a trade-off between risk and benefit. Vaccine hesitancy occurs when the public perceive the urgency of vaccination as low (referred to as complacency) and have concerns about the efficacy and safety of the vaccination (referred to as confidence).

Confidence includes trust in a vaccine's safety and efficacy, the healthcare system that provide the services, and the motivations of policymakers who make vaccine decisions. A lack of trust in vaccination is worsened by a poor understanding of vaccine effectiveness as well as mistrust in government and healthcare authorities and in the vaccine's innovativeness. In addition, the ease of obtaining vaccination (referred to as convenience) may be considered. Vaccination convenience is important when it comes to physical availability, affordability, and accessibility. Other reasons for hesitancy that have been recognized include social processes such as norms, lack of altruistic purposes, and lack of collective responsibility (5).

The COVID-19 vaccination program in Indonesia started in January 2021. In the early days of the pandemic, the government set up two phases for delivering COVID-19 vaccination. Phase 1 (January–April 2021) focused on health workers and support staff, medical students, older people (60+ years old), and front-line workers such as public transport drivers, army and police. Phase 2 (April–March 2021) focused on individuals younger than 60 years old with comorbidities. If vaccine doses were available, additional individuals were to be vaccinated. Ten COVID-19 vaccines are allowed by the government authority, including Sinovac, AstraZeneca, Sinopharm, Moderna, Pfizer, Novavax, Sputnik-V, Janssen, Convidencia, and Zifivax. All COVID-19 vaccines are available for free in public healthcare (1). Despite the availability of COVID-19 vaccination in the country, Indonesia had a low vaccination uptake, with roughly 67% of the adult population did the COVID-19 vaccine by May 2021. Hence, this study aimed to assess and identify factors associated with COVID-19 vaccine hesitancy in Indonesia, focusing on Malang, the second-largest district in East Java Province.

Materials and methods

Study setting

This study was conducted in Malang District, East Java Province, Indonesia, between July 07 and August 02, 2021, when the second wave of COVID-19 reached Indonesia. The COVID-19 vaccination program had already been launched in the district. Malang is the second-largest district in East Java Province, with a population of 2,542,963 people (2015 census) distributed across 33 sub-districts and 390 villages, 273 (70%) of which are rural and 117 (30%) of which are urban. It has 39 primary health centers, or *Pusat Kesehatan Masyarakat* (*Puskesmas*; one for every 65,000 people), and 390 village health clinics, or *Pondok Kesehatan Desa* (*Ponkesdes*; one for every 7,000 people). Malang District classifies 10.15% of its population as "poor or near poor," compared to 11.46% in East Java overall (6). The Malang authority carried out its first COVID-19 vaccination program in January 2021. The government provided 1 million doses of vaccine in the first period. It then provided an additional 2 million doses beginning in April 2021. To accelerate the rollout of vaccination, the government has been employing front-line health workers in all 390 village health clinics to deliver vaccination.

Study design and participants

This study was a cross-sectional study among individuals aged 17–85 years. KoboToolbox (a simple, robust, and powerful data collection tool) was used to generate a semi-structured questionnaire (7). The survey apps were utilized by 39 trained field researchers in charge of data collection. The sampling population was determined using a stratified-based sampling design, with the population stratified into urban and rural areas. The total population for rural areas was 1,780,074 individuals and that for urban areas was 762,889 individuals. Based on the confidence level of 99.9% and the margin of error of 5%, we found the minimum samples for rural and urban areas to be 1,082 and 1,081 individuals, respectively. Initially, 3,600 potential participants (1,990 for rural areas and 1,610 for urban areas) provided written informed consent. To encourage participants to participate in the survey, we provided a door prize for 10 randomly selected participants at the end of the survey. Of these, 3,014 completed the survey (1,698 for rural areas and 1,316 for urban areas), yielding an 83.7 percent response rate.

Measures

Vaccine hesitancy scale

The Oxford COVID-19 vaccine hesitancy scale was used to measure hesitancy. This scale consists of seven items (see online Supplementary material). Higher scores indicate higher levels of vaccine hesitancy. In addition, Shapiro et al.s' vaccine hesitancy scale was employed to test the convergent validity of the Oxford COVID-19 vaccine hesitance scale (8). The questions were translated into

Bahasa Indonesia and re-translated following the Oxford COVID-19 vaccine hesitancy scale guidelines. A language expert from Brawijaya University performed the initial translation into Bahasa Indonesia. Then, two independent language experts were hired as outside translators; they translated the questions back into English. The English re-translation agreed with the original questionnaire in English. The set of translated questions was pre-tested on 42 respondents. The pre-test stratified respondents by age, gender, and education. The results showed that even those with little formal education were able to understand the questions correctly. Similar procedures of questionnaire adaption were implemented for other scales used in this study.

Coronavirus vaccine confidence and complacency scale

The Oxford COVID-19 vaccine confidence and complacency scale was used to assess respondents' confidence in and complacency regarding COVID-19 vaccines (9). It assesses attitudes of vaccine complacency (e.g., the collective value of vaccine and the belief that an individual could contract the coronavirus and the vaccine would not work) and confidence (e.g., regarding vaccine innovation speed and side effects). The responses to each item were coded from 1 to 5. A "don't know" option was also available, but it was not scored. Higher scores imply a greater level of negative attitudes toward the vaccine.

Vaccination knowledge scale

The vaccination knowledge measure developed by Zingg and Siergrist was used to measure respondents' knowledge about vaccines (10). Participants were asked to assess a set of statements as correct or incorrect. Incorrect or "do not know" answers were scored as zero, while accurate/correct answers were counted as one. As a result, higher scores imply a greater understanding of vaccines.

Trust in doctors and developers questionnaire

The Oxford trust in doctors and developers questionnaire was used to measure trust in doctors and vaccine developers. This questionnaire includes 11 items about interpersonal disrespect from doctors and five items about distrust in vaccine developers (9). Each item was assessed on a scale of 1 (totally disagree) to 4 (absolutely agree), with a "don't know" option that was not scored. Higher scores suggest that respondents found doctors to be more disrespectful and less respected, and that respondents had more negative perceptions of vaccine developers.

Attitudes toward doctors and medicine questionnaire

Nineteen items from Marteau's questionnaire on doctors and medicine were used to measure respondents' attitudes toward doctors and medicine (11). Each item was graded on a scale of 1 (strongly disagree) to 6 (strongly agree). Higher scores indicate more positive attitudes toward doctors and medicine, whereas lower scores suggest more negative attitudes toward doctors and medicine.

The MacArthur scale of subjective social status

The MacArthur scale of subjective social status, consisting of two different items, was used to examine where people saw themselves on a social ladder compared to other people in their social circle (12). Each item has a rating of 0–10. Higher scores indicate a poorer subjective social position.

Brief core schema scales

The brief core schema scale developed by Fowler et al. was used to assess respondents' beliefs about themselves (13). Twelve items examine beliefs about oneself, ranging from "do not believe" (0) to "completely believe" (4). Higher scores indicate greater agreement with the items.

Medical doctor practice assessment questionnaire

A general practice assessment questionnaire with eight items was used to evaluate how respondents had been treated by their doctors (14). Each item was rated from 1 (very good) to 5 (very poor). Higher scores suggest less pleasant experiences with doctors.

Primary care or Puskesmas experience questionnaire

This study used eight questions to assess favorable and unfavorable experiences of primary community care. Each item is scored on a three-point scale ranging from 1 (no) to 3 (yes) (9). Higher ratings imply that respondents had fewer favorable primary care experiences and more negative primary care experiences.

OCEANS coronavirus conspiracy scale

The OCEANS coronavirus conspiracy scale, consisting of a seven-item general conspiracy scale and a 14-item COVID-19 conspiracy scale was used to measure respondents' levels of belief in coronavirus conspiracy theories (9). Each item was assigned a value from 1 ("do not agree") to 5 ("totally agree"). A "don't know" response option that was not factored into the score was also provided. Higher scores imply a stronger belief in coronavirus conspiracy theories.

Vaccine conspiracy beliefs scale

A seven-item questionnaire was employed that asked participants how strongly they agreed with vaccine conspiracy statements on a seven-point scale (8). Higher scores reflect stronger support for conspiracy theories.

Everyday discrimination scale

This study used William et al.s' everyday discrimination scale, which has nine items (15). On a scale of 1 (almost every day) to 6 (never), individuals were asked to rate how frequently they found themselves in nine bad situations. Higher scores suggest that respondents have had fewer discriminatory experiences.

TABLE 1 Sample characteristics and bivariate correlation with COVID-19 vaccine hesitancy.

Variables	Mean or %	SD	Odds ratio	95% CI	
				Lower	Upper
Age	32.39	9.52	0.99	0.99	1.00
Female	49%		1.13**	1.00	1.29
Education level					
Elementary or less	2%		Ref.		
Junior secondary	16%		0.63	0.35	1.11
High school	18%		0.67	0.38	1.17
College	64%		0.62*	0.35	1.07
Marital status					
Single	25%		Ref.		
Married	72%		0.60***	0.52	0.69
Divorced	2%		1.11	0.71	1.74
Widowed	2%		1.45	0.86	2.44
Working status					
Job not affected by the pandemic	53%		Ref.		
Job affected by the pandemic	47%		0.92	0.81	1.04
Employed	90%		Ref.		
Unemployed	10%		1.46***	1.19	1.79
Type of family					
Nuclear family	61%		Ref.		
Joint family	39%		1.30***	1.15	1.47
Household income					
<1 million rupiah	57%		Ref.		
1–3 million rupiah	35%		1.69***	1.47	1.96
3–5 million rupiah	5%		2.00***	1.48	2.69
>5 million rupiah	3%		3.40***	2.32	5.01
Religious belief					
Muslim	99%		Ref.		
Non-Muslim	1%		0.46**	0.22	0.97
Residency					
Rural	78%		Ref.		
Urban	22%		1.26**	1.08	1.47

*Significant at 0.01.
**Significant at 0.05.
***Significant at 0.001.

Dimensions of anger reactions

Five items of anger reactions from Forbes et al., assessed on a scale of 1 (none) to 5 (all the time), were employed (16). Higher scores imply a higher level of anger.

Need for chaos

Eleven items to assess the "need for chaos" were used to measure respondents' desire to undermine the established political system to raise one's social position. They are rated on a scale of 1 (strongly disagree) to 7 (strongly agree) (17). Higher scores imply a greater need for chaos.

Lifestyle and economic/government liberty

Seven items from Iyer et al. were used to assess the libertarian worldviews of respondents (18). Responses range from 1 (strongly disagree) to 6 (strongly agree). Higher scores reflect more libertarian views.

Populist views

Five questions from Akkerman et al. were used to assess the populist views of respondents. Each was scored on a scale of 1 (strongly disagree) to 6 (strongly agree) (19). Higher scores imply more populist views.

Perceived religious influence on health behavior and illness as punishment by God for sin

The Holt et al. questionnaire was used to measure the impact of religion on an individual's health beliefs (20). Each of the 15 questions was evaluated on a scale of 1 (strongly disagree) to 4 (strongly agree). Higher scores imply that religion has a bigger influence on health behavior and that disease is viewed as a punishment.

Socio-demographic factors include age, sex (female = 1, male = 0), education (elementary or less = 0, junior secondary school = 1, high school or higher education = 2), marital status, employment status (unemployed = 1, employed = 0), job status: whether affected by the pandemic or not, place of living (urban = 1, rural = 0), family monthly income [< Indonesian rupiah (IDR) 1 million = 1, IDR 1–3 million = 2, IDR 3–5 million = 3, IDR > 5 million = 4], and religion (Muslim = 1, non-Muslim = 0) (21). The Indonesian language version of the questionnaire used in the study is available in Supplementary material 1.

Statistical analysis

To ensure that the sample was representative of people living in Malang at large, descriptive statistics [percentages and 95% confidence intervals (CI)] for the outcomes were generated using cross-sectional weights. Since the independent variable was an ordinal scale, ordered logistic regression was performed (22). STATA 17.1 was used to clean and analyse the data. Listwise deletion was used to remove missing data from the analyses, allowing each model to include a different number of participants.

Ethics and consent

The survey was prefaced with a participant information statement and consent form in simple Bahasa (the local language). A trained interviewer read the statement and consent for every participant *via* the KoboToolbox survey app and confirmed that participants had understood the participant information statement to proceed to the survey; completion of the survey constituted consent. Ethics approval was granted by the Brawijaya University Ethical Board (Reference: 11/EC/KEPK/04/2021).

Results

Sample characteristics

Table 1 describes the socio-demographic characteristics of the respondents. Overall, the characteristics of the study sample are similar to the district's socio-demographic characteristics (7). The average age of respondents was 32 years old (standard deviation or SD = 9.5), which is similar to the average age of the district population in 2021. In 2021, the proportion of the female population in Malang was 49.6%, which is comparable to the proportion of female respondents in our study (49%).

However, the proportion of respondents who graduated from college or university in this study was higher than that of the general population. Almost two-thirds (64%) of the study respondents graduated from college or university, while the proportion of individuals who graduated from college in the district in 2021 was about 36%. Most respondents in this study were married (72%) and employed (90%). These proportions are comparable with the proportion of the Malang population in 2021. Almost half of respondents (47%) reported that their job was affected by the pandemic, including losing their job or having their work hours reduced. The proportion of respondents living with their parents or other family members was 61%, and 57% reported having a monthly per capita income of <IDR 1 million (equal to USD 70). It was reported in 2021 that 10.5% of the Malang population had a daily expenditure of <USD 1.00). Most of the respondents in this study were Muslim (99%) and lived in rural areas (78%); these figures are nearly identical to the proportions of the Malang population in 2021. Results of unadjusted ordered logistic regressions show that being female, less educated, unemployed, single, living in a joint family, earning a higher income, being Muslim, and living in an urban area were associated with higher COVID-19 vaccine hesitancy.

Vaccine hesitancy

Table 2 describes respondents' responses to each of the questions on COVID-19 vaccine hesitancy. Only 39.8% reported that they would definitely take the vaccine if the government offered it to them. About 44.6% of the respondents reported wanting to get the vaccine as soon as possible. Likewise, 42.4% of respondents reported that they would get the vaccine as soon as possible when it became available through *Puskesmas* or primary healthcare. Accordingly, 23.3% of respondents said they would get the vaccine at *Puskesmas* when they had time. Regarding attitudes toward receiving the COVID-19 vaccine, 37.3 and 23.3% of respondents were very keen and quite positive about it. However, less than half of respondents (40.9%) reported that they would strongly encourage their family or friends to get the vaccination. Less than half of respondents (39.8%) said they were eager to get the vaccine, while 28.0% were willing to. Accordingly, 12.1% of respondents reported being anti-vaccination, and 14.0% said that being vaccinated was either unimportant or very unimportant.

Reasons for vaccine hesitancy

Table 3 describes the socio-demographic determinants of vaccine hesitancy. Being older (OR = 1.015; 95% CI = 1.005–1.025) and being female (OR = 1.360; 95% CI = 1.181–1.567) were associated with higher vaccine hesitancy. Participants with high school and college educations had less likely vaccine hesitancy than those with elementary school or less education (OR = 0.557; 95% CI = 0.290–1.069 for high school and OR = −0.432; 95% CI = 0.227–0.819 for college). Null association was found for junior secondary school. Married individuals were less likely to reject vaccination than single

TABLE 2 Distribution of responses on each of the Oxford COVID-19 vaccine hesitancy items.

If offered, would you take a COVID-19 vaccine (approved for use in Indonesia)?	*N* (%)
Definitely	1,199 (39.8%)
Probably	706 (23.4%)
I may or I may not	558 (18.5%)
Probably not	299 (9.9%)
Definitely not	118 (3.9%)
Don't know	134 (4.4%)
If there is a COVID-19 vaccine available:	
I will want to get it as soon as possible	1,344 (44.6%)
I will take it when offered	847 (28.1%)
I am not sure what I will do	364 (12.1%)
I will put off (delay) getting it	138 (4.6%)
I will refuse to get it	185 (6.1%)
Don't know	136 (4.5%)
I would describe my attitude toward receiving a COVID-19 vaccine as:	
Very keen	1,125 (37.3%)
Pretty positive	700 (23.2%)
Neutral	534 (17.7%)
Quite uneasy	311 (10.3%)
Against it	200 (6.6%)
Don't know	144 (4.8%)
If a COVID-19 vaccine was available at my *Puskesmas*, I would:	
Get it as soon as possible	1,279 (42.4%)
Get it when I have time	700 (23.2%)
Delay getting it	349 (11.6%)
Avoid getting it for as long as possible	241 (8.0%)
Never get it	243 (8.1%)
Don't know	202 (6.7%)
If my family or friends were thinking of getting a COVID-19 vaccination, I would:	
Strongly encourage them	1,233 (40.9%)
Encourage them	596 (19.8%)
Not say anything to them about it	492 (16.3%)
Ask them to delay getting the vaccination	362 (12.0%)
Suggest that they do not get the vaccination	128 (4.2%)
Don't know	203 (6.7%)
I would describe myself as:	
Eager to get the COVID-19 vaccine	1,201 (39.8%)
Willing to get the COVID-19 vaccine	843 (28.0%)
Not bothered about getting the COVID-19 vaccine	416 (13.8%)
Unwilling to get the COVID-19 vaccine	188 (6.2%)
Anti-vaccination for COVID-19	366 (12.1%)
Don't know	

(Continued)

TABLE 2 (Continued)

If offered, would you take a COVID-19 vaccine (approved for use in Indonesia)?	*N* (%)
Taking a COVID-19 vaccination is:	
Really important	1,091 (36.2%)
Important	901 (29.9%)
Neither important nor unimportant	398 (13.2%)
Unimportant	264 (8.8%)
Really unimportant	157 (5.2%)
Don't know	203 (6.7%)

These questions ask how you would respond if there were an approved COVID-19 vaccine from the Indonesian government.

individuals (OR = 0.559; 95% CI = 0.442–0.708). Null associations were found for divorced and widowed individuals. Individuals who reported that their jobs had been affected by the pandemic (OR = 0.878; 95% CI = 0.761–1.014) were less likely to refuse vaccination after controlling for all covariates. There was no association between employment status or family type and vaccine hesitancy. Higher-income individuals demonstrated a higher level of vaccine hesitancy independent of all covariates. Non-Muslims were also linked with a lower level of vaccine rejection. Null association was found in the relationship between individuals living in urban areas and vaccine hesitancy. In addition, the interaction between education and household income on hesitancy was examined to influence education for household income status. We found individuals educated at the junior secondary school level or higher and from households with incomes >5 million rupiahs to be associated with less hesitancy (detailed estimate results for the interaction variables are available in Supplementary material 2).

Table 4 shows the results from multivariate ordered logistic regressions showing the reasons for vaccine hesitancy. The regression results were adjusted with all socio-demographic factors in Table 3. Regarding confidence and complacency, lower confidence in and complacency toward the COVID-19 vaccine are associated with hesitancy (OR = 1.229, 95% CI = 1.195–1.264 for the collective importance of a COVID-19 vaccine, OR = 1.049, 95% CI = 1.011–1.089 for respondents' perceptions that they may contract the disease, OR = 1.049, 95% CI = 1.011–1.089 for the perception that vaccination is an effective solution, OR = 1.210, 95% CI = 1.165–1.258 for the rapidity with which the vaccines were developed, and OR = 1.199, 95% CI = 1.160–1.240 for vaccine side effects). However, general knowledge about vaccines (OR = 0.831, 95% CI = 0.768–0.899) and knowledge about childhood vaccines (OR = 0.952, 95% CI = 0.899–1.009) are negatively associated with hesitancy. People's trust in doctors and vaccine developers influences vaccine hesitancy. In this study, we observed that respondents' perceptions of disrespect on the part of doctors (OR = 1.055, 95% CI = 1.025–1.086) and their negative view of vaccine developers (OR = 1.055, 95% CI = 1.027–1.082) were associated with vaccine hesitancy. However, positive attitudes toward doctors, positive attitudes toward medicine, and negative attitudes toward medicine had no significant association with COVID-19 vaccine hesitancy. A negative attitude toward doctors had a positive and significant association with vaccine hesitancy (OR = 1.025, 95% CI = 0.997–1054). Negative beliefs about oneself, positive beliefs about oneself, and assessments of health workers were not associated with vaccine hesitancy. Negative experiences with public health providers were associated with higher vaccine hesitancy (OR = 1.064, 95% CI = 1.026–1.102). A higher score on the OCEANS coronavirus conspiracy scale was associated with greater vaccine hesitancy (OR = 1.011, 95% CI = 1.001–1.022), but general coronavirus conspiracy beliefs had no association with vaccine hesitancy. Other behaviors, including disrespect and having fewer discriminatory experience, were not associated with vaccine hesitancy. Anger reactions were associated with greater COVID-19 vaccine hesitancy (OR = 1.019, 95% CI = 0.998–1.040). A stronger need for chaos was also linked to COVID-19 vaccine hesitancy (OR = 1.044, 95% CI = 1.022–1.067). While lifestyle libertarians and economic/government liberty were not associated with hesitancy, populist views were significantly associated with COVID-19 vaccine hesitancy (OR = 1.028, 95% CI = 1.000–1.056). The influence of religion on health behavior was not related to COVID-19 vaccination hesitancy.

Discussion

This study measured coronavirus vaccination hesitancy and its determinants in the second-largest district in East Java, Indonesia. Only 39.8% of the Malang District population was willing to get the COVID-19 vaccine. This proportion was substantially lower than those observed in prior studies in other developing countries, including China (91.3%) (23), Malaysia (94.3%) (24), Brazil (85.4%), South Africa (81.6%), Mexico (76.3%), India (74.5%), and Nigeria (65.2%) (25). A study in Indonesia in 2020 found that 93.3% of respondents wanted to be vaccinated provided that the vaccine is 95% effective and provided by the government free of cost (26). However, that study was performed before the first COVID-19 vaccine deployment in the United Kingdom on December 08, 2020. The changes in disease progression, information and social media, vaccine availability, and government policies may have affected COVID-19 vaccine hesitancy over time. A longitudinal study in the United States found a decline in pro-vaccine attitudes and in COVID-19 vaccination intentions during the 6-month study period (27). Political ideology and media exposure were among the determinants of the decline.

The high level of vaccine hesitancy in Indonesia confirms the country's low vaccine uptake. According to a Ministry of Health study brief based on data obtained between April and May 2021, vaccination uptake remained low, with roughly 67% of Indonesia's adult population likely to take the coronavirus vaccine once it became

TABLE 3 Results of multivariate ordered logistic regression measuring the association of socio-demographic variables of interest with COVID-19 vaccine hesitancy.

Variables	Odds ratio	Std. err.	95% CI	
			Lower	Upper
Age	1.015***	0.005	1.005	1.025
Female	1.360***	0.098	1.181	1.567
Education level				
Elementary and lower (ref.)				
Junior secondary	0.620	0.207	0.322	1.194
High school	0.557*	0.185	0.290	1.069
College	0.432**	0.141	0.227	0.819
Marital status				
Single (ref.)				
Married	0.559***	0.067	0.442	0.708
Divorced	0.798	0.206	0.481	1.324
Widowed	1.092	0.355	0.578	2.065
Working status				
Job not affected by the pandemic (ref.)				
Job affected by the pandemic	0.878*	0.064	0.761	1.014
Employed (ref.)				
Unemployed	1.208	0.192	0.886	1.649
Type of family				
Joint family (ref.)				
Nuclear family	1.059	0.109	0.865	1.296
Household income				
IDR <1 million (ref.)				
IDR 1–3 million	1.904***	0.151	1.630	2.224
IDR 3–5 million	2.480***	0.386	1.828	3.366
IDR >5 million	3.687***	0.756	2.467	5.509
Religious belief				
Muslim (ref.)				
Non-Muslim	0.463*	0.197	0.201	1.066
Residency				
Rural (ref.)				
Urban	1.152	0.103	0.967	1.372

*Significant at 0.01.
**Significant at 0.05.
***Significant at 0.001.

available to them. Another survey, conducted by the Center for Strategic and International Studies, noted that 63 and 55% of youth in Jakarta and Yogyakarta, respectively, did not intend to become vaccinated against COVID-19. Those two regions were the epicenter of COVID-19. Furthermore, a survey conducted by the Indonesian Medical Association between February and March 2021 reported that only 45% of Indonesians aged 22–25 intended to get a COVID-19 vaccination (28). These high proportions of hesitancy are a cause of great concern for the government, which set an optimistic target of up to 2 million doses per day to reach the national vaccination coverage target of 208 million (28).

This study found that complacency and confidence in vaccine decision-making are related to vaccine hesitancy. The findings confirm those of prior studies, which explain that a set of beliefs tightly bound to a willingness to take the COVID-19 vaccine are plausible drivers of vaccine uptake (9). Freeman et al. explained that acceptance of a vaccine is tied to beliefs about its collective importance: that a vaccine will save lives and

TABLE 4 Results of multivariate ordered logistic regression measuring the association of reasons for vaccine hesitancy with COVID-19 vaccine hesitancy.

Variables	Odds ratio	Std. err.	95% CI	
			Lower	Upper
Collective importance of a COVID-19 vaccine	1.229***	0.018	1.195	1.264
Belief that the respondent may contract COVID-19 and that the vaccine would work	1.049**	0.020	1.011	1.089
Speed of vaccine development	1.210***	0.024	1.165	1.258
Side effects	1.199***	0.020	1.160	1.240
General knowledge about vaccines	0.831***	0.033	0.768	0.899
Knowledge about childhood vaccines	0.952*	0.028	0.899	1.009
Interpersonal disrespect on the part of doctors	1.000	0.012	0.977	1.023
Respondent's perception of doctors' respect toward them	1.055***	0.015	1.025	1.086
Negative views of vaccine developers	1.054***	0.014	1.027	1.082
Positive attitude to doctors	1.008	0.021	0.968	1.049
Negative attitude to doctors	1.025*	0.015	0.997	1.054
Positive attitude to medicine	1.033	0.025	0.986	1.082
Negative attitude to medicine	1.014	0.020	0.976	1.054
Negative beliefs about self	1.004	0.011	0.982	1.026
Positive beliefs about self	0.991	0.012	0.968	1.014
Assessment of health workers	1.007	0.013	0.982	1.032
Positive experiences with public health providers	1.018	0.019	0.982	1.055
Negative experiences with public health providers	1.064***	0.019	1.026	1.102
OCEANS coronavirus conspiracy scale	1.011**	0.005	1.001	1.022
General coronavirus conspiracy beliefs	1.005	0.007	0.991	1.018
Others disrespectful	1.006	0.015	0.977	1.035
Others react negatively	1.030	0.029	0.974	1.089
Anger reactions	1.019*	0.011	0.998	1.040
Need for chaos	1.044***	0.011	1.022	1.067
Lifestyle and economic/government liberty	1.007	0.014	0.980	1.035
Populist views	1.028**	0.014	1.000	1.056
Religious influence on health behavior	0.979	0.015	0.949	1.010
Illness as punishment for sin	0.986	0.012	0.964	1.009

*Significant at 0.01.
**Significant at 0.05.
***Significant at 0.001.
The results were adjusted to all socio-demographic factors in Table 3.

help the community and that it will be dangerous if residents do not get vaccinated (9). This corresponds to evidence from a study on collective responsibility in the context of climate change mitigation emphasizing that collective rather than personal responsibility may lead to greater change in individual behaviors (29, 30). This study also found three other key types of beliefs about a COVID-19 vaccine to be associated with hesitancy: that a respondent thought it unlikely that they would be infected and that the vaccine would work; that the speed of development of the vaccine would affect its safety and efficacy; and that receiving the vaccine might be physically unpleasant and that the recipient would feel experimented upon. All of these findings are highly consistent with the framing in the vaccine hesitancy literature of the importance of complacency and confidence in vaccine decision-making (9).

Furthermore, prior research has identified a frequent theme of vaccination safety concerns as a factor in COVID-19 vaccine hesitancy; these safety concerns include the vaccine's potential unexplained side effects, views about the disease itself, and a general impression that vaccine trials were rushed through (29–31). These findings are also confirmed in the present study. This study found low confidence in the speed of vaccine development and concerns about side effects to be associated with vaccine hesitancy in Malang District. Earlier research highlights the impact of both factors on vaccine hesitancy. For example, prior studies have found that, rather than actual vaccine side effects, fear of side effects is one of the main reasons for which individuals refuse to be vaccinated (32). In a randomized control trial study, Sudharsanan et al. found that although COVID-19 vaccine serious side effects are rare, the media's presentation of these risks may amplify concerns. Thus, addressing public concerns over vaccine side effects will help to improve the uptake of vaccines. Likewise, prior studies have found that individuals who do not perceive COVID-19 as a deadly disease and believe that they could be easily treated may then refuse vaccination as they think that the disease does not present a danger to them (33). A review revealed that concerns about the rapid development of the COVID-19 vaccines, as well as the belief that COVID-19 vaccines are harmful and ineffective, present barriers to vaccine uptake (33). These studies also show that vaccine hesitancy is significantly associated with concerns about vaccine safety, vaccine development speed, and longer-term vaccine side effects (33), which is confirmed in the present study.

Knowledge about COVID-19 vaccines is an important determinant of vaccination acceptance. A lack of knowledge about COVID-19 vaccines creates vaccine hesitancy. In this study, the variables measuring participants' knowledge about the COVID-19 vaccines and general knowledge about the importance of childhood vaccination are both associated with lower hesitancy. These findings confirm prior studies that suggest the important roles of effective vaccine education and campaigns to address vaccine hesitancy (34, 35). Such studies suggest that individuals with knowledge and positive attitudes toward vaccines are likely to have a higher willingness to accept vaccination (36, 37). Community education regarding vaccination programs is needed to improve individual knowledge of the benefits as well as the side effects of vaccination before the inoculation campaign, especially in communities with significant exposure to misinformation about COVID-19 vaccines and vaccine fake news.

For most people, taking a vaccination is a matter of trust; they believe that the vaccine is necessary, will work as expected, and is safe (38, 39). Therefore, unwillingness to receive the vaccination is more likely when excessive mistrust is part of an individual's general attitude (40). If a person is skeptical of experts, authorities, and organizations, he or she will likely be skeptical of vaccinations. Distrust is more likely when people feel mistreated and prone to exploitation (marginalized), think that doctors look down on them, believe in conspiracy theories, embrace specific worldviews (e.g., individualism), and are ignored (e.g., exhibit a "need for chaos") (41). A prior study in Indonesia found that trust in both science and government is linked to higher vaccine acceptance. Due to mistrust of the government among Indonesians, the country's response to the COVID-19 situation has also been delayed by denial, reluctance, and rejection (42, 43). Confirming these earlier findings, the present study also reveals that vaccine hesitation is significantly associated with certain confidence and complacency beliefs about COVID-19 vaccines and that it is correlated with sources of mistrust.

This study has found that mistrust of doctors and COVID-19 vaccine developers is related to vaccine hesitancy. These results are in line with the results of previous studies, which have shown a relationship between levels of trust in public institutions and in COVID-19 vaccination (9). However, Quinn and Fremitus reported that individuals who do not trust their government tend to refuse COVID-19 vaccination (4). In contrast to this study, the study found that only mistrust in doctors and COVID-19 vaccine developers was related to respondents' refusal of vaccines. Concerns about scientists' personal bias and corporate motivations, as well as a lack of communication with the general public about COVID-19 advances and vaccinations, are the key issues facing scientists and may result in loss of faith in them (44). This could explain two things that have been observed in Malang District and in Indonesia in general. First, even before the COVID-19 pandemic, citizens had poor perceptions of and experiences with doctors' services. Second, there is a great deal of exposure to fake news, misinformation, disinformation and infodemics about COVID-19 and COVID-19 vaccination. As has been explained in various mass media regarding conspiracy theories about COVID-19 and the COVID-19 vaccination program as well as misleading news about vaccines, people do not have faith in vaccine developers (9).

Accordingly, our findings also highlight the relationship between the OCEANS coronavirus conspiracy beliefs and vaccine hesitancy. The findings also confirm prior studies both in developed and developing countries (45, 46). Pertwee pointed out that conspiracy theories and rumors about COVID-19 and vaccines should not be understood simply as false beliefs. Rather, they can be read as expressions of popular fears and anxieties (47). A study using the conspiracy mentality and COVID-19 phobia scales found a positive correlation between the belief in conspiracy theories and increased vaccine hesitancy (48). Conspiracy theories represent attempts to impose narrative coherence on frightening pandemic situations. Many of the anxieties fuelling COVID-19 rumors and conspiracy theories long predate the pandemic; they have probably been exacerbated by the widespread social uncertainty that existed before COVID-19 pandemic. For example, issues surrounding globalization and capitalism, Muslims, and terrorism have led to anti-imperialist and anti-Western colonialist movements in some developing countries.

Anger reactions and the need for chaos are associated with hesitancy. Respondents with higher levels of anger and need for chaos are likely to reject vaccination. These findings support literature that explains the negative effect of negative emotional reactions such as anger and the need for chaos on individual vaccine decisions (16, 17). Since the beginning of the pandemic crisis, members of the public may be experiencing various emotions such as anger, fear, sadness, and anxiety. For example, some participants in the present study reported feeling angry after hearing of unexpected adverse effects or rumors about COVID-19 vaccines. These negative emotional experiences may influence participants' decisions to reject vaccination. Populist views are likewise associated with vaccine hesitancy. These findings confirm earlier studies in Europe that have found a positive association between vaccine hesitancy and political populism. These studies identify some key drivers among populists, such as distrust in institutions, elites, and experts, of refusal of vaccination programs offered by authorities (19). Some similar evidence is also revealed in the present study.

Certain socio-demographic factors show an association with vaccine hesitancy. Older people have been more hesitant to get the COVID-19 vaccine. This finding contrasts with findings in Japan (49). A review of 49 studies also revealed that youth was associated with a lower willingness to receive vaccination (33). Our finding that older people are more hesitant to get vaccinated may be due to cognitive barriers (50, 51). Older adults in Indonesia generally received fewer years of formal education and have less social contact than younger people (52). Another plausible explanation is that older adults are more susceptible to misinformation and digital exclusion (38). Among the risk factors for vaccine hesitancy in this study were being female, having a high income with little education, being Muslim, and living in an urban area. According to studies from the United States, women are more likely to believe that the COVID-19 vaccine is harmful (39). However, this result requires further investigation as a prior study found that immunization rates among women for other vaccines, including influenza, were higher than those among men (41). Our results that respondents with higher incomes exhibit greater vaccine hesitancy contrast with prior studies (37). However, this correlation was indeed found, especially for high earners with low levels of education. On the other hand, the intention to accept the vaccine was observed to differ among various socio-economic groups (50, 51). People living under different socio-economic conditions may have different views regarding COVID-19 vaccination. Religiosity was negatively correlated with COVID-19 vaccination, and we observed that some people were avoiding vaccination on religious grounds (37, 53). Our findings further emphasize the necessity of education in increasing COVID-19 vaccine acceptance. People with less education have a lower acceptance rate (37). Lower parental educational level is also a predictor of refusal of COVID-19 vaccine uptake among children (32).

Limitations

The present study is not without limitations. First, the design of this study is cross-sectional, and the pandemic continues to evolve. Vaccine hesitancy may change due to various factors, including public health interventions, the appearance of new viral variants, and new vaccine availability. Longitudinal surveys should thus be performed to examine how vaccine hesitancy evolves. Second, in addition to quantitative surveys, a qualitative analysis could be employed to improve understanding of factors related to vaccine hesitancy. Third, invitations to participate were distributed through e-mail and text messages to the participants. The sample for this research did not include any potential responders without internet access. Further study with wider sampling should be undertaken to identify factors of vaccine hesitancy.

Implications

Vaccine hesitancy in Indonesia as observed in this study is quite high compared to that found in other countries. One plausible explanation for this is that many vaccine-preventable infectious diseases are still causing a substantial number of deaths annually in Indonesia. The unsuccessful efforts to tackle vaccine-preventable infectious diseases in the country may lead to a lower perceived need for or value of the COVID-19 vaccine. High-income countries, in contrast, have successfully eliminated vaccine-preventable diseases; therefore, more people are confident in the impact of the COVID-19 vaccine. Our findings could contribute to overcoming misunderstandings about public health, particularly regarding vaccination. Providing accurate knowledge about COVID-19 and especially regarding vaccinations, using simple language so that people of all socio-economic and educational backgrounds can understand, may enhance health literacy and vaccine awareness. A variety of personalized, simple-to-understand health communications delivered *via* several modalities may help people make better-informed health decisions and increase their likelihood of getting the COVID-19 vaccination. Our findings show that specific populations, such as older people, who are prone to digital exclusion, have a higher level of vaccine hesitancy. Using traditional media such as television, newspaper, or radio to inform the population about COVID-19 could thus be a beneficial choice for the government.

The COVID-19 vaccine initiative is a crucial pillar in the struggle against COVID-19. Currently, governments and policymakers worldwide are racing to expand the vaccination program as they believe that the program's effectiveness is key to public health interventions fighting the virus. Effectiveness is defined here as achieving high uptake among adult inhabitants, preferably enough to produce herd immunity of the country's population. Effectiveness also entails equal access, acceptability, and delivery to prevent disparities in care and disease outcomes. Widespread acceptance of vaccines is vital to achieving sufficient immunization coverage so that the pandemic can be brought to an end. However, vaccine hesitancy could continue to undermine efforts to control the coronavirus.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Brawijaya University Ethical Board (Reference: 11/EC/KEPK/04/2021). The participants provided their written informed consent to participate in this study. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

S, H, RS, and SA prepared the study design. S, H, and RS collected data and conducted data analysis. S and RS wrote the main manuscript text. S, AM, SA, EP, DO, and GT reviewed the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.1030695/full#supplementary-material

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Is heterologous prime-boost COVID-19 vaccination a concern or an opportunity for Ethiopia?

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Introduction

Mass vaccination has become a pressing need to attenuate the ongoing coronavirus disease 2019 (COVID-19) pandemic. Despite considerable efforts, only one-third of the population in Ethiopia has been fully vaccinated so far (1), in stark contrast to the proportion of fully vaccinated people in developed countries. According to the Ethiopian Ministry of Health (MoH), 52.5 million COVID-19 vaccine doses have been administered in the country since the 30th of August 2022. With the increasing concern over waning vaccine-induced immunity and the continuous emergence of new variants of concern, including the Omicron variants (2, 3), countries with limited resources, such as Ethiopia, need to consider alternative strategies for the timely COVID-19 vaccination.

Though Ethiopia is the second-most populous country in Africa, it has no local vaccine research and production capacity and remains highly dependent on imports, primarily through the support of the Global Alliance for Vaccines and Immunizations (GAVI). The COVID-19 vaccine rollout in Ethiopia has been constrained by two major factors: the unpredictable and intermittent COVID-19 vaccine supply and increased hesitancy to take the vaccine even when available due to the low-risk perception of COVID-19 (4). This can potentially be mitigated by switching to intradermal or intranasal vaccination, as these use a much smaller volume/fraction of the routine vaccine dose (5). Alternatively, heterologous vaccination regimes, with one vaccine type as a first dose and another as a second dose, could also be considered (5, 6). Besides the vaccine supply shortage and suboptimal vaccine uptake (7, 8), vaccine thermostability impacted the COVID-19 vaccine rollout in Ethiopia. In this opinion paper, we discuss COVID-19 vaccine rollout challenges in Ethiopia with possible mitigation strategies (Figure 1), with particular emphasis on a heterologous prime-boost vaccination approach as a means to curb the observed intermittent vaccine supply shortage in the country.

Heterologous prime-boost vaccination schedule as a means to spare vaccine doses

Global initiatives such as the COVID-19 vaccines global access (COVAX), along with other key delivery partners such as UNICEF, have shown impressive progress in ensuring equitable access to COVID-19 vaccines. However, the solidarity initiatives encountered a challenge and thus were not optimal, mostly due to vaccine nationalization (9), increasing demand in developed countries, and the need for several subsequent booster doses for fully vaccinated individuals following the emergence of the Omicron variant (10). As a result, Ethiopia was forced to receive different COVID-19 vaccines from multiple suppliers that use different manufacturing platforms and doses. Some of the first COVID-19 vaccines received included the CoronaVac (Sinopharm, 13.7 million doses) from the Chinese government, the ChAdOx1 (Oxford–AstraZeneca, >6.99 million doses), the Ad26.COV2.S (Janssen, >34.5 million doses), BBIBP-CorV (∼4 million doses) and the BNT162b2 (BioNTech-Pfizer, ∼6.5 million doses) through the COVAX initiative, while the Ad26.COV2.S (>7.5 million doses) was provided through the African Union's African Vaccine Acquisition Trust (AVAT) initiative (Table 1).

According to Ethiopia's national COVID-19 vaccination program (11), the recommended primary series two-dose regimens in 2021 were intramuscular (IM) administration of homologous BBIBP-CorV-BBIBP-CorV, homologous ChAdOx1-ChAdOx1, and homologous BNT162b2-BNT162b2, whereas Ad26.COV2.S vaccine was accepted as a single dose with an IM route of administration (12). The majority of frontline healthcare workers and elderly people received their first dose of ChAdOx1. However, the emergence of the Delta variant aggravated the global shortage of the ChAdOx1 vaccine (10). In addition, the production of ChAdOx1 was on hold in several countries due to concern over rare side effects, such as thrombosis, particularly in women (13). This resulted in an inadequate stock of the ChAdOx1 vaccine to administer the second booster dose to all who were vaccinated with the initial dose of the same vaccine and to boost all those individuals who had been primed with the ChAdOx1 vaccine. This subsequently forced the MoH to implement a heterologous prime-boost vaccination strategy. To mention a few, those healthcare workers who received ChAdOx1 as a first dose were later vaccinated with the Ad26.COV2.S vaccine as a second dose. Moreover, a third booster dosage would probably have required yet another type of COVID-19 vaccination for the elderly and healthcare professionals who had previously received two doses of ChAdOx1. This prompted us to question whether a heterologous prime-booster vaccination strategy for COVID-19 could become a concern or an opportunity in controlling the pandemic, particularly in the Ethiopian context.

The first-generation COVID-19 vaccines have been shown to be less effective against newly emerging or future re-emerging coronaviruses (2, 3). Therefore, it has become imperative to develop broad-spectrum anti-SARS-CoV-2 vaccines and therapeutics. In response to this demand, several second-generation pan-coronavirus vaccines have been developed, some in the preclinical stage and others in the clinical stage (14). Until pan-coronavirus vaccines become commercially available, heterologous prime-boost vaccination regimens with the best "mix and match" of currently available COVID-19 vaccines (Table 2), which could potentially result in the induction of breadth protective immunity against different variants of concerns, could be deployed as a valid alternative vaccination strategy (15, 16).

Such heterologous vaccination also seems to be applicable and productive compared to homologous vaccination in a pragmatic approach to COVID-19 vaccination (5), and other diseases such as HIV (6) and Ebola (21). On the contrary, short-term reactogenicity was higher with heterologous regimes than with homologous regimes (22). Results from studies in developed countries indicate the safety (tolerability) and effectiveness of

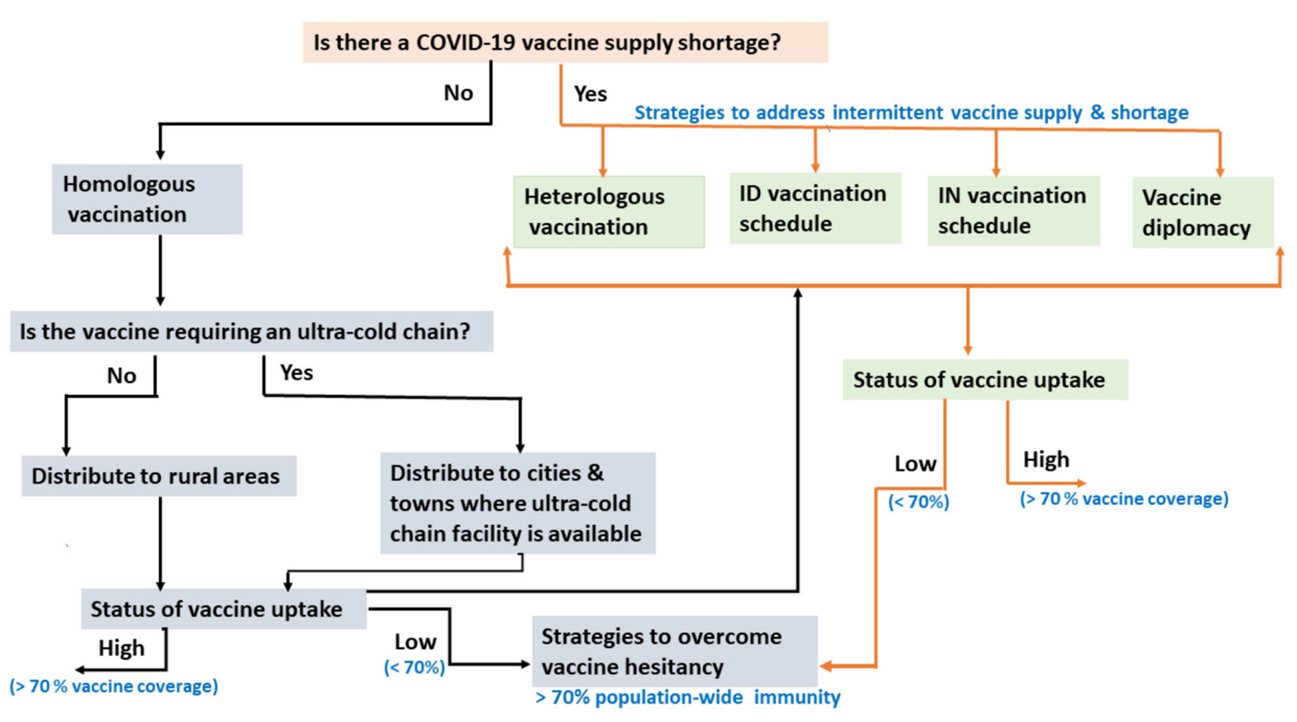

FIGURE 1
Flow chart showing the challenges of COVID-19 vaccination rollout in Ethiopia, with possible mitigation strategies. ID, Intradermal; IN, Intranasal.

TABLE 1 The sources, types and number of doses of COVID-19 vaccines received in Ethiopia as of 15/11/2022.

No	Vaccine type	Source			Grand total
		Bilateral from The Republic of China (doses*)	COVAX[a] (doses*)	AVAT[b] (doses*)	
1	ChAdOx1	_	6,979,440	_	6,979,440
2	Ad26.COV2.S	_	34,533,350	7,516,800	42,050,150
3	BBIP-CorV	13,700,000	3,890,400	_	17,590,400
4	BNT162b2	_	6,465,420	_	6,465,420
	Grand total	13,700,000	51,868,610	7,516,800	73,085,410
	By proportion	18.7%	71.0%	10.3%	100.0%

*Numbers given in relation to vaccine dose; [a]COVAX, COVID-19 vaccines global access; [b]AVAT, African Union's African Vaccine Acquisition Trust.

TABLE 2 Immunogenicity and reactogenicity of heterologous mix-and-match COVID-19 vaccination regimens in comparison to homologous vaccination for selected licensed COVID-19 vaccines.

Prime vaccine brand	Boost vaccine brand	Target population	Immunogenicity	Reactogenicity	Reference
ChAdOx1	BNT162b2	Adult healthcare workers	Superior immunogenicity	No difference in reactogenicity	(15)
Ad26.COV2.S	BNT162b2 or mRNA-1273	Healthy adults	No inferior immunogenicity	No safety concerns were identified	(16)
CoronaVac	ChAdOx1	Healthy adults older than 18 years	Superior immunogenicity	Not available	(17)
ChAdOx1	CoronaVac	Healthy adults older than 18 years	Lower immunogenicity compared to homologous ChAdOx1/ ChAdOx1 vaccinations	Not available	(17)
BNT162b2	ChAdOx1	Healthy adults aged 50 years and older	Higher immunogenicity compared with ChAdOx1/ ChAdOx1	Increased systemic reactogenicity in heterologous schedule	(18)
ChAdOx1	BNT162b2	Healthy adults aged 50 years and older	Higher immunogenicity compared with ChAdOx1/ ChAdOx1	No increased reactogenicity in the heterologous schedule	(18)
ChAdOx1	BNT162b2	Healthy healthcare workers	Higher immunogenicity	Tolerated reactogenicity	(19)
ChAdOx1	mRNA-1273	Healthy healthcare workers	Robust and strong immunogenicity	Relative higher reactogenicity, but well tolerated	(19)
Ad26.COV2.S	BNT162b2	Healthcare workers	Higher immunogenicity	Well-tolerated reactogenicity, which resolved in 48 h	(20)
Ad26.COV2.S	mRNA-1273	Healthcare workers	Higher immunogenicity	Well-tolerated reactogenicity, which resolved in 48 h	(20)

heterologous prime-boost vaccination (13). Table 2 summarizes the immunogenicity and reactogenicity of heterologous prime-boost vaccination schedules with the selected licensed COVID-19 vaccines.

Although the highest antibody response is induced by mRNA vaccines as a heterologous second dose (22), the combination of heterologous prime-boost schedules with inactivated vaccines (like CoronaVac) and adenovirus-based vaccines (such as Ad26.COV2.S and ChAdOx1) is recommended as a feasible vaccine distribution in developing countries like Ethiopia (23) due to the extremely low or ultra-cold supply chain requirement (which is highly prone to product storage error) and cost of mRNA vaccines (24). Nevertheless, given the limited evidence from low-income countries, Ethiopia needs to assess the safety of different combinations of heterologous prime-boost vaccines to determine which mixing provides long-term protection for its population. When supply-chain distributions are limited, local data on immunogenicity and reactogenicity would give health policymakers more confidence to deploy a heterologous vaccination strategy in the future.

Administrating a third dose (booster, either homologous or heterologous) of vaccination has been shown to produce an immune response against different variants of concern, including the Delta and Omicron (25). Following the fourth COVID-19 wave in Ethiopia, presumedly related to the Omicron wave, the Ethiopian vaccination program has considered third booster dose vaccinations for the elderly, frontline healthcare workers, individuals with comorbid health conditions, and other high-risk populations. Given that 65% of the Ethiopian population is still not fully vaccinated, the mass administration of a third (booster) vaccine dose in Ethiopia is debatable (26) and we recommend against administering a third dose to population groups that are less exposed and at lower risk. If Ethiopia is forced to consider mass administration of a third dose in the future, third dose administration to individuals who have already been naturally infected and received two doses should be carefully considered only after (i) administering two doses to the remaining infection naive and unvaccinated people, (ii) administering the second dose to people primed with Ad26.COV2 and (iii) administering third-dose to high-risk populations and to people who received two doses of inactivated vaccines (e.g., CoronaVac) given inactivated vaccines have been found to be less immunogenic (22).

Overall, a heterologous vaccination schedules seem more practical in settings such as Ethiopia, where intermittent vaccine supply is prevalent and sustainable vaccination programs must be maintained. In addition, heterologous vaccination schedules can also reduce vaccine hesitancy (Figure 1) by providing alternative booster vaccination options (a different vaccine from the primed vaccine) to those individuals who experienced adverse events (AEs) after their prime (first dose) vaccination (16, 17).

Fractional intradermal vaccine administration as a means to spare vaccine doses

Currently, all the licensed COVID-19 vaccines are administered by IM injection (12). IM tissue is known to bear transient antigen-presenting dendritic cells (APCs) (12). By contrast, the skin (dermis), which is targeted by intradermal (ID) delivery, contains a higher density of APCs such as dermal dendritic cells (DDCs) than muscle (27). In addition, the dermal lymphatic system is organized into several plexus systems, which aid in the efficient transport of vaccine antigens and APCs to the draining regional lymph nodes where further activation of B- and T-lymphocytes takes place (28). Studies have shown that ID delivery of a reduced or fractional vaccine dose (1/5th, 1/6th, or 1/10th of the standard dose of ChAdOx1, BNT162b2, and mRNA-1273) vaccines could elicit similar immunogenicity and reactogenicity to IM inoculation (28–30). Although these promising studies require validation in controlled randomized clinical trial studies in developing countries such as Ethiopia, ID immunization has great potential to be deployed as a vaccine dose-sparing strategy in the future. When there is a vaccine shortage, Ethiopia should also consider a fractional dosing scheme to save doses and achieve herd immunity quickly (Figure 1). As of 30 December 2022, 52.5 million doses of the COVID-19 vaccine have been administered in Ethiopia. If these doses had been administered with a one-fifth fractionation, the entire eligible population of the country could have already been fully vaccinated. In addition, ID administration may increase vaccine uptake among those who are hesitant about receiving a shot due to safety concerns about standard IM injection (30). One of the challenges regarding the large-scale implementation of ID administration is its technical difficulty (5). However, Ethiopia already has an adequate number of trained healthcare workers due to decades of routine administration of Bacillus Calmette–Guérin (BCG) and rabies vaccines, and they could successfully implement mass ID inoculation of COVID-19 vaccines.

Intranasal vaccines as a strategy to spare vaccine doses

Protecting individuals from mucosal pathogens, including SARS-CoV-2, through vaccination may require the induction of both mucosal and systemic immune responses. However, existing IM vaccinations are meant to induce a systemic immune response without generating mucosal protection against viral replication and nasal shedding in the upper respiratory tract, leading to an asymptomatic or mildly symptomatic infection that can still transmit the virus (31). By contrast, intranasally (IN) administered COVID-19 vaccines have been shown in preclinical studies to induce mucosal protection and systemic immune responses (5, 32), some of which have entered different stages of clinical trials (31). If those IN vaccines are proven to be effective, they would be attractive alternatives to block the transmission of SARS-CoV-2. The fact that IN vaccines do not require needle injections makes them one of the most cost-effective vaccination strategies to enhance global vaccine coverage, particularly in resource-constrained countries (Figure 1). IN vaccines could also be given as a booster to those individuals who have already received their first dose through IM delivery.

Vaccine diplomacy as a means to mitigate the vaccine supply shortage

Over 36 low-income countries have received COVID-19 vaccines from the Indian government through global vaccine diplomacy (33). However, Ethiopia has not yet exercised vaccine diplomacy as a valid alternative strategy to address its vaccine supply shortage. Thus, in addition to the existing vaccine supply platforms such as COVAX, Ethiopia should make use of vaccine diplomacy to meet its vaccine needs for fighting present and future pandemics (Figure 1).

Considerations for using thermostable vaccines

Thermostable COVID-19 vaccines would be valuable to expedite vaccine rollout and thereby achieve the desirable population-wide immunity in low- and middle-income countries like Ethiopia (24). Despite efforts to develop thermostable COVID-19 vaccines, including DNA, inactivated, or protein subunit platforms, no approved thermostable vaccine that can be stored for prolonged periods at room temperature (20°C) has been developed until now (34). COVID-19 vaccine storage requirements currently range from ultra-cold temperatures (<-70°C) to refrigerator temperatures (2 to 8°C) (35). When different vaccines are available, their thermostability, alongside their efficacy and safety, should also be considered prior to their import and distribution across countries located in temperate regions. Unlike mRNA-based vaccines, which require stringent ultra-cold storage facilities, adenovirus-vectored vaccines (e.g., Ad26.COV2.S) are more compatible with the existing vaccine-cold chain system in Ethiopia and seem to be more attractive for achieving a population-wide immunity in rural and remote areas of the country (Figure 1).

Local vaccine production

Technology transfer and waiver of vaccine technology intellectual property (IP) could help Ethiopia and other developing countries invest and develop their own manufacturing capabilities and capacities, which could help not only the ongoing COVID-19 pandemic but also future ones (36). At the moment, there is no existing local vaccine manufacturing facility in Ethiopia. As a result, waiving vaccine technology (IP) has little or no effect on meeting the current vaccine demand. However, there are ongoing discussions to produce vaccines for cholera, rabies, typhoid, yellow fever, meningitis A, and tuberculosis locally (37), and IP waivers could also aid in the realization of these ongoing plans.

COVID-19 vaccine hesitancy and mitigation strategies

According to WHO, vaccine hesitancy has been one of the global threats to vaccine-preventable diseases (38), including COVID-19. Several studies in Ethiopia reported varying levels (ranging from 14.1 to 68.7%) of reluctance for COVID-19 vaccine uptake among healthcare workers (7, 39) and in rural and urban communities with a wide range of economic and social status (39–42). Some of the major factors reported for vaccine uptake hesitancy among healthcare workers included inadequate evidence and concerns over vaccines' safety, efficacy, and quality; a prior history of SARS-CoV2 infection; and the duration of vaccine effectiveness (7, 38, 41). Similarly, other factors such as gender (being female), younger age, the primary source of information (particularly social media), and safety, tolerability, and quality concerns over the available vaccines were reported among other communities, contributing to the acceptability of the uptake of the vaccine (39–42).

In addition to addressing the vaccine supply shortage and intermittent supply, identifying and understanding factors associated with vaccine hesitancy while also designing and implementing effective mitigation are essential to accelerate the uptake of COVID-19 vaccination and thereby achieve the WHO-recommended minimum vaccination coverage of at least 70% to achieve herd immunity in Ethiopia (Figure 1). It is therefore imperative that the MoH works with regional health authorities, the Ethiopian Food and Drug Authority (EFDA), and all other stakeholders to seriously address vaccine hesitancy and develop cost-effective national mitigation strategies using different platforms (41, 43). The mitigation strategies should include educational campaigns using multimedia (government media and social media), social mobilization and communication campaigns such as house-to-house youth campaigns, and institutionally-based (hospitals, schools, and universities) campaigns to increase individuals' level of compliance and confidence regarding the COVID-19 vaccine and thereby their decision to be vaccinated once vaccine becomes available (43). It is also important to note that vaccine hesitancy mitigation campaigns should be aligned with subsequent mass-vaccination campaigns. Without such collaborative efforts and innovative implementation strategies, population-wide immunity through mass vaccination campaigns may not be achieved, despite efforts to resolve vaccine supply shortages.

Conclusion and future prospects

In conclusion, a heterologous prime-boost vaccination strategy should be considered a safe and reliable opportunity for African countries, including Ethiopia, to achieve the higher (>70%) national COVID-19 vaccination coverage, as recommended by WHO. At this time, we support the MoH initiative to administer a third vaccine dose to at-risk population groups. It is critical to generate local evidence on the immunogenicity and reactogenicity of various heterologous prime-boost combinations. Furthermore, technology transfer and investment in building its local human capacity and facility, in addition to collaboration and partnership efforts with international vaccine manufacturing platforms, are needed to meet the region's current and future epidemic and pandemic needs. While developing local vaccine manufacturing capacity, Ethiopia should consider vaccine diplomacy as a cost-effective supplement strategy for meeting its current COVID-19 vaccine demand.

Author contributions

TG conceptualized the study, drafted and finalized the manuscript. TG and LWo contributed to national vaccination data retrieving. TG, LWa, AA, AMu, LWo, AMi, and MA contributed to reviewing. All authors approved the final version of the manuscript, contributed to preparing the manuscript, and their authorship meets the International Committee of Medical Journal Editors (ICMJE) criteria.

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Conflict of interest

LWo is a senior advisor to the MoH in Ethiopia.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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What motivated residents of Saudi Arabia to receive the COVID-19 vaccine?

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Background: Acceptance of vaccination is a multifactorial issue. The unprecedented speed at which the COVID-19 disease spread globally has meant that people have had to face the idea of receiving novel vaccines for a novel disease.

Purpose: Studies conducted earlier in the pandemic had shown high vaccine hesitancy in Saudi Arabia, therefore we wanted to understand the motivating factors for people living in Saudi Arabia with regards to accepting the COVID-19 vaccine, our survey was conducted when the government had already mandated vaccination to enter public spaces. Saudi society is not particularly outspoken and therefore it was of special importance to the authors to explore the motivation behind COVID-19 vaccines.

Methods: This is a cross-sectional survey of 802 participants living in Saudi Arabia. The questionnaire was distributed to staff, visitors, and patients in a hospital in Saudi Arabia and *via* electronic means to the general population.

Results: A total of 521 (65%) of the respondents were women, and 281 (35%) were men. A total of 710 (88.5%) were Saudi, and 55 (6.9%) were non-Saudi. The majority of participants (496, 65.7%) stated that they registered for the vaccine as soon as it was available, with 185 (24.5%) stating that they registered when they were mandated to do so and 74 (9.8%) registered only when they felt cases were increasing. Most participants (316, 41%) stated that the main reason for taking the vaccine was one of a self-protective nature, followed by indirect vaccination (240, 31.1%), paternalistic reasons (157, 20.4%) and altruistic reasons (58, 7.5%).

Conclusions: With the increased burden on healthcare that is being faced by COVID-19, other resources need to be carefully allocated. This paper may aid the Saudi government in understanding the motivation for the population to take the vaccine and therefore facilitate any future vaccination campaigns to ensure the best utilization of resources.

KEYWORDS
Saudi Arabia, COVID-19, vaccine, SARS CoV-2, population

Introduction

In December 2019, a novel virus was discovered, which was later named "severe acute respiratory syndrome coronavirus 2" (SARS CoV-2); later, the disease was more commonly known as COVID-19. The associated virus has had a devastating global impact.

Vaccine research began as soon as it became evident that self-limiting measures, such as social distancing and lockdowns, were not a practical long-term solution and that a

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pharmaceutical intervention would be the quickest and most efficient method of controlling the pandemic (1). A rapid cycle of research, development, and testing meant that vaccines became available for mass distribution barely 1 year after the novel virus was first identified.

The first confirmed case of COVID-19 in Saudi Arabia was in March 2020, and the first dose of the vaccine in Saudi Arabia was administered on December 17th of 2020. As of December 2022, globally, there have been more than 645 million confirmed cases of COVID-19 and more than 6.6 million deaths (2). As of December 2022, over 69 million doses of the vaccine have been given to residents of Saudi Arabia and the total number of deaths attributed to COVID-19 in Saudi Arabia is 9,471 (3).

Saudi Arabia is fortunate to have a very robust, modern healthcare system, with free healthcare being offered to all citizens and legislation requiring that all residents have healthcare insurance (4). The Saudi government benevolently announced early on in the pandemic, that all citizens and residents alike would have access to free healthcare in the event of being infected with COVID-19.

The Saudi culture is generally very family-oriented. The typical living situation is families living together, often in multi-generational households, with unmarried members often not moving out until marriage. The average size of a Saudi household is 6.4 family members and 4.1 for a non-Saudi household (5). With the average number of members living together in a household in Saudi Arabia being so much higher and therefore more people living in close proximity, the chance of catching a communicable disease, such as COVID-19 can be expected to be comparatively higher than, for example, the United Kingdom where the 2021 average household size was only 2.36 (6). It has been estimated that older individuals are at higher risk of death from COVID-19 (7), thankfully in this respect, Saudi Arabia has a comparatively smaller population of older inhabitants, with only an estimated 3.2% of the population being aged 65 years and above (8), compared to almost six times the proportion (18.9%) of the U.K. population belonging to the same age range (9).

The expedited administration of the COVID-19 vaccine was shown to be crucial in reducing both the COVID-19-associated healthcare burden and the number of related deaths. One study estimates that approximately 168,000 hospitalizations were prevented and 59,000 lives saved in Brazil, with a hypothetical additional 104,000 hospitalizations that could have been prevented and 48,000 lives saved if they had carried out an accelerated COVID-19 vaccine rollout (10). Although Brazil's population is approximately six times that of Saudi Arabia, they have very similar health scores (63 and 61% respectively) (11), therefore accelerated vaccine rollouts in Saudi Arabia could have also led to a considerable number of avoided hospitalizations and deaths.

The reluctance or refusal to receive a vaccination commonly referred to as "vaccine hesitancy," is a global concern. It was soon realized that a high percentage of the population would need immunity to curb the rapid spread of COVID-19. Several studies have found high levels of hesitancy (12–14). One meta-analysis (including studies from Saudi Arabia) reported global COVID-19 vaccine hesitancy between female and male respondents of 38.9–40.0% respectively (14). Another study of 36,958 Arabs, found a very high hesitancy rate amongst Arabs of between 81 and 83%, amongst the 3,588 Saudi respondents vaccine hesitancy was reported to be 78.7% (15).

Motivation for receiving any type of vaccine is a multifactorial matter across different sociodemographic groups. Several studies have been conducted regarding the attitudes of Saudi citizens and residents toward the COVID-19 vaccine. Non-adoption of the COVID-19 vaccine has been linked to gender, age, nationality, marital status, educational level, socioeconomic factors, the perceived risk from COVID-19 and underlying health conditions (1, 15–30). However, the majority of these other studies were conducted before the vaccine is available, therefore our survey can show the population perspective when the vaccine was already a reality.

One proposed theory is that the motivational rationale for vaccination can be classified as to *who* people take it for, for example, whether the reasoning behind the decision is that they take it for themselves or others (31). We aimed to examine the timing of registration for the vaccine and the motivation for residents of Saudi Arabia to take the COVID-19 vaccine. By understanding what motivated individuals in Saudi Arabia to receive the vaccine we hope to assist local public health decision-makers with future vaccine campaigns should a similar situation arise.

Materials and methods

This was a cross-sectional survey of people living in Saudi Arabia. The inclusion criteria included all persons living in Saudi Arabia at the time of the survey. Exclusion criteria included anyone younger than 14 years old. The study was approved by King Fahad Medical City Institutional Review Board (approval number 21–342). No personal identifying information was gathered from the participants.

Data collection tool

As we did not find a questionnaire in the literature that fully suited our purpose, therefore we constructed our own, drawing inspiration from some of the questions on previous questionnaires in the literature. This questionnaire was initially written in English and was tested for face and content validity among the authors, healthcare professionals and laypeople. Some changes were made, for example, we added additional reasons for taking the vaccine and a question regarding the willingness of taking a booster dose was added. The revised format was forward-translated into Arabic by two native Arabic speakers who have expertise in this field. Minor differences between their translations were agreed upon with the help of a third native speaker. The translation was then back-translated into English by two native English speakers. Any differences between the translations were agreed upon with the help of a third native speaker. The questionnaire was then piloted to a group of 20 people, from within our social network and amongst colleagues, and the feedback received facilitated some changes which were mainly minor semantic changes, but also, for example, included the expansion of an answer regarding who the respondent had felt pressured them to take the vaccine and removal of a question about the respondent's living situation. To reduce the primacy effect, that a respondent might be more likely to choose the first answers, we randomized the order of the answers for the electronic version.

The questionnaire encompassed the following two sections:

1. Demographic and clinical characteristics; which included age, gender, nationality, educational level, occupation, if working whether there is contact with other people and how often, and medical history, specifically if there is a medical condition from a checklist of the following conditions deemed to be higher risk if they contracted COVID-19 according to the CDC at that time: cardiac disease (heart failure, coronary artery disease, or cardiomyopathy), pregnancy and recent pregnancy, cancer, chronic kidney disease, diabetes mellitus, cerebrovascular disease, obesity, chronic pulmonary disease (COPD, asthma) other lung diseases, pulmonary fibrosis, pulmonary hypertension, Down syndrome, Human Immunodeficiency Virus, sickle cell disease, solid organ or blood stem cell transplantation, cystic fibrosis, thalassemia, immune deficiencies, liver disease, hypertension, and venous thromboembolism (32). Also, history of previous exposure to COVID-19 infection was recorded.
2. COVID-19 vaccination history; which comprised of whether or not the vaccine had been taken, plans to take a booster shot (if not done so), the timing of registration (due to the understandable demand for the vaccination, in some instances, there were delays for lower-risk individuals to be vaccinated; therefore, we asked about the timing of registration rather than the first dose date), the main reason for taking the vaccine or not taking the vaccine as appropriate. The 13 possible answers to the main reason for taking the vaccine in our questionnaire, were grouped into four categories namely: self-protection (taking it to protect oneself), indirect vaccination (taking it because someone recommended it/mandated it), paternalistic (taking it to protect one's family and loved ones) and altruistic reasons (taking it to protect the wider population). There was a big difference in the total number of responses between the different groups of rationale.

   Moreover, Vaccine hesitancy was addressed in this survey with a registration question, with the option to choose "I have not registered / nor had the vaccine until now."

Data collection procedure

Over a period of 3 months between January and March of 2022, we used a dual-based approach to questionnaire distribution. Utilizing both a paper-based format and an electronic link to the questionnaire which was distributed to patients, and visitors attending the outpatient clinics and also staff in King Fahad Medical City. The questionnaire was intended to be a self-administered questionnaire, however, in a few instances, we found that the respondent asked the distributor to help them in completing the questionnaire, which they did. Concurrently, an electronic version of the same questionnaire *via* the messaging application "WhatsApp" was distributed by the authors to the general public, creating a snowball sampling distribution. In this way, we were able to have a sample of both medically compromised and healthy respondents. The paper-based questionnaires were collected shortly after completion and the electronic version utilized the Google Forms software. All procedures for data collection were treated with confidentiality. The questionnaire included a statement that by proceeding the respondent implicitly agreed for the data in their responses to be utilized for the research analysis and that no personally identifiable information would be taken.

Sampling technique and statistical analysis

The sampling technique was a convenience sample, and the sample size was estimated to be a minimum of 385 responses based on the estimated population of Saudi Arabia using the Raosoft® sample size calculator (33).

All categorical variables, such as gender, nationality, education, etc., are presented as numbers and percentages. Continuous variable only age was expressed as the mean ± SD. Nonparametric tests were used when data were skewed. The Kolmogorov–Smirnov test was used to check the assumption of a normal distribution. Chi-square/Fisher's exact test was used according to whether the cell expected frequency was smaller than 5, and it was applied to determine the significant association between categorical variables.

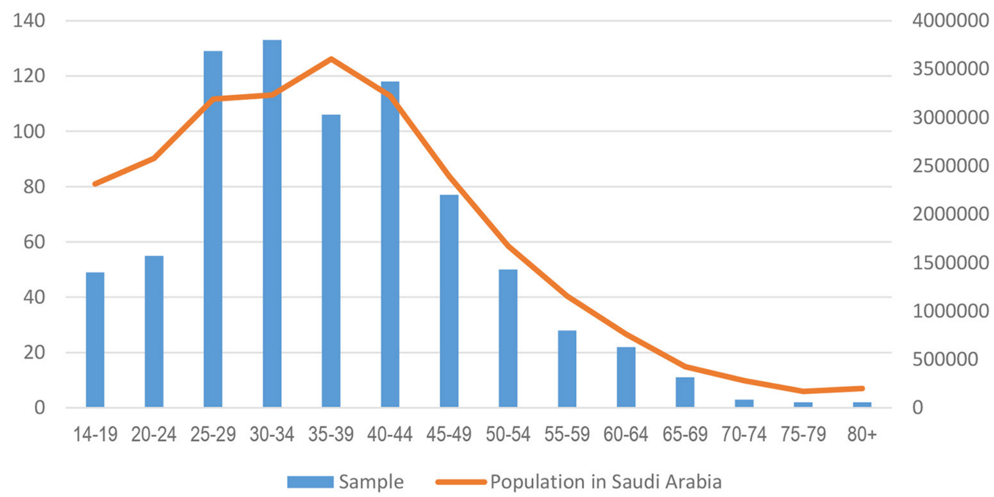

FIGURE 1
Age of respondents (in years) compared to the estimated population in Saudi Arabia.

ANOVA was performed to determine the mean significant difference between age and vaccine registration. A two-tailed $p < 0.05$ was considered statistically significant. All data were entered and analyzed using the statistical package SPSS 25 (SPSS Inc., Chicago, IL, USA).

Results

There were 820 responses in total, and after removing invalid responses, there were 802 participants included in the final analysis.

The sample included 521 female respondents (65%). The majority of respondents were Saudi citizens 710 (88.5%)and 99 non-Saudi respondents from 17 different countries.

The respondents were aged between 14 and 92, with a mean age of 36.96 ± 12.14. Figure 1 below shows that the sample follows the curvature of the Saudi population figures quite closely, especially from those aged 25 and above.

The majority of respondents (618 participants, 77.3%) stated that they had attained some college or higher level education, this is a lot higher than the general population due to the relatively high number of healthcare workers included in the sample, according to one estimate of the percentage of tertiary qualifications among Saudis aged between 25 and 64 calculates it to be approximately 30% (34).

Two hundred sixty-two (33.8%) respondents were healthcare workers. A large proportion of respondents, 225 (44.9%) stated that they worked in a job where there were multiple daily contacts with other people, and an additional 58 (11.6%) were working in an area specifically treating COVID-19 patients. 158 (31.5%) of the respondents were not working outside the home at the time of the survey; 60 (12.0%) respondents stated that they were working outside the home; however, they indicated that their contact with other people was "limited."

TABLE 1 Demographic and clinical characteristics of the study participants (n = 802).

Variables	Description	*n* (n%)
Gender	Male	281 (35.0%)
	Female	521 (65.0%)
Age (years)	Mean ± SD	36.96 ± 12.14
Nationality	Saudi	710 (88.5%)
	Non-Saudi	88 (10.9%)
Education	High school or below	181 (22.7%)
	College/university graduate/institution	518 (64.8%)
	Postgraduate	100 (12.5%)
Healthcare worker	Yes	262 (33.8%)
	No	514 (66.2%)
Occupation	At home	158 (31.5%)
	In a job where there are multiple daily contacts with people	225 (44.9%)
	In a job where there is limited contact with other people	60 (12.0%)
	In an area specifically treating COVID-19 positive patients	58 (11.6%)
Presence of medical condition	Yes	287 (35.8%)
	No	333 (41.5%)
	Unknown	182 (22.7%)
History of exposure to COVID-19	Close family members (with who I live with) were infected but I was not	102 (13.0%)
	I am not sure	28 (3.6%)
	I do not think I have ever had COVID-19	361 (45.9%)
	I think that I probably have had COVID-19 (but not proven through a test result)	39 (5.0%)
	I was previously infected with COVID-19 (as shown by a test result)	256 (32.6%)
Vaccination registration	As soon as available	496 (65.7%)
	I registered when I had to (because of regulations)	185 (24.5%)
	I registered when I noticed cases were increasing	74 (9.8%)
Reasons for taking the vaccine	Altruistic (e.g., to prevent the spread of COVID-19)	58 (7.5%)
	Indirect vaccination (e.g., government mandates)	240 (31.1%)
	Paternalistic (e.g., so as not to infect family members)	157 (20.4%)
	Self-protective (e.g., so as not to become infected)	316 (41.0%)

Categorical data are presented as frequencies (%), while continuous data are expressed as the mean ± SD.

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TABLE 2 Study participants' medical conditions categorized by gender and age.

Characteristics	Description	Females $n = 521$ (% out of all female participants)	Males $n = 281$ (% out of all male participants)
Medical condition	No medical condition	211 (40.5%)	122 (43.4%)
	Unknown	111 (21.3%)	71 (25.3%)
	Anemia	43 (8.3%)	12 (4.3%)
	Diabetes	26 (5.0%)	21 (7.5%)
	Obesity	30 (5.8%)	15 (5.3%)
	Cancer	24 (4.6%)	9 (3.2%)
	Hypertension	17 (4.0%)	15 (5.3%)
	Cardiac	9 (3.3%)	13 (4.6%)
	Chronic pulmonary disease	12 (2.3%)	4 (1.4%)
	Venous thromboembolism (VTE)	11 (2.1%)	3 (1.1%)
	Immunocompromised	5 (0.96%)	1 (0.4%)
	Sickle cell disease	4 (0.8%)	2 (0.7%)
	Asthma	3 (0.6%)	0 (0.0%)
	Chronic kidney disease	0 (0%)	2 (0.7%)
	Downs syndrome	2 (0.4%)	0 (0.0%)
	Cystic fibrosis	1 (0.2%)	0 (0.0%)
	Liver disease	0 (0%)	1 (0.4%)
	Neurological	0 (0%)	1 (0.4%)
	Renal failure	1 (0.2%)	0 (0.0%)
		Average age in years (females)	Average age in years (males)
Medical condition	No medical condition	33.2	33.7
	Unknown	36.5	36.1
	Anemia	34.5	32.0
	Diabetes	46.3	50.8
	Obesity	40.1	38.3
	Cancer	45.4	42.5
	Hypertension	51.4	47.5
	Cardiac	38.3	59.3
	Chronic pulmonary disease	29.4	32.3
	Venous thromboembolism (VTE)	40.9	35.3
	Immunocompromised	26.8	45
	Sickle cell disease	33.0	20.5
	Asthma	28.0	*
	Chronic kidney disease	*	29
	Downs syndrome	14	*
	Cystic fibrosis	50	*
	Liver disease	*	75
	Neurological	*	53
	Renal failure	35	*

*No respondents with this medical condition.

The majority of respondents stated that they had not previously been infected with COVID-19 463 (58.9%), with 295 (37.5%) respondents stating that they had previously tested positive or suspected that they had been positive, and only 28 (3.6%) respondents were unsure whether they had previously had COVID-19 (Table 1).

Out of pre-listed medical conditions, the male participants accounted for 99 (34.3%) and the female participants for the remaining 188 (65.7%), which mirrors the distribution of males to females in the sample (35.0 and 65.0% respectively). The second major category of medical conditions for both male and female respondents was unknown (25.3 and 21.3% respectively), the respondents had not checked an option (Table 2).

Of those respondents who took the COVID-19 vaccine, the majority 65.7% of the participants either registered or went directly for vaccination as soon as the vaccine was available (Figure 2). The differences in gender and the timing of registration were not statistically significant ($P = 0.057$).

In our survey, only 11 (1.4%) of the respondents stated that they had not received the vaccine (at the time of the survey which was at least 1 year from the start of the vaccination program in Saudi Arabia). Of those who had not received the vaccine, they cited the following reasons: four cited medical conditions (including pregnancy and allergies), three cited accessibility of the vaccine as the main reason, and one said that they did not think that the COVID-19 disease would cause them a problem even if they caught it, and one expressed concern about the speed at which the vaccine had been produced. There was no reason stated for the remaining two.

One notable difference between the Saudi and non-Saudi respondents was that more Saudi respondents indicated that they registered for the vaccine only when they noticed that the number of cases had started to increase. This finding was statistically significant ($P = 0.044$). The respondents were from 17 different countries,

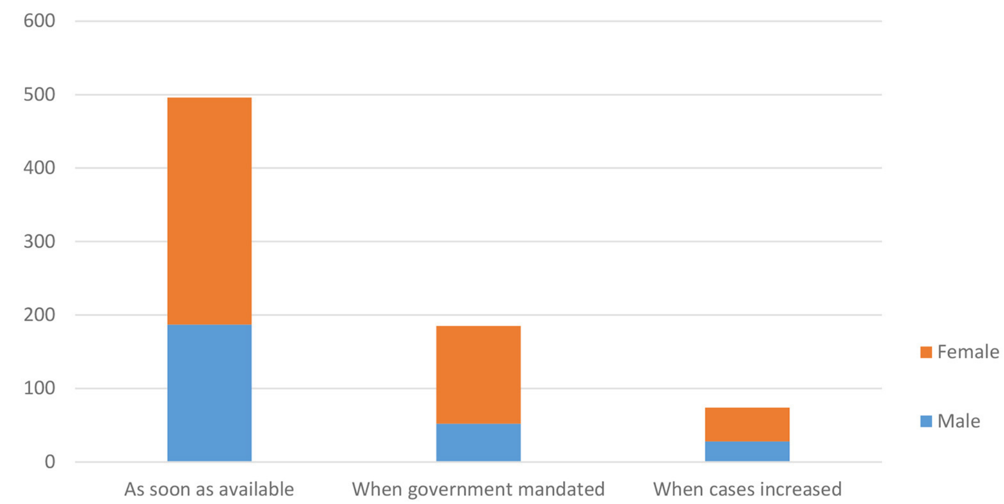

FIGURE 2
Timing of registration for the vaccine among the study participants.

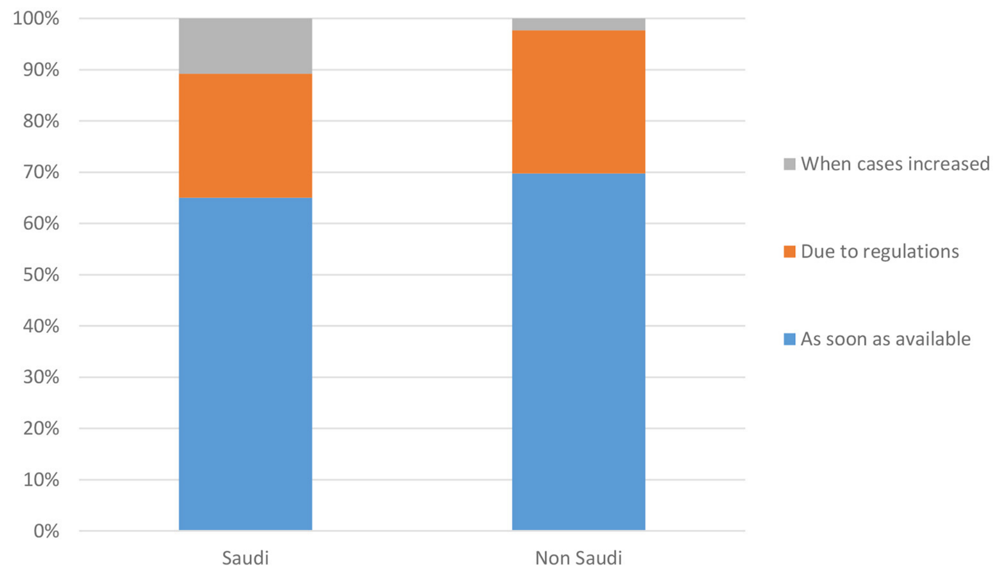

FIGURE 3
Nationality differences when respondents registered for the vaccine.

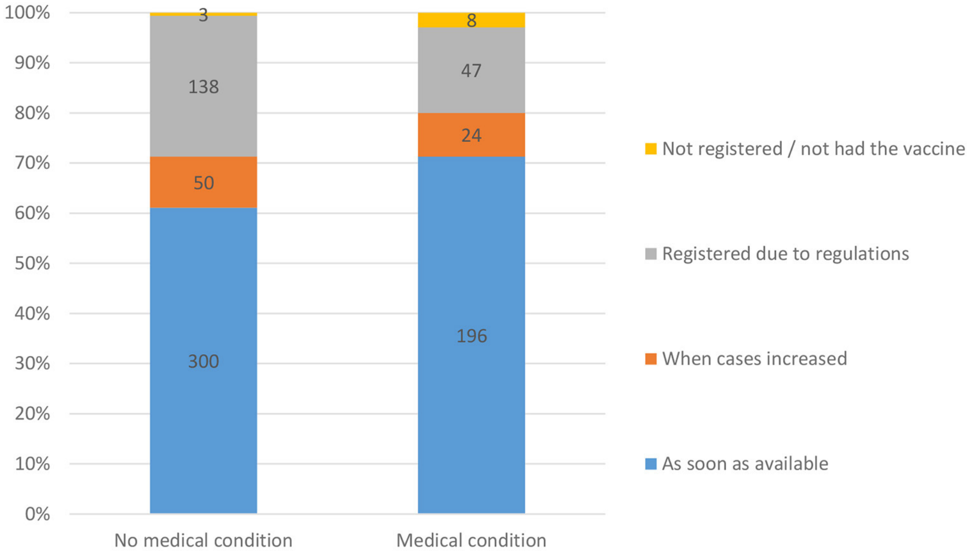

FIGURE 4
Respondents' willingness to register for vaccination as per the present or absence of medical condition.

and the highest number of non-Saudi respondents were from the Philippines (30, 32.6% of the non-Saudis) (Figure 3).

A greater percentage of the participants with the medical conditions registered as soon as registration started (P = 0.022). Only 47 (25.4%) of those with medical conditions stated that the main reason was due to government mandated regulations, compared to 138 (74.6%) of those without medical conditions (Figure 4).

The respondent's previous history of COVID-19 infection was statistically significant only for those respondents who did not think that they had previously been infected with the virus, they were more likely to register as soon as the vaccine was available ($P = 0.003$) (Table 3).

The largest number of responses were categorized in the "self-protective" category 316 (41%). Only 30 (3.89%) responded that their medical condition was the main reason for them taking the vaccine. Those respondents in this category were more likely to take the vaccine as soon as it was available ($P = 0.001$).

The second largest category was for those whose responses were in the "indirect vaccination" category, with 240 (31.1%) responses. The majority of respondents said that they registered for the vaccine when mandated by regulations, this result was statistically significant P = 0.001. Eighteen (2.34%) of the respondents stated that travel was the main reason for taking the vaccine. Only 11.5% of the total respondents were non-Saudi, and almost two-thirds of those who responded that travel was the main reason for taking the vaccine were non-Saudi.

The third largest category was the "paternalistic" category, with 157 (20.4%) responses.

The smallest category was the "altruistic" category, with only 58 (7.5%) responses. These respondents answered that their main reason for taking the vaccination was to prevent the spread of COVID-19.

Discussion

We found that the majority of respondents answered that the main reason for vaccination was of self-protection (Table 4). This echoes findings from another local study, where self-efficacy was the highest significant predictor of behavioral intentions toward COVID-19 (35). Given that the family unit is very important in Saudi Arabia, this finding was initially surprising for the authors, but after considering that Saudi Arabia is now considered only a slightly collectivist society, whereas previously it was considered a strongly collectivist society (36). Seen in this light it may be considered less surprising.

The second largest group was those who were impacted by a decision made by someone other than themselves or someone who may "receive a primary benefit" from the vaccination, i.e., by government mandates. Saudi Arabia was fortunate in many respects that they were able to implement a very robust system of ensuring access to public areas was limited mainly to those who were not currently infected and either vaccinated or exempt from vaccination due to a medical condition. Because this group was so large, it cannot be denied that official mandates (regardless of their popularity), were effective in ensuring people were vaccinated. It is worth noting here that Saudi society is used to government mandates regarding vaccinations, there are existing regulations in place to ensure that other childhood vaccinations are completed before children entering full-time education, "anti-vaxxer" is not a term generally associated with Saudi Arabia.

The third largest group of responses was that they took the vaccine for paternalistic reasons. A notable difference between the sexes was that comparatively more men answered with paternalistic types of reasons for being vaccinated. Saudi Arabia has a strong family structure and therefore it is not surprising that one-fifth of respondents (20.4%) said that their main reason for taking the vaccine was to protect family members. Part of the COVID-19 vaccination campaign in Saudi Arabia was aimed at evoking these paternalistic

TABLE 3 Relationship between vaccine registration and demographic and clinical characteristics.

Variables	Description	Vaccination registration			P-value
		As soon as available	I registered when I had to (because of regulations)	I registered when I noticed cases were increasing	
Gender	Male	187 (37.7%)	52 (28.1%)	28 (37.8%)	0.057
	Female	309 (62.3%)	133 (71.9%)	46 (62.2%)	
Age (years)	Mean ± SD	37.28 ± 12.54	35.23 ± 10.12	36.00 ± 11.11	0.126
Nationality	Saudi	433 (87.8%)	161 (87.0%)	72 (97.3%)	*0.044
	Non-Saudi	60 (12.2%)	24 (13.0%)	2 (2.7%)	
Education	College/university graduate/institution	326 (66.1%)	122 (65.9%)	50 (67.6%)	0.998
	High school or below	110 (22.3%)	30 (16.2%)	19 (25.7%)	0.415
	Post graduate	57 (11.6%)	33 (17.8%)	5 (6.8%)	0.113
Healthcare worker	Yes	170 (35.5%)	65 (36.5%)	16 (21.9%)	0.057
	No	309 (64.5%)	113 (63.5%)	57 (78.1%)	
Occupation	At Home	93 (31.6%)	30 (22.4%)	19 (38.8%)	0.541
	In a job where there are multiple daily contacts with people	133 (45.2%)	66 (49.3%)	22 (44.9%)	0.275
	In a job where there is limited contact with other people	35 (11.9%)	18 (13.4%)	5 (10.2%)	0.834
	In an area specifically treating COVID-19 positive patients	33 (11.2%)	20 (14.9%)	3 (6.1%)	0.314
Presence of medical condition	Yes	194 (39.1%)	47 (25.4%)	24 (32.4%)	*0.022
	No	196 (39.5%)	86 (46.5%)	39 (52.7%)	0.187
	Unknown	106 (21.4%)	52 (28.1%)	11 (14.9%)	0.185
History of exposure to COVID-19	Close family members (with who I live with) were infected but I was not	67 (13.8%)	26 (14.2%)	4 (5.5%)	0.393
	I am not sure	15 (3.1%)	10 (5.5%)	3 (4.1%)	0.705
	I do not think I have ever had COVID-19	244 (50.1%)	60 (32.8%)	31 (42.5%)	*0.003
	I think that I probably have had COVID-19 (but not proven through a test result)	18 (3.7%)	15 (8.2%)	4 (5.5%)	0.211
	I was previously infected with COVID-19 (as shown by a test result)	143 (29.4%)	72 (39.3%)	31 (42.5%)	0.050
Reasons for taking the vaccine	Altruistic	46 (9.6%)	6 (3.3%)	5 (6.8%)	0.130
	Indirect vaccination	90 (18.7%)	119 (65.4%)	19 (25.7%)	*0.001
	Paternalistic	114 (23.7%)	18 (9.9%)	15 (20.3%)	*0.004
	Self-protective	231 (48.0%)	39 (21.4%)	35 (47.3%)	*0.001

Categorical data are presented as frequencies (%), while continuous data are expressed as the mean ± SD; *shows that the P value is significant at $P < 0.05$.

emotions, with billboard posters portraying elderly persons, with a phrase that the vaccination was there to protect them. However, when another study in a very different population is considered, the paternalistic rationale also is ranked high, being the third most common reason in a study of American workers (37). This result was statistically significant, with 75.7% of respondents noting that they had registered for the vaccine as soon as it was available ($P = 0.004$). This was the only category where there was a somewhat noticeable difference in gender percentages compared to the overall study sample. The male/female ratio for all respondents was 35% male and

TABLE 4 Relationship between demographic/clinical characteristics and taking the vaccine.

Variables	Description	Reasons for taking the vaccine				*P*-value
		Altruistic	Indirect vaccination	Paternalistic	Self-protective	
Gender	Male	19 (32.8%)	80 (33.5%)	70 (44.6%)	106 (33.5%)	0.079
	Female	39 (67.2%)	159 (66.5%)	87 (55.4%)	210 (66.5%)	
Nationality	Saudi	48 (82.8%)	212 (88.7%)	151 (97.4%)	271 (85.8%)	*0.001
	Non-Saudi	10 (17.2%)	27 (11.3%)	4 (2.6%)	45 (14.2%)	
Education	College/university graduate/institution	43 (74.1%)	145 (60.7%)	103 (65.6%)	210 (66.7%)	0.863
	High school or below	9 (15.5%)	56 (23.4%)	42 (26.8%)	63 (20.0%)	0.875
	Postgraduate	6 (10.3%)	38 (15.9%)	12 (7.6%)	42 (13.3%)	0.727
Healthcare worker	Yes	17 (29.8%)	72 (30.6%)	49 (33.8%)	117 (37.9%)	0.300
	No	40 (70.2%)	163 (69.4%)	96 (66.2%)	192 (62.1%)	
Occupation	At home	13 (32.5%)	43 (27.7%)	42 (42.9%)	52 (27.4%)	0.551
	In a job where there are multiple daily contacts with people	15 (37.5%)	67 (43.2%)	35 (35.7%)	101 (53.2%)	0.828
	In a job where there is limited contact with other people	9 (22.5%)	22 (14.2%)	11 (11.2%)	17 (8.9%)	0.508
	In an area specifically treating COVID-19 positive patients	3 (7.5%)	23 (14.8%)	10 (10.2%)	20 (10.5%)	0.968
Medical Condition	Yes	17 (29.3%)	77 (32.1%)	57 (36.3%)	123 (38.9%)	0.921
	No	26 (44.8%)	111 (46.3%)	71 (45.2%)	118 (37.3%)	0.796
	Unknown	15 (25.9%)	52 (21.7%)	29 (18.5%)	75 (23.7%)	0.988
History of exposure to COVID-19	Close family members (with who I live with) were infected but I was not	9 (15.8%)	20 (8.4%)	22 (14.6%)	47 (15.0%)	0.727
	I am not sure	1 (1.8%)	12 (5.1%)	5 (3.3%)	10 (3.2%)	0.988
	I do not think I have ever had COVID-19	24 (42.1%)	99 (41.8%)	80 (53.0%)	141 (45.0%)	0.918
	I think that I probably have had COVID-19 (but not proven through a test result)	2 (3.5%)	14 (5.9%)	2 (1.3%)	20 (6.4%)	0.690
	I was previously infected with COVID-19 (as shown by a test result)	21 (36.8%)	92 (38.8%)	42 (27.8%)	95 (30.4%)	0.605

Categorical data are presented as frequencies (%), while continuous data are expressed as the mean ± SD; *shows that the P value is significant at $P < 0.05$.

65% female; however, the paternalistic rationale was cited by males in 44.6% of the responses compared to 55.4% for females (Figure 5).

Lastly, the smallest group of responses was in the altruistic category, the wish to protect others in general, i.e., outside of the immediate family group, accounting for only 7.5% of the responses. One behavioral study which considered altruism as a motivator compared to framed messages also found that people were generally less motivated by altruism (38).

The return to normalcy of the pre-pandemic times has been the goal of every country, some countries achieved this quicker than others and some are still implementing restrictions until now. Vaccination has been shown to be a major weapon in battling the spread of COVID-19. Speedy acceptance and implementation of vaccination programs have undoubtedly saved many lives and eased the tremendous economic burden which has been borne by governments around the world (10).

This survey has highlighted motivational factors for those taking the COVID-19 vaccine, by understanding the differences between the factors we can better allocate resources in future vaccine campaigns, should a similar situation arise. At the individual level, understanding that motivational factors have multifactorial backgrounds and therefore guidance could be individualized may help to guide healthcare workers in steering their patients toward vaccination.

The vast majority of respondents to the survey were Saudi ($n = 710$, 88.5%), and out of the non-Saudi respondents, 64.7% were healthcare workers ($n = 57$), which is not surprising considering the high percentage of non-Saudi healthcare workers working in Saudi Arabia (approximately 60%) (39). Nationality highlighted differences regarding when the respondents registered to receive the vaccine; non-Saudis were less likely to register due to noticing that the number of COVID-19 cases increased but were slightly more likely to register either due to regulations or to request vaccination as soon as it

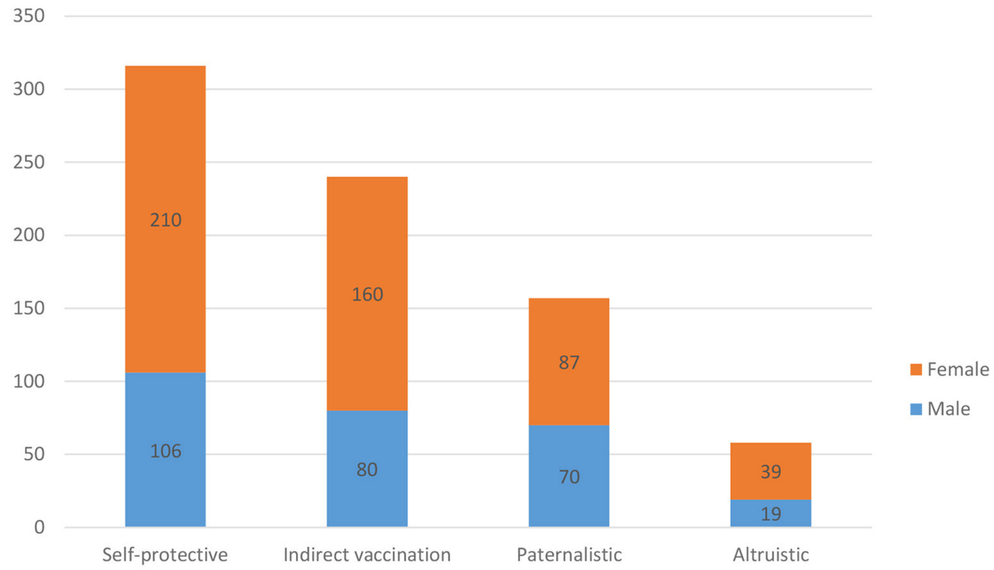

FIGURE 5
Respondents' reason for taking the vaccine according to the categorization of vaccine rationale and gender.

became available. This is because since August 1st, 2021, vaccination was mandated to enter the workplace (apart from those who were medically exempted) (40), and most adult non-Saudi residents are in Saudi Arabia on work visas.

Of the 265 respondents who indicated that they had one or more of the seventeen conditions listed and categorized by the CDC as being at higher risk from COVID-19 (see Table 2), only 30 (11.3%) stated that their medical condition was the most important reason for taking the vaccine. However, they were more likely to register for the vaccine as soon as it was available (194, 73.2%) compared to 196 (61.1%) with no medical conditions. A greater percentage of those with no medical conditions registered for the vaccine only when mandated 86 (26.8%) compared to 47 (17.7%) of those with medical conditions. These findings were statistically significant ($P = 0.022$). Although previous studies have indicated that people are concerned about the medical side effects of the vaccine (41), our sample appears to show that those with medical conditions were more likely to register early for vaccination, but only 17 (2.2%) of respondents indicated that the main reason they took the vaccine was upon advice from their physician. Physicians and other healthcare workers play a vital role in reducing patient apprehension about vaccination and if we are faced with a similar pandemic situation in the future, they should be prepared to pro-actively open a dialogue with patients about their intentions regarding the vaccine and answer any concerns that they might have regarding the effect of the vaccination in their particular medical situation.

The majority of respondents appeared to believe in the efficacy of the COVID-19 vaccine they answered that the main reason for receiving the vaccine was to prevent the occurrence or reduce the severity of infection, comparatively, very few respondents were convinced primarily by their physician (2.2%) however rather than this indicating the lack of trust in physicians it is probably because the majority of those respondents had medical conditions regarded to put them at higher risk. Although we don't have the figures for how many of the participants were advised to be vaccinated by their physician, but hadn't indicated that was the main reason for them to take the vaccine, we must not underestimate the value of physician advice to those patients, if a healthcare worker is themselves hesitant to be vaccinated this could be concerning for the public health authorities who may to some extent expect to rely on healthcare workers is a source of confidence and encouragement for the general public. One large study of healthcare workers found COVID-19 vaccine hesitancy levels ranging between 25.9 and 70.3% depending on race (42). One local study among women who were pregnant or planning to get pregnant indicated high levels of COVID-19 vaccine hesitancy (53.3–65.0%) (43).

Occupation did not appear to greatly impact the timing of vaccine registration. There was little difference between those in work environments with limited, multiple person-contact or even those in areas specifically treating COVID-19 patients; in fact, those mainly based at home were slightly more likely to register early on, and as they saw the number of cases increasing, they were less likely to register because of regulations. This lack of difference mirrors findings from another local study about preventive behaviors in healthcare workers between those being in the workforce and those who were not (35).

A previous history of infection with COVID-19 shows that a greater percentage of respondents who had not been infected or also had close family members who had been infected were more likely to register for the vaccine as soon as registration began compared to those who did not know whether they had previously had COVID-19. Unfortunately, within the context of this study, we do not know whether those who registered early were able to avoid COVID-19 because they were the precaution-taking type of people who also registered early or whether it was due to early registration and thus early immunity that helped them to thus far avoid infection.

In the case of future COVID-19 outbreaks or the emergence/re-emergence of other similar viruses, the government could utilize this information to better understand the reasons for Saudi citizens' and residents' willingness to take the vaccine to target those with vaccine hesitancy, although the importance of tailoring a campaign to an individual must not be underestimated.

Although not an objective of this study, previous studies have shown a correlation between COVID-19-related anxiety, trypanophobia and willingness to be vaccinated (44), the impact that this anxiety has on vaccine hesitancy specifically those amongst those living in Saudi Arabia could be studied in the future.

Limitations

As the questionnaire was self-administered, we hoped to reduce any false reporting by the respondent being embarrassed by responding with a certain answer; conversely, there is always the risk that respondents may not understand the question correctly and therefore enter a wrong answer. However, this is an issue with any self-administered survey, we do not believe that the validity was impaired as from our experience with the questionnaires that we handed out, very few patients needed minor clarifications about the survey. Occasionally, some questions were left unanswered on the manually completed forms, and any questionnaires with the majority of questions unanswered were disregarded. We started the survey once we felt that a substantial number had received the vaccine, as the vaccine rollout was done in stages (higher risk first and ending with the lower risk, younger population) we had to wait for a few months; this delay may introduce some amount of recall bias. Due to the low numbers of those who had not taken the vaccine in our sample, we were unable to perform much analysis.

Conclusions

The motivation to take the COVID-19 vaccination is multifactorial. By asking the question, for *who* do we take the vaccine, interesting insights appear. We found that most of our sample population appeared to take the vaccine with a view to self-protection, followed by indirect (for others) paternalistic and lastly altruistic reasons. Government regulations mandating vaccination appeared to have an effect in influencing a percentage of the population to register and become vaccinated, the percentage of vaccination among those living in Saudi Arabia is similar to countries without such widespread and enforceable mandates.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by King Fahad Medical City IRB. The patients/participants provided their written informed consent to participate in this study.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Conflict of interest

JG, AA, FA, AA-S, MB, and MA were employed by Riyadh Second Health Cluster.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1065157/full#supplementary-material

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COVID-19 vaccination status in Germany: Factors and reasons for not being vaccinated (yet)

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Introduction: The COVID-19 pandemic has demonstrated that effective vaccines constitute a central element of successful pandemic control. Although everyone in Germany has had the opportunity to receive a COVID-19 vaccine, some people remain hesitant or refuse to get vaccinated. To address this phenomenon as well as to examine the unvaccinated population more closely, the present study investigates (RQ1) factors explaining the COVID-19 vaccination status (RQ2) trust in different types of COVID-19 vaccines, and (RQ3) people's specific reasons for not getting vaccinated against COVID-19.

Methods: We base our findings on a representative survey that we conducted in Germany in December 2021 with 1,310 respondents.

Results: In response to the first research question, a logistic regression shows that trust in specific institutions (e.g., medical experts and authorities) is positively related to vaccination status, whereas trust in companies and COVID-19-related social and alternative media consumption decreases the likelihood of being vaccinated. Furthermore (RQ2), while vaccinated people trust mRNA-based vaccines (e.g., BioNTech), most unvaccinated people put greater trust in recently developed protein-based vaccines (e.g., Novavax), albeit on a low level. Finally, our study reveals (RQ3) that the most important reason why people choose not to get vaccinated is that they wish to make their own decisions about their bodies.

Conclusion: Based on our results, we suggest that a successful vaccination campaign should address COVID-19 risk groups and lower income populations, increase trust in different public institutions and newly developed vaccines in advance, establish a multisectoral approach, and debunk fake news and misinformation. Furthermore, since unvaccinated respondents state that the desire to make their own choices about their body is the main reason why they have not gotten vaccinated against COVID-19, an effective vaccination campaign should emphasize the need for general practitioners who have a closer relationship with their patients who, in turn, trust their doctors.

KEYWORDS
COVID-19, vaccination status, vaccines, trust, Germany

Introduction

By the end of February 2022, the COVID-19 pandemic had caused over 430 million infections with more than 6.3 million deaths worldwide (1). For Germany, approximately 27.3 million infections and more than 141,000 deaths had been reported by this time (2). With serious short- and long-term symptoms (e.g., long-term symptoms such as fatigue, headache, and attention disorder) (3), the virus continues to pose a serious threat to public health worldwide. Therefore, the implementation of preventive measures in society, such as social distancing, appears to be all the more important. However, vaccinations, described as "the most successful public health measure in history," are the key preventive measure, saving approximately 2.5 million lives worldwide every year (4).

In terms of the prevention of COVID-19 infections, 20 November 2020, was seen as a turning point in the pandemic. On this date, the mRNA-based COVID-19 vaccine by BioNTech/Pfizer was first submitted for emergency use authorization in the United States (5). It was approved in Germany in late December 2020. By February 2022, further vaccines had been released in Germany, developed by Moderna (mRNA-based), Astra-Zeneca (vector-based), Johnson & Johnson (vector-based), and, more recently, Novavax and Valneva (protein-based). Although certain groups (e.g., high-risk groups) were prioritized initially, all such restrictions were lifted in June 2021 (6). When the COVID-19 vaccination program was first rolled out, demand was high, but it stagnated after a while (6). Despite a large-scale German vaccination media campaign in 2021 and 2022, a substantial portion of the population has refused the COVID-19 vaccination or remained hesitant toward it [as of 07 July 2021, ∼9.2 million people aged 18 years or older (7)] — a phenomenon observed not only in Germany but also in many other countries [e.g., in the United States (8)].

The so-called vaccine hesitancy describes a refusal of or hesitancy toward vaccines despite their availability (9). The WHO includes it in its list of the top ten global health threats (10). In the context of the COVID-19 pandemic, many studies have examined factors explaining both vaccination hesitancy and willingness before a vaccine was even developed [e.g., (11, 12)]. The results indicate that vaccination willingness is linked to basic sociodemographic factors such as sex, age, and socioeconomic background [e.g., (11–13)], region [West Germany vs. East Germany: (6)] migration status (14), and belonging to a risk group and knowing people being hospitalized with COVID-19 (15). It is evident that trust in the state and its institutions is positively related to willingness to vaccinate [e.g., (16)], while right-wing views are related negatively (17). Moreover, various studies indicate that social media use represents a new factor concerning vaccination willingness (18). Social media channels are widely used by both governmental institutions to explain the effects of vaccination and anti-vax movements to spread misinformation, such as the claim that vaccination causes infertility (19).

Even though previous studies have generated broad knowledge of the factors of vaccination willingness, the abovementioned results were mostly compiled at a time when the vaccines were still being developed or their use was prioritized, as they were available only to risk groups or specific professions rather than to the public at large. Comparing the vaccination willingness in Germany during the prioritization phase with the actual vaccination rate after its lifting, data demonstrate a discrepancy of 22% between the willingness to get vaccinated and the actual vaccination rate (20, 21). In other words, the number of people willing to get vaccinated exceeded the actual vaccination rate. Therefore, we assume that measuring vaccination willingness cannot be equated with actual vaccination status. Against this background, the first research question (RQ1) examines the extent to which factors related to vaccination willingness also apply to vaccination status:

RQ1: What individual factors explain the COVID-19 vaccination status?

While many people recognize the benefit of COVID-19 vaccinations, there are individuals who distrust COVID-19 vaccinations. They do so for several reasons. Interestingly, there is higher trust on the whole in newly developed mRNA-based vaccines (e.g., BioNTech/Pfizer) than in other vaccine technologies (22), perhaps owing to the pioneering role of BioNTech/Pfizer, which received the first approval for a COVID-19 vaccine worldwide (23). Yet, the unvaccinated continue to mistrust this new vaccine technology (24). The most prevalent reasons include concerns about mRNA-based vaccination safety and the lack of long-term studies due to its relatively fast development and roll-out. Vaccinated people, however, are rather confident about the future of mRNA-based vaccines and medications and emphasize that this technology is safe because it has been explored for some time (24). Thus, compared with the unvaccinated population, vaccinated people put greater trust in these types of vaccines. In contrast, protein-based vaccines, such as the recently developed Novavax, are based on a "traditional" technology that has been used for influenza vaccines for a longer time. These protein-based vaccines could, therefore, be seen as a potential alternative for vaccination skeptics (25). A special campaign in Germany was implemented to educate the population about the different "new" and "old" vaccination technologies and to reduce mistrust [e.g., (26)]. This information was widely disseminated to the public, but it remains difficult to pinpoint to what extent knowledge about the technology or attitudes toward the manufacturers — based, for instance, on brand awareness — affects trust in the vaccines. To the best of the authors' knowledge, no study has investigated the trust of the vaccinated and unvaccinated populations in different specific types of COVID-19 vaccines. Findings could inform vaccination campaigns targeted toward these specific groups for the different vaccines. This includes the Valneva vaccine, which was not yet released during the survey period. Thus, we derive the second research question as follows:

RQ2: To what extent does trust in COVID-19 vaccines differ between vaccinated and unvaccinated individuals?

Although we can assume that trust is linked to vaccination status, previous studies have examined further reasons for vaccine hesitancy or refusal before vaccinations were available. These studies found that the most important reasons were largely of an internal nature, including concerns about safety, side effects, and the fast development of vaccines (27–29). External reasons, such as a lack of support from doctors, were less important for people not intending to get vaccinated (29). This raises the question of whether the reasons stated in previous studies remain constant over time or whether they evolve when vaccines become available. To the best of our knowledge, there is a lack of research analyzing the specific reasons and their relative importance for the unvaccinated population's choice in Germany not to get vaccinated. Therefore, it is important to investigate current reasons for vaccine hesitancy or refusal in greater detail to derive implications for addressing those not (yet) vaccinated more effectively:

RQ3: What is the most important reason why people in Germany do not get vaccinated against COVID-19?

Materials and methods

Procedure

To answer our research questions, we conducted a cross-sectional, online representative survey (in terms of age, sex, and German federal state) using an ISO-certified panel provider (Respondi, now called Bilendi, Germany). We conducted the survey across a stratified quota sample, interviewing an online panel of respondents in Germany from 20 December 2021 to 02 January 2022. In the first step, based on sociodemographic information, a random sample from the population of the online access panel is drawn. After this, a stratification or a quote module is used.

The interviews lasted for 26.8 min on average. Those who stated that they had not been vaccinated against COVID-19 were presented with a list of reasons for not being vaccinated. The whole study was conducted according to the Code of Ethics of the World Medical Association (30). Moreover, all subjects involved in the study gave their written informed consent. All information was collected anonymously.

Participants

In total, 1,456 persons (18 years and older) completed the survey. However, the sample was restricted to 1,310 observations, since further analyses only included those with valid responses other than "I do not know" or "Answer refused" in all variables. As can be seen in Table 1, 49% were women and 51% were men; the age ranged from 18 to 74 (M = 45.71, SD = 15.04 years). Of the sample, 85% were located in West Germany and 15% in East Germany. The last column in Table 1 shows the true population values of sex, age group, and German state in 2021. Differences in age groups are due to the online representativeness of our sample.

Approximately 51% of interviewees reported either a university or college entrance degree, while 48% achieved a middle-school or secondary-school diploma and 0.38% had no degree (yet). Most of the respondents reported their net household income to be between €2,600 and €4,999 (41%).

Of the sample, 83% had no so-called migration background, and 17% belonged either to the group of first-generation (6%) or second-generation immigrants (11%). A little over half of the respondents had children themselves (51%).

Notably, 36% stated that they belonged to a COVID-19 risk group, and 92% had not tested positive for COVID-19. However, 50% reported that a relative had tested positive for a COVID-19 infection. With 88%, our sample shows a slightly higher rate of vaccinated people aged 18 years or older than the official statistics in December 2021 with 84% (34).

Measures

To determine the factors related to COVID-19 vaccination status (RQ1), we measured sociodemographic variables as well as those related to COVID-19 status, trust in institutions, political views, and COVID-19 media usage. On a descriptive level, we measured trust in different types of vaccines by vaccination status (RQ2) and by the most important reason for not being vaccinated (RQ3). Table 1 depicts the detailed descriptive statistics for all measures.

COVID-19 vaccination status

COVID-19 vaccination status was measured by the item "Have you already been vaccinated against COVID-19?" on a nominal scale including 0 (no) and 1 (yes). This variable serves as a dependent variable in the logistic regression model (RQ1) and as a variable differentiating the trust put in vaccines by those who are vaccinated and by those who are not (RQ2).

Sociodemographic variables

As sociodemographic characteristics, we measured common variables such as respondents' sex, age, and the German state in which they lived (grouped into the categories of "West Germany" and "East Germany"). Questions about the highest school degree received and the average net household income in Euro reflected the interviewees' socioeconomic status. For the questions about the highest school degree, the category "no degree (yet)" included both those who responded that they had no degree and those who had not yet received it. "Lower secondary school diploma" and "higher secondary school diploma" were grouped into the category "low or high secondary degree." Finally, "advanced technical college entrance qualification, completion of a specialized secondary school" and "general or subject-related university entrance qualification" were grouped into the category "university/college entrance qualification," while "other degree" remained the same (0.76%). Household income was split into the following four categories: "€0–€1,499," "€1,500–€2,599," "€2,600–€4,999," and "Over €5,000." Furthermore, we incorporated migration status in the categories "no migration background," "first generation," and "second generation," which we generated on the basis of the respondents' and his/her parents' place of birth ("Were you born in Germany?"; "Were either of your parents born abroad?"; yes, no). Finally, we included information on whether the respondents had children [based on answers to the question "Do you have children? (yes, no)].

COVID-19 status variables

Furthermore, we assume that there is a link between belonging to a group at risk for a severe course of infection and vaccination status. Hence, we asked, "Would you say that you belong to a risk group?" (yes, no). Finally, we surveyed (a) the respondent's infection status ["Have you tested positive for COVID-19 (Coronavirus SARS-CoV-2)?"; yes, no] and (b) whether anybody in the respondent's family or acquaintances had tested positive for COVID-19 ["Have any individuals in your family or among your acquaintances tested positive for COVID-19 (Coronavirus SARS-CoV-2)?"; yes, no].

Trust in institutions and political views

We decided to survey trust in institutions and political views separately and in detail to investigate the relationship between specific public institutions and respondents' vaccination status and to derive implications and communication strategies for those factors that significantly impact people's tendency to be vaccinated. Political

TABLE 1 Descriptive statistics of all variables.

	M	SD	Frequencies	Sample Percent	Percent German population 2021 (31–33)
Sex					
Male			666	50.84	49.00
Female			644	49.16	51.00
Age	45.71	15.04			
Age group					
18 to 29 years			256	19.54	13.20
30 to 39 years			243	18.55	13.08
40 to 49 years			249	19.01	12.01
50 to 59 years			289	22.06	15.70
60 to 74 years			273	20.84	18.18
Region					
West Germany			1,111	84.81	84.97
East Germany			199	15.19	15.01
Highest school degree					
University/college			665	50.76	
No degree (yet)			5	0.38	
Low or high secondary			630	48,09	
Another			10	0.76	
Household income (net)					
€0-€1,499			290	22.14	
€1,500–€2,599			351	26.79	
€2,600–€4,999			542	41.37	
Over €5000			127	9.69	
Migration status					
No migration			1,082	82.60	
1st Generation			80	6.11	
2nd Generation			148	11.30	
Children					
No			643	49.08	
Yes			667	50.92	
COVID-19 risk group					
No			841	64.20	
Yes			469	35.80	
Own COVID-19 infection					
No			1,204	91.91	
Yes			106	8.09	
Relative COVID-19 infected					
No			651	49.69	
Yes			659	50.31	
Trust in institutions					
Politics	3.10	1.24			
Authorities/medical experts	3.59	1.23			

(Continued)

TABLE 1 (Continued)

	M	SD	Frequencies	Sample Percent	Percent German Population 2021 (31–33)
Hospitals/rescue workers	3.93	1.11			
Enterprise (e.g., food supply)	3.28	1.14			
State authorities	3.33	1.21			
Legal authorities	3.19	1.21			
Political views	5.01	1.63			
COVID-19 media usage					
Newspapers	1.79	1.72			
Tabloid media	0.75	1.34			
Public	2.79	1.68			
Private	1.94	1.74			
Official sources	1.90	1.51			
Science	1.35	1.48			
Social media	1.45	1.73			
Alternative media	0.56	1.23			
Vaccinated against COVID-19					
No			159	12.14	
Yes			1,151	87.86	

N = 1,310; M, mean; SD, standard deviation.

(right-wing) views are integrated as a single factor, since they may impact vaccination status independent of trust.

To assess trust in institutions, we used a battery of six items, measuring dimensions using a 5-point Likert scale ranging from 1 (do not agree at all) to 5 (fully agree). The topic was introduced as follows: "Now we will talk about your general attitudes toward dealing with COVID-19 (Coronavirus SARS-CoV-2). Please indicate the extent to which you agree with the following statements." The six institutions include the following dimensions: "politics (federal government, state parliaments)"; "authorities and medical experts (e.g., Robert Koch Institute)"; "hospitals, rescue workers, and other aid organizations"; "companies, such as those in the food supply business"; "state authorities, such as the police and the public order office"; and "legal authorities, such as administrative or district courts." All items were worded in the same way, beginning with the phrase "I trust that [respective institution] will do the right thing to protect me." The scale was partially adapted from reference (35).

Political views were culled in response to the question, taken from reference (36), "Many people use the terms 'left' and 'right' to label different political attitudes. We present a scale from left to right. When you think of your own political views, where would you rank those views on this scale?" Responses were measured on a 10-point scale, ranging from 1 (left) to 10 (right).

COVID-19 media usage

To assess COVID-19 media usage, we employed a battery of eight items measuring different types of media with 6 points that ranged from 0 (never), 1 (less than once a week), 2 (once a week), 3 (several times a week), 4 (once a day), to 5 (several times a day), adapted from reference (37). To introduce the different types of media, we asked, "How often do you look for information about the COVID-19 pandemic on the following media?" The eight media types included "newspapers" (e.g., *Süddeutsche Zeitung*), "tabloid media" (e.g., *Bild*), "public media" (e.g., ARD, DLF), "private media" (e.g., RTL), "official sources" (e.g., Ministry of Health, Robert Koch Institute), "science" (e.g., journals, Nature), "social media" (e.g., Facebook), and "alternative media" (e.g., Ken FM, Nachdenkseiten).

Trust in COVID-19 vaccines

Trust in vaccines was measured by responses to the question, "How much trust do you have in the following COVID-19 vaccines?," using a 5-point Likert scale, ranging from 1 (no trust at all) to 5 (very great trust) for six different types of vaccines, including the mRNA-based types BioNTech/Pfizer and Moderna, vector-based types Astra-Zeneca and Johnson & Johnson, and the recently developed protein-based types Novavax and Valneva.

Most important reasons for not being vaccinated

We measured the most important reason for not being vaccinated by presenting the interviewees with a list of 23 statements against COVID-19 vaccination (e.g., "Vaccines are not safe," "I am fundamentally opposed to vaccinations," or "My social contacts advised me against vaccination"). The participants were asked as follows: "You have indicated that you are currently not (yet) vaccinated against the Coronavirus. Below is a list of statements expressing why someone may not yet be vaccinated against Coronavirus. Please select up to five statements that most closely reflect your vaccination decision." The participants ranked their choices in order of importance from 1 to a maximum of 5. In our analysis, we focused on the reasons that the participants selected as most important. These reasons were adapted from several scales [e.g., (27, 28, 38)].

Statistical analyses

We used the statistical software Stata 17 SE to prepare and analyze the data. After data cleaning and checks, we conducted univariate analyses for all variables related to RQ1 and RQ2 (see Table 1). To analyze factors related to COVID-19 vaccination status in RQ1, we showed bivariate relationships between vaccination status and independent variables before conducting various multiple logistic regressions with the criterion of COVID-19 vaccination status. Therefore, all the factors described above were analyzed separately, leading to a final model comprising all variables related to the respondents' vaccination status. Since the dependent variable is dichotomous (0 "not vaccinated against COVID-19" and 1 "vaccinated against COVID-19"), we used a logistic regression model rather than a linear probability model (OLS regression model). The logistic function means that the range of predicted values lies between 0 and 1, although the linear combination of independent variables has no limits. Furthermore, the odds ratios are displayed, that is, the ratio of the probability of getting vaccinated and not getting vaccinated.

Therefore, we focused on the odds ratios, the standardized coefficients based on the logit coefficients, their direction and significance, and on the pseudo-R^2 showing the goodness-of-fit. To analyze trust in vaccines as depicted in the responses to RQ2, we showed means of vaccine trust by vaccination status, using 95% coefficient plots and the unpaired *t*-tests to check statistical significance between unvaccinated and vaccinated persons. Finally, we addressed RQ3 by showing the univariate distribution of the most important reason for not being vaccinated.

Results

RQ1: Factors related to COVID-19 vaccination status

The second column in Table 2 displays the bivariate relationship between each independent variable and the criterion of vaccination status, using a simple logistic regression model and the unadjusted odds ratios of every single predictor based on our data. For the sociodemographic variables, both age and higher income relate positively to being vaccinated, while respondents living in East Germany (compared with West Germany) and those with no school degree (compared with college/university degree) are less likely to be vaccinated. By contrast, there is no relationship between the respondents' vaccination status and either their migration status or whether or not they have children. All COVID-19 status variables correlate significantly with the participants' vaccination status. While belonging to a COVID-19 risk group and knowing someone infected with COVID-19 are factors that relate positively to being vaccinated, a respondent's own COVID-19 infection relates negatively to being vaccinated. While all variables depicting trust in institutions increase the likelihood of a COVID-19 vaccination, the level of right-wing political attitude decreases this probability. The likelihood of getting the COVID-19 vaccination also depends on the type of media a respondent consumes. While those who consume newspapers, public and private media, as well as official sources are significantly more likely to be vaccinated, the likelihood is low for those consuming more social and alternative media.

Based on our first research question, we performed five logistic regression models to investigate to what extent the individual dimensions of sociodemographic background, COVID-19 status variables, trust in institutions and political views, and COVID-19 media usage related to the respondents' COVID-19 vaccination status. Table 2 shows all models of the logistic regression analyses.

Model 1 comprises all sociodemographic variables and demonstrates that age and a household income >€5,000 increase the likelihood of being vaccinated, while residence in East Germany and a lack of school degrees decrease the likelihood. All other factors, such as sex, migration background, and having children, show no relationship to the respondents' vaccination status. However, the explanatory power of all the sociodemographic variables is rather low (pseudo-$R^2 = 0.06$).

Model 2 comprises variables directly related to COVID-19. Belonging to a risk group as well as knowing people with a COVID-19 infection increase the likelihood of being vaccinated, whereas one's own infection decreases it. With a pseudo-R^2 of 0.04, the COVID-19 status variables are correlated with vaccination status very weakly.

Trust in institutions as well as political views, as shown in model 3, have a rather high explanatory power (pseudo-$R^2 = 0.29$). Trust in medical experts and authorities as well as in hospitals, rescue workers, and aid organizations increases the likelihood of being vaccinated, whereas trust in companies makes vaccination is less likely. Political views also do not relate to vaccination status compared with the unadjusted model.

According to model 4, those who turn to public and official media to inform themselves about COVID-19 are more likely to be vaccinated. By contrast, those using social media and alternative information channels are less likely to be vaccinated. With a pseudo-R^2 of 0.21, COVID-19 media usage has the second highest explanatory power after trust in institutions.

Finally, model 5 comprises all variables related to vaccination status and shows a high model fit of pseudo-$R^2 = 0.39$. In terms of sociodemographic background, sex, age, and migration status do not correlate significantly with vaccination status. However, respondents from East Germany and people without a school degree are less likely to be vaccinated, while those with a household income of €5,000 or more are more likely to be vaccinated. Furthermore, belonging to a risk group increases the likelihood of being vaccinated against COVID-19, while both the respondents' own and a relative's COVID-19 infection status show no effect. Concerning attitudes toward institutions, trust in political institutions, medical experts and authorities, hospitals, rescue workers, and aid organizations increases the likelihood of being vaccinated, while trust in companies is negatively related. However, trust in state and legal authorities and political views show no correlation with being vaccinated against COVID-19. Where COVID-19 media usage is concerned, consuming information from social media and alternative media corresponds negatively with being vaccinated against COVID-19,

TABLE 2 Logistic regression results using vaccination status (0 "not vaccinated against COVID-19," 1 "vaccinated against COVID-19") as the criterion.

		M1: Sociodemographic	M2: COVID−19 status	M3: Trust in institutions	M4: COVID−19 media usage	M5: All
Factor	Unadjusted odds ratios (unadjusted logit coefficient)	Adjusted odds ratios (standardized coefficient based on adjusted logit coefficient)				
Female (ref. = male)	0.949 (−0.053)	1.080 (0.020)				0.756 (−0.051)
Age	**1.021*** (0.021)**	**1.028*** (0.220)**				1.008 (0.046)
East Germany (ref. = West Germany)	**0.391*** (−0.938)**	**0.420*** (−0.163)**				**0.468** (−0.100)**
Highest school degree						
University/college	Ref.	Ref.				Ref.
No degree (yet)	**0.083** (−2.483)**	**0.062** (−0.090)**				**0.040* (−0.073)**
Low/high secondary	0.849 (−0.164)	0.751 (−0.075)				0.803 (−0.040)
Another	1.127 (0.119)	0.965 (−0.002)				0.241 (−0.045)
Household income (net)						
€0-€1,499	Ref.	Ref.				Ref.
€1,500-€2,599	1.132 (0.124)	1.060 (0.013)				0.852 (−0.026)
€2,600-€4,999	**1.563* (0.447)**	1.472 (0.100)				0.977 (−0.004)
Over €5,000	**2.732* (1.005)**	**2.362* (0.133)**				**3.459* (0.135)**
Migration status						
No migration	Ref.	Ref.				Ref.
1st generation	1.096 (0.092)	1.235 (0.027)				2.443 (0.078)
2nd generation	1.004 (0.004)	1.116 (0.018)				1.139 (0.015)
Children (ref. = no)	1.153 (0.142)	0.804 (−0.057)				1.194 (0.032)
COVID-19 status						
Risk group (ref. = no)	**2.536*** (0.931)**		**2.546*** (0.237)**			**2.032** (0.125)**
Own infection (ref. = no)	**0.561** (−0.578)**		**0.525* (−0.093)**			0.626 (−0.047)
Relative infected (ref. = no)	**1.542* (0.433)**		**1.694** (0.139)**			1.104 (0.018)
Trust in institutions						
Politics	**2.771*** (1.019)**			1.273 (0.127)		**1.471* (0.175)**
Authorities/medical experts	**3.071*** (1.122)**			**2.386*** (0.458)**		**2.354*** (0.387)**
Hospitals/rescue workers etc.	**2.333*** (0.847)**			**1.488*** (0.187)**		**1.377* (0.130)**
Companies (e.g., food supply)	**1.648*** (0.500)**			**0.717** (−0.162)**		**0.743* (−0.124)**
State authorities	**2.518*** (0.924)**			1.220 (0.103)		1.087 (0.037)
Legal authorities	**2.144*** (0.763)**			0.784 (−0.125)		0.780 (−0.110)
Political views	**0.801*** (−0.222)**			0.915 (−0.062)		0.887 (−0.072)
COVID-19 media usage						
Newspapers	**1.287*** (0.252)**				1.160 (0.113)	1.062 (0.038)
Tabloid media	0.921 (−0.083)				0.928 (−0.044)	1.004 (0.002)

(Continued)

TABLE 2 (Continued)

		M1: Sociodemographic	M2: COVID−19 status	M3: Trust in institutions	M4: COVID−19 media usage	M5: All
Factor	Unadjusted odds ratios (unadjusted logit coefficient)	Adjusted odds ratios (standardized coefficient based on adjusted logit coefficient)				
Public media	**1.616*** (0.480)**				**1.442*** (0.274)**	1.131 (0.076)
Private media	**1.175** (0.161)**				1.078 (0.058)	0.986 (−0.009)
Official sources	**1.490*** (0.399)**				**1.483*** (0.265)**	1.087 (0.046)
Science	1.052 (0.051)				0.890 (−0.077)	0.862 (−0.081)
Social media	**0.882** (−0.126)**				**0.859* (−0.117)**	**0.852* (−0.102)**
Alternative media	**0.618*** (−0.482)**				**0.579*** (−0.299)**	**0.680*** (−0.173)**
Observations	1,310	1,310	1,310	1,310	1,310	1,310
Pseudo-R^2		0.055	0.036	0.287	0.209	0.393

*p <0.05, ** p < 0.01, ***p < 0.001.

while consuming information from newspapers, tabloids, public and private media, and official sources or science does not relate to vaccination status.

RQ2: Trust in COVID-19 vaccines by vaccination status

Overall, vaccinated people have a significantly higher trust in all types of vaccines than unvaccinated people [BioNTech: $t_{(1234)} = -27.65$, $p < 0.001$; Moderna: $t_{(1233)} = -25.11$, $p < 0.001$; Astra-Zeneca: $t_{(1220)} = -12.97$, $p < 0.001$; Johnson & Johnson: $t_{(1193)} = -10.95$, $p < 0.001$; Novavax: $t_{(689)} = -8.02$, $p < 0.001$; Valneva: $t_{(462)} = -4.48$, $p < 0.001$].

Vaccinated people have the highest trust in BioNTech, whereas unvaccinated people trust Novavax the most. By contrast, vaccinated people express the lowest trust in Valneva, while those who are not vaccinated trust Astra-Zeneca the least.

All in all, those who have been vaccinated trust mRNA-based vaccines the most, whereas those who have not been vaccinated put their highest trust in the recently developed protein-based vaccines, which use the same technology as influenza vaccines. Regarding unvaccinated people, our data reveal no significant differences between trust in traditional vaccines and other types of vaccines, except for Astra-Zeneca. Figure 1 depicts trust in different types of COVID-19 vaccines.

RQ3: The most important reason for not being vaccinated against COVID-19

Among unvaccinated individuals, the wish to "make my own decisions about my body" plays a major role ($N = 33$), followed by safety concerns ("Vaccines are not safe," $N = 25$) and "lack of trust in government" ($N = 10$). To explain the last three reasons, only three people in the total state that they had a "bad experience with other vaccinations" ($N = 1$), that "other means help better" (against COVID-19, $N = 1$), or that they are "fundamentally opposed to vaccinations" ($N = 1$). Figure 2 shows the most important reason for not being vaccinated.

Discussion

RQ1: Factors related to COVID-19 vaccination status

Our first research question addresses individual factors that may explain the COVID-19 vaccination status. In many regards, our results (based on model 5) identify previous findings on factors related to vaccination willingness. For instance, our results document a moderate correlation between socioeconomic factors, such as income, and vaccination status (11–13). Interestingly, these correlations are especially prevalent in margin categories (e.g., low income is related to low vaccination status). Current scholarship often explains these relationships by pointing to a lack of understanding of vaccine importance and insufficient access to medical care (39). It remains unclear to what extent the latter applies to a sample in Germany, where access to healthcare is comparatively secure. Nevertheless, it seems essential to educate the public about the advantages of vaccination in general and to emphasize that vaccinations are accessible to all and free of charge.

Contrary to previous research on vaccination willingness, our analyses do not show that sociodemographic background, including factors such as age, sex, and migration status, plays a significant role in predicting vaccination status (11–14, 39). Regarding age and vaccination status, it seems plausible that the risk of the severe course of disease eliminates this relationship. Hence, we assume that belonging to a risk group relates to both vaccination willingness and status more than age does. For sex and migration status, none of our models documented a link to vaccination status. As the SAGE vaccine hesitancy determinants matrix (9) suggests, individual and group factors, such as perceived risk and benefits, influence vaccination status, which may explain the non-significant correlation

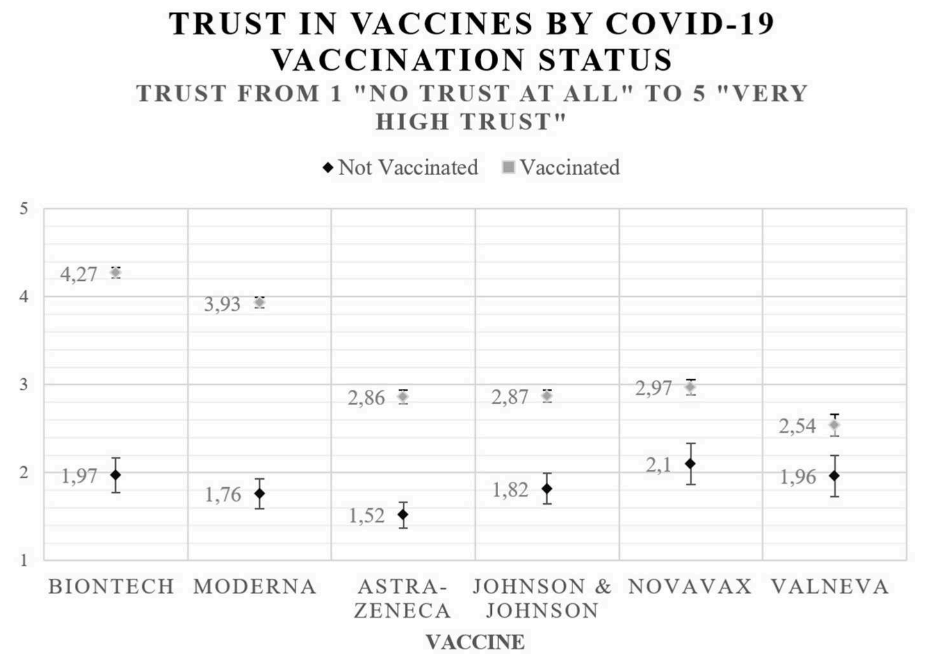

FIGURE 1
Trust in COVID-19 vaccines.

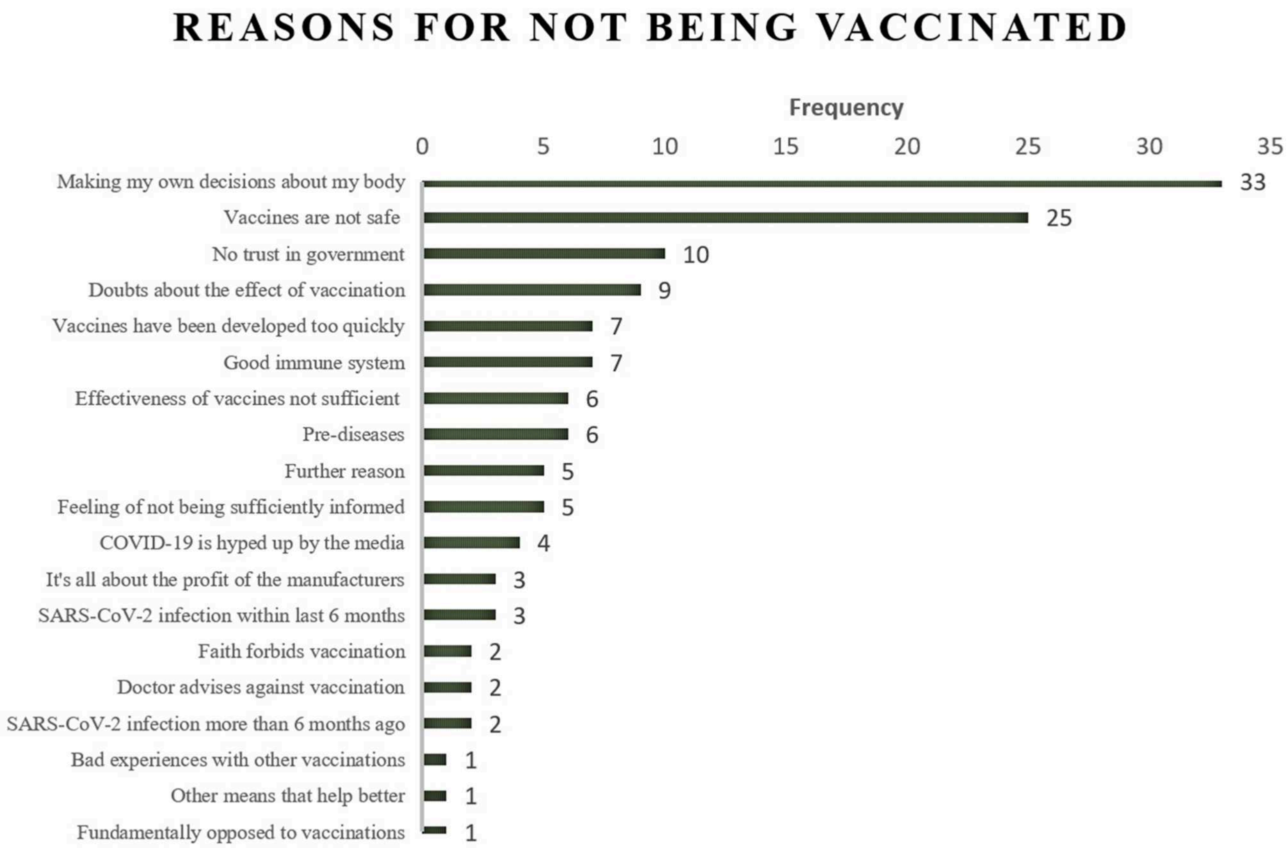

FIGURE 2
Most important reason for not being vaccinated against COVID-19 ($N = 132$). Not vaccinated respondents could state up to five reasons. Here the most important reason is displayed.

in the present study. Thus, future research should focus on these contradicting results by considering additional factors (e.g., risk perception and language barriers).

Apart from socioeconomic and sociodemographic factors, our study partly replicates results from previous surveys. Thus, it corresponds to previous findings [e.g., (15)] that people who belong to a COVID-19 risk group have a higher vaccination rate. This finding is not surprising, since those in a risk group have a high likelihood of a severe course of infection, hospitalization, and death. This raises the concern that people over 60 years of age are at higher risk of serious infection, due to older age and related comorbidity (40) alone. However, in this age group, there is a massive immunization gap of 1.9 million people in Germany [July 2022, (7)]. Although these people do not see themselves as being at risk, we cannot deny the objective risk of advanced age. Thus, it is important to address unvaccinated people in this risk group both by encouraging general practitioners to educate them individually and by launching public campaigns that inform older people about the immediate risks caused by an infection.

In contrast to belonging to a risk group, which seems to be a reliable factor for vaccination status and willingness, the results regarding respondents' own infection status and knowing someone who was or is infected are inconsistent [e.g., (11, 15)]. Future research should investigate this potential relationship in greater detail, for instance, by focusing on the role of the severity of the course taken by the disease, the impact of infection waves (Delta vs. Omicron variant), the number of subsequent infections, and the strength of social tie to the infected person.

Corresponding with the official COVID-19 statistics, people from East Germany are less likely to be vaccinated than those from West Germany (6). This finding depicts a new phenomenon and differs from the correlation between residence and other disease-related vaccinations (e.g., tetanus or diphtheria), which shows higher vaccination rates for East Germans than for West Germans (41). One explanation may be that in East Germany, there is widespread support of the right-wing populist party AfD (Alternative for Germany), which is skeptical of or refuses COVID-19 measures, such as wearing masks (42), a fact associated with a lower trust in public and state institutions. Thus, fostering trust in public institutions, debunking populist parties' false claims about the COVID-19 measures, and locally targeted health campaigns may help further increase the vaccination rate in the regions concerned.

Furthermore, trust in institutions shows the most significant correlation with vaccination status. A novel finding of our study is that the more people put trust in companies (e.g., food supply), the less likely they are to get vaccinated. One explanation might be that as part of the private sector in the free market, companies tend to symbolize a libertarian point of view, suggesting that the decision to get vaccinated is related to an individualistic, liberal attitude fostering vaccination. This means it is more a personal, private choice rather than a matter of public health. To resolve this association, private companies should be actively involved in a vaccination campaign to increase the percentage of the vaccinated population. Therefore, Dhama et al. (43) proposed a multisectoral approach, defined as an alliance between various agencies from the public and private sectors, to build long-lasting trust in vaccines. In Germany, more than 150 companies advertised a vaccination against COVID-19 together and, therefore, temporarily changed their branding [e.g., chocolate manufacturer Rittersport or supermarkets like LIDL; (44)]. Such strategies could be implemented more extensively to raise vaccination rates in the future.

In contrast to previous research [e.g., (17)], political views as measured on a left-right political scale have no significant relationship to vaccination status. This may be so because trust in public institutions eliminates that relationship. Thus, being politically right-wing decreases institutional trust, which, in turn, relates to being vaccinated negatively. Consequently, building trust in public institutions is more important to the objective of reaching a high vaccination rate, as the next section explains in further detail.

In line with previous research, trust in politics, in hospitals/rescue workers, and, above all, in medical experts and authorities (11, 16, 17, 45) increases the likelihood of getting vaccinated. It is evident that trust plays an important role in ensuring compliance with public health measures in general (45), is related to prevention measures, such as getting vaccinated, in particular, and thus constitutes a highly relevant resource that must be maintained by public institutions. For instance, to cope with a crisis and maintain trust, these institutions must have a stringent communication strategy, which was lacking during the pandemic in public perception (46) (p. 55). Hence, building trust in public health institutions is vital to the objective of increasing the overall vaccination rate. It could be achieved by clear, target-oriented, and effective communication addressing those not fully convinced by the vaccination yet.

As Yang and Huang (47) hold, health communication that combines high-quality information with a traditional communication style, e.g., through banners and posters, leads older people in particular to develop greater trust in science and health professionals. However, social media as a means of communication can decrease trust, demonstrating that the quick spread of misinformation on social media negatively influences people's opinions (48). Corroborating the findings of previous research [e.g., (45)], our study shows that those who get COVID-19 information from social and alternative media are less likely to be vaccinated. There is an especially high negative correlation to vaccination status for those who consume the alternative media on COVID-19 that spread on social media channels such as Telegram. This is due to the fact that fake news, scientific misinformation, and conspiracy theories about health risks are widely distributed through alternative media (49) and shared on social media such as Telegram (50), which then raises these media consumers' concerns about public health measures such as vaccinations. By contrast, our final model suggests that traditional media consumption has no impact on vaccination status. Given that social media consumption is likely to have a negative impact on vaccination status, it is advisable that content from traditional media be disseminated on social media. Although this is already partly the case, future studies should test the strategies for communicating traditional media on social media so as to generate the greatest possible benefit for reaching sufficiently high vaccination rates.

The implications of this study are 2-fold. First, countermeasures, such as online fact checks, marking false statements, and social and alternative media surveillance and regulations, should be increased to both debunk false claims about the COVID-19 vaccinations and alleged side effects and communicate clearly and openly with people who are hesitant to get a COVID-19 vaccine. For instance, Facebook uses tools to alert users that they have read a post containing incorrect information and to make these posts less visible (51). Second, since our study shows that trust in medical experts and authorities is most closely associated with a higher likelihood of getting vaccinated, relevant institutions should reclaim the high ground of COVID-19 coverage on social media to "turn around" the relationship between social media and vaccination status as shown in our results above.

RQ2: Trust in COVID-19 vaccines by vaccination status

Since we can assume that trust in vaccines is related to vaccination status, our second research question examines the difference of trust in the COVID-19 vaccines between vaccinated and unvaccinated individuals. Our results demonstrate that those who are vaccinated show higher trust in all vaccines, especially in mRNA-based vaccines, than those who are not vaccinated. This is because most people in Germany received mRNA-based vaccines (6) and so place the greatest trust in these vaccines in order to, for instance, reduce cognitive dissonance (52). In line with the rather negative media coverage (53), Astra-Zeneca is rated badly compared with other vaccines. Such a correlation is not a new phenomenon and can also be observed when persons are exposed to health media in mass media, decreasing patients' belief in the benefits of medication (54). This phenomenon also emerged for other vaccines, such as that against human papillomavirus (HPV) (55). Furthermore, people tend to place greater weight on negative media reports (56), which could lead to a more elevated risk perception of possible side effects and so to decreased trust.

The vaccines Novavax and Valneva, based on a "traditional" technology used for influenza vaccines, are often seen as an alternative for unvaccinated people, who trust these vaccines the most, and thus as a way to increase the vaccination rate (25). However, trust in these vaccines is still low and does not differ from other vaccines so much, which is also reflected in the fact that Novavax has not increased the demand for vaccinations significantly since its roll-out in February 2022 (57). According to the German Minister of Health, this might be due to fake news on social media claiming Novavax would cause cancerous tumors, among other things (58). Such claims spread faster than public vaccination campaigns for the use of Novavax. This demonstrates the need to implement a vaccination campaign for the other protein-based vaccine Valneva before its release so as to build trust long in advance and debunk false claims as soon as they start to spread even on a small scale.

Although the results of our survey demonstrate a relationship between trust and vaccination status, it remains unclear to what extent this trust is generated by knowledge about the vaccine and attitudes toward the manufacturer arising from brand awareness. Recapitulating the massive media presence of the manufacturers and the intensive coverage of side effects [e.g., Astra Zeneca; cerebral venous thrombosis (53)], it seems plausible that trust cannot be traced back solely to knowledge about the vaccines. Therefore, future studies should investigate factors (e.g., knowledge and brand awareness) that may explain the relationship between trust and vaccination status.

RQ3: The most important reason for not being vaccinated against COVID-19

Our last research question aims to identify the most important reason for not being vaccinated against COVID-19. Our analyses revealed that the first reason is the respondents' wish to make their own decisions about their bodies, followed by doubts about vaccine safety. This result partly contradicts research on people's reasons for refusing vaccination when vaccines were not available yet. These studies cited concerns about safety, side effects, and the vaccines' fast development as people's most prominent reasons against vaccination (27–29), demonstrating a move from "general" safety reasons to highly individual reasons concerning the conditions of one's own body. Moreover, a lack of trust in the government fully corresponds to previous research (16) and findings in this study on factors related to vaccination status as described above.

In other words, the issue at hand mainly concerns decisions about and control of one's own body, which is relatively difficult to address in public vaccination campaigns compared with the safety worries expressed in former studies. Our study reveals a more affective and very individual statement about the desire to keep full control of one's own body and the freedom to do so. Because public vaccination campaigns on traditional or social media platforms may fail to address that highly individual and ethical reason, a person who knows the other's specific body condition well enough is central: Therefore, general practitioners play a key role since doctors know their patients' body condition best, while patients "[...] are likely to establish trust with known health professionals, as their experience of that person increases" (59) (p. 2). Hence, healthcare providers' recommendations have a strong positive relationship to vaccination willingness [e.g., (60) for hepatitis B vaccination]. At the same time, studies have shown that healthcare practitioners' training is essential in treatment to counteract existing fears about vaccination by informing and involving patients in the process of decision-making. Doing so increases the adherence to medical recommendations [e.g., (61)]. Conversations with the general practitioner, called "second-tier" or informal support, are essential to making an informed decision about whether to get vaccinated (62) and are thus an effective element in increasing the vaccination rate against COVID-19. According to Bartoš et al. (63), while ~90% of medical doctors trust COVID-19 vaccines, most respondents from the general public believe that only half of the doctors trust the vaccines. Future vaccination campaigns should address this misconception by actively integrating medical doctors.

Limitations

Due to research and survey design, our study is subject to several methodological limitations. First, our data were generated using an online panel. Even though we aimed to fully represent the German population, our data are only online representative of sex, age groups from 18 to 74 years, and federal state. Moreover, our data did not gather specific groups, such as people younger than 18 years or older than 74 years or those with no online access at all, which is clear from the demographic differences between our sample and the actual German population in 2021 as shown in Table 1. Therefore, future studies should also conduct telephone (CATI) or personal interviews (CAPI), in order to minimize these restrictions. Furthermore, our study was designed as a cross-sectional survey to collect data. Consequently, interpretations of the data are linked to the time and location of data collection and are thus subject to a certain reactivity, since surveys concerning vaccination status depend on dynamic contextual factors. While the cross-sectional design prevents us from drawing other causal conclusions, repeating this survey using longitudinal data with the same sample could allow for more causal statements.

Conclusion

This study analyzes factors related to the COVID-19 vaccination status as well as trust in specific types of COVID-19 vaccines and the most important reason for not being vaccinated at a given point in time, when everybody has had the opportunity to receive a vaccine that protects them from a severe course of illness, long-term effects, or hospitalization caused by a viral infection. The study shows that it is vital, from a public health perspective, to address COVID-19 risk groups and lower income populations, elevate trust in different institutions and newly developed vaccines in advance, establish a multisectoral approach, and implement campaigns to debunk misinformation. However, unvaccinated people's lack of trust in all COVID-19 vaccines, along with the most prominent reason cited against vaccination of wanting to make one's own decisions for one's body, suggests that general practitioners should be involved in an effective vaccination campaign, while scientific predictions of rising infection numbers (64) and future virus variants should play a role in developing efficient and effective vaccination campaigns for adapted vaccines in the future.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

Author contributions

Conceptualization, methodology, formal analysis, investigation, writing the original draft preparation, and visualization: SS and DS. Software and data curation: SS. Validation and writing–reviewing and editing: SS, DS, NL, and LG. Resources, supervision, project administration, and funding acquisition: LG. All authors have read and agreed to the published version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Vaccine hesitancy and post-vaccination adherence to safety measures: A mixed-method study

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Background: Despite being recognized as one of the most successful public health measures, vaccination is still considered to be unnecessary and unreliable in the context of the COVID-19 pandemic. The current study utilized a two-pronged approach in analyzing vaccine hesitancy and health behaviors after vaccination by employing a mixed-method design. Phase 1 was aimed at identifying predictors of COVID-19 vaccine hesitancy and acceptance among the Pakistani population using protection motivation theory (PMT), whereas Phase 2 was aimed at exploring the factors related to the vaccination of COVID-19.

Method: A convenient sample of 1,736 individuals from the vaccine-eligible population (12 years and above) was selected to collect data on vaccine hesitancy and acceptance (Phase 1). Phase 2 of the study explored post-vaccination health behaviors, especially adherence to safety measures for COVID-19, through 23 in-depth interviews with the vaccinated population.

Results: Multiple regression analyses showed that response cost is a major predictor of vaccine hesitancy (in Phase 1). In terms of the role of demographic variables, the results showed that being male (for severity: $B = -0.481$; threat appraisal: $B = -0.737$), old age ($B = -0.044$), not vaccinated, and not infected with COVID-19 (themselves and family members) are strongly associated with vaccination hesitancy. Results of thematic analysis in Phase 2 revealed that perceived individual experience and insensitivity toward the severity of the disease are strongly associated with a lack of adherence to safety measures of COVID-19. Faith and religious beliefs and reliance on traditional remedies are also key predictors of people's general non-compliance to health behaviors. One interesting aspect that was revealed in the analysis was the general financially and socially destabilized situation in the context of developing countries that contributed to general apathy in the pandemic situation.

Conclusion: The findings of the current study may help in devising a health model for the public from the developing world to deal with future pandemic situations.

KEYWORDS

COVID-19, vaccine hesitancy, protection motivation theory, vaccination behavior, safety measures, Pakistan

1. Introduction

Vaccine hesitancy refers to the delay of acceptance or complete refusal of vaccine administration despite its free-of-cost availability to the public (1). People who hesitate to take vaccines are a heterogeneous group of individuals who usually fall on the continuum of complete acceptance and rejection which means they can refuse some vaccines and may accept few others (2). Therefore, the concept of vaccine hesitancy is multi-dimensional because its determinants are context-specific, which varies across time, place, and type of vaccines, influenced by socioeconomic (3), political, religiocultural, and scientific reasons (4), and increase the complexity of the decision-making about rejection or acceptance of vaccines (1). The determinants of vaccine hesitancy include confidence, complacency, and convenience toward vaccination (1). The contextual factor of hesitancy toward any vaccination program is also determined by historical, personal, and sociocultural factors; confidence in the country's health system; and risk/benefits attached to the vaccine (5). Education (6), poor communication (7), gender, minority groups, socioeconomic status, and information-seeking pattern (8) all impact confidence on vaccines and, conversely, hesitancy.

The World Health Organization (WHO) mentioned vaccine hesitancy as one of the top 10 threats to global health (9). The global research on coronavirus disease 2019 (COVID-19) vaccine hesitancy also showed mixed evidence of acceptance and reluctance rates. For example, this vaccination drive faced issues in the acceptability, reluctance, and hesitancy in different populations, such as in Portugal (10), Indonesia (11, 12), China (13–15), India (16), the United Kingdom, Ireland (17), and Italy (18). Psychological constructs of personality, altruism, religiosity, and internal locus of control were also essential indicators of COVID-19 vaccine hesitancy in the UK and Irish populations (19). On the contrary, in the Japanese population, people of older age groups, people living in rural areas, people with some medical conditions, and men showed more acceptance toward the COVID-19 vaccine (20). Vaccine literacy also contributes to building positive attitudes toward vaccine acceptance. An adequately informed public has reduced anxiety, improved behavior, and reduced disease transmission of COVID-19 (21). Similarly, vaccine efficacy is also an important indicator of hesitancy or acceptance of the COVID-19 vaccine in Southeast Asian countries (11). During the peak of the pandemic period, people were more favorable toward vaccine acceptance (22). Therefore, many factors influence people's attitudes toward approving or rejecting vaccines, especially COVID-19, in different socioeconomic, geographical, and demographic variables.

1.1. Pakistani context of vaccine hesitancy and adherence to safety

Pakistan has a history of reluctance toward all vaccines, and a prominent example of this attitude shows the plight of polio vaccination in the country (23). Several vaccines available for children in the Expanded Program on Immunization (EPI) showed a fall in the acceptance rate in Pakistan between 2015 and 2019 (8). Confidence fell in the importance, safety, and effectiveness of vaccines. Confidence was the strongest indicator of vaccine hesitancy compared to safety or efficacy, and religious beliefs also played an important role (8). The case of COVID-19 vaccination shows similar trends. In Pakistan, conspiracy beliefs, acceptability, preference, and willingness to pay are common factors for COVID-19 vaccine hesitancy (24). Yasmin et al. (25) also reported that more than half of the participants in her study were unsure of the safety (50%) and efficacy (51%) of the COVID-19 vaccine, whereas 42% were concerned about its side effects and 72% of the respondents planned to get vaccinated, whereas 28% refused to do so. Similarly, a meta-analysis of eight studies by Khalid et al. (26), including Arshad's and Yasmin's studies, reported that conspiracy beliefs, vaccine availability, healthcare system, religious matters, vaccine literacy, side effects, perceived fear, and natural immunity philosophy served as vaccine hesitancy indicators in Pakistan. Although a few of these studies included larger populations with diverse demographical backgrounds for generalizing the results of COVID-19 vaccine hesitancy, safety, and effectiveness in Pakistan, they only focused on quantitative data sets. However, no study to date has focused on post-vaccination adherence to safety measures. Therefore, this article aimed to fill the gap by focusing on larger quantitative data to measure vaccine hesitancy and also aimed to obtain in-depth information from respondents using a qualitative approach through in-depth interviews for post-vaccination adherence and safety of individuals. Thus, the generalization of the results could be performed with a certain confidence by converging the findings of both qualitative and quantitative data.

1.2. Protection motivation theory

Current research utilized the model of protection motivation theory (PMT). It is a widely used model in the health sector to understand and reflect on the attitudes and practices that motivate an individual toward performing protective behaviors. Rogers developed PMT in 1975 and it focuses on people's attitudes and behaviors in fear-instigating situations. According to this theory, threat appraisal and coping appraisal are two main components that describe a person's attitude toward fear-instigating situations. Threat appraisal is further explained with the help of four constructs: severity of the threat, vulnerability toward that threat, internal reward, and external reward. Coping appraisal comprises self-efficacy, response efficacy, and response cost. The theory explains that factors of severity, vulnerability, reward, self-efficacy, and response efficacy are associated with adaptive behaviors while response cost is related to maladaptive behaviors (27, 28). PMT has been tested in more than 30,000 studies. Applied in the context of the COVID-19 pandemic, Okuhara et al. (29) showed that perceived severity and self-efficacy significantly correlated with staying-at-home behavior during the first wave of the pandemic in Japan. Farooq et al. (30) also concluded that perceived severity and self-efficacy significantly correlated with the intention to self-isolate, but response cost negatively affected this intention. Literature on PMT application on vaccination behaviors reported by Linga et al. (31)

predicted intention to get vaccinated against seasonal influenza in the United States. The PMT's significant predictors of getting vaccinated were perceived severity, vulnerability, self-efficacy, and response efficacy. Evidence of the applicability of PMT on COVID-19 vaccine hesitancy is scarce. Only a few studies have reported the COVID-19 vaccine hesitancy protection motivation theory. Results showed that severity, self-efficacy, response efficacy, and response cost emerged as significant predictors of COVID-19 vaccine acceptance/hesitancy (32). Further evidence is needed to validate the application of PMT constructs to explain COVID-19 vaccine hesitancy and post-vaccination adherence to safety measures.

These studies have also not focused on psychological constructs influencing reluctance or acceptance toward COVID-19 vaccination. Post-vaccination safety behaviors are also not the focus of research based on vaccine hesitancy. Therefore, the present research is conceptualized with two main objectives. The first objective was *to assess the predictive role of PMT constructs in COVID-19 vaccine hesitancy* and the second objective was *to understand the factors involved in adapting safety behaviors after vaccination.* A mixed-method approach was utilized to achieve these objectives. This approach helped to uncover the social and personal realities through multiple lenses (11, 12). Current research employed the convergence method of the mixed-method approach, which is used when there is a need to understand the research problem by employing both quantitative and qualitative approaches simultaneously (33, 34). This would help in drawing a clear picture of factors associated with vaccine hesitancy and adherence to safety behaviors in the Pakistani context.

2. Methods

2.1. Sample

For the quantitative part, the sample consisted of 1,736 (58.9% female subjects and 41.1% male subjects) individuals from the vaccine-eligible population [12 years and above, as per criteria of the National Command and Operation Centre (35)] with a mean age of 29 years, mostly unmarried (63.4%), and having an undergraduate education (62.4%) to the criteria. The sample size was calculated using Krejcie and Morgan (36) formula, s = X2NP (1-P) ÷ d2(N1)+X2P(1-P), where s = required sample size, X2 = the table value of chi-square for 1 degree of freedom at the desired confidence level (3.841), N = the population size, and P = the population proportion. Using this formula, Krejcie and Morgan (36) suggested that for any number of populations over 20,000, a sample size of 384 is sufficient. We have used this approach as the minimum criteria for the required sample size calculation. The sample was selected using the convenience-sampling technique. Most of the sample was vaccinated with at least with one dose (89.6%), never contracted the disease (75.3%), and had close relatives getting infected with COVID-19 (66.4%).

For the qualitative study, the sample consisted of 23 individuals (47.8% female subjects and 52% male subjects) with ages ranging from 13 to 59 years (M = 35.52, SD = 14.14 years). Sampling was performed using a purposive sampling technique in which participants were selected based on vaccination status and willingness to provide data. For further sample characteristics, see Tables 1, 2.

2.2. Instrument

For the quantitative part, a self-generated questionnaire was used for this cross-sectional research. The questionnaire was developed and validated (37) in the national language of Pakistan, Urdu, to reduce the language barrier (see Table 3). Therefore, everyone, including those who do not have a strong educational background, can understand and fill out the questionnaire without any difficulty. The comprehensive procedure of scale development was followed to generate the scale involving problem identification, literature review, item generation, expert review, pilot testing, and final scale. The reliability of the scale was within the acceptable range (0.71–0.89). To assess face validity, subject experts were asked to review the items and gauge their suitability and clarity for measuring the variable of interest.

For the qualitative part, semi-structured interviews were conducted to collect the data. This technique of interviews is useful in exploring the meaning behind respondents' experiences through open-ended questions. The interview guide was developed based on the conceptual framework, literature review, and research questions. The interview guide comprised open-ended questions based on the subjective experiences of the respondents. The questions of the interview protocols are as follows:

1. What are the factors that influence your attitude toward safety behaviors?
2. In your opinion, what is the importance of getting a vaccine against COVID-19?
3. Have you been voluntarily vaccinated or forcefully?
4. In your opinion, what are the chances of being re-infected with COVID-19 after vaccination?
5. How much are you aware of the safety behaviors and standard operating procedures (SOPs) to prevent COVID-19 infection?
6. Is it necessary to wear masks, wash hands regularly, and maintain social distancing even after vaccination?
7. Do you wear masks, wash hands regularly, and maintain social distancing even after vaccination?
8. What are the factors that influence your attitude toward safety behaviors?

The researchers also used different probes, such as *"Please elaborate[sic] this point"* and "*Can you explain this further*" to give respondents a chance to fully explain their views.

2.3. Procedure and data collection

The data for the quantitative part were collected using the survey method. A total of 2,500 questionnaires were distributed, out of which 1,736 participants responded. The return rate was 69.4%. The consent form, in Urdu, was also distributed along with the questionnaire to obtain the consent of participants for the research. Furthermore, the questionnaire was also forwarded online by generating a link in Google Forms. The link was distributed on different social media platforms, i.e., Facebook, WhatsApp, LinkedIn, and Instagram. However, the focus was kept on collecting data in person to avoid false or untrue responses. Nonetheless, the majority of the data was collected in hard copy.

TABLE 1 Sample characteristics ($N = 1,736$).

Characteristics	M(SD)/f (%)	Characteristics	M(SD)/f (%)
Age	29.00 (12.16)	**Education level**	
Gender	Below 12 years	492 (18.3)	
Male	713 (41.1)	13–16 years	1,083 (62.4)
Female	1,023 (58.9)	Above 16 years	161 (9.3)
Marital status		**Current work status**	
Unmarried	1,104 (63.4)	Employed	489 (28.2)
Married	585 (33.7)	Student	911 (52.5)
Divorced/widowed	47 (2.7)	Unemployed	117 (6.7)
Region		Retired	44 (2.5)
Punjab	935 (53.9)	Housewife	175 (10.1)
Sindh	45 (2.6)	**Average family income**	
Balochistan	24 (1.4)	Below Rs. 30,000	302 (17.4)
Khyber Pakhtunkhwa	135 (7.8)	Between Rs.30,000–50,000	473 (27.2)
Gilgit Baltistan	37 (2.1)	More than Rs. 50,000	961 (55.4)
Islamabad Capital Territory	447 (25.7)	**Area of residence**	
Azad Jammu and Kashmir	113 (6.5)	Urban	1,396 (80.4)
		Rural	340 (19.6)
Chronic illness		**Psychological illness**	
Yes	90 (5.2)	Yes	62 (3.6)
No	1,646 (94.8)	No	1,674 (96.4)

F, Frequency; %, Percentage, M; Mean; SD, Standard Deviation.

For the qualitative part, we conducted a qualitative study using a phenomenological approach to evaluate the factors related to COVID-19 safety behaviors. This approach aims to focus on the similar characteristics and personal experiences of the respondents (38). This method is useful for in-depth analysis of factors associated with adherence to safety behaviors to prevent COVID-19 infection. Thematic analysis was used to analyze the data. The reported results followed the Consolidated Criteria for Reporting Qualitative Study (COREQ) checklist. A total of 33 participants were interviewed. The consent form was used to receive data from only those participants who were genuinely willing to participate in this study. Participants were approached by personal and social contacts. Rapport and regular contact were built *via* communication. The average duration of an interview lasted from 20 to 25 min based on the convenience and answers of the respondent. Interviews were recorded with the participant's consent for in-depth analysis.

2.4. Analysis scheme

Statistical Package for the Social Sciences, IBM SPSS (Version 23), was used to analyze quantitative data in Phase 1. The statistical procedures that were applied included descriptive statistics, frequencies, mean, reliability analysis, and regression analysis, which are reported in tables. The data acquired through interviews were transcribed. Themes were sorted and proposed inductively without using the pre-existing coding framework as guided by Braun and Clarke (39). Braun and Clarke's (39) six phases were followed for thematic analysis: (1) Initially, the potential themes were identified by re-reading the data from transcriptions and familiarizing with it. (2) The codes were reviewed to retain the themes that were representative of diverse factors to include subthemes. The research questions helped to select the relevant themes for analysis. (3) Theme-relevant quotes were identified. (4) Themes were reviewed again to verify the relevance and representation of the data, leading to a thematic map. (5) Then, the themes were reviewed to define and name them. (6) The write-up was carried out verbatim with themes and sub-themes. This method helped to explore in-depth factors associated with compliance and non-compliance to safety behaviors related to COVID-19 infection.

The reliability of the process was assured by making the research procedure transparent by reporting data collection to data analysis step-by-step. The second and third authors rechecked the generated codes with consensus indicating the good status of the codes. To address conformability, i.e., objectivity, all data were audio-to-text transcribed and analyzed with insightful discussions with all authors to minimize subjectivity and cater

TABLE 2 Participants characteristics in Phase 2 ($N = 23$).

Characteristics	M (SD)/f (%)
Age	35.52 (14.14)
Gender	
Male	12 (52.17)
Female	11 (47.83)
Marital status	
Unmarried	10 (43.48)
Married	13 (56.52)
Education level	
Below 12 years	03 (13.04)
13–16 years	14 (60.87)
Above 16 years	06 (26.09)
Current work status	
Employed	14 (60.87)
Student	07 (30.43)
Housewife	02 (8.70)
Vaccination status	
Completely vaccinated	10 (43.48)
Partially vaccinated	12 (52.17)
Vaccinated with booster shots	01 (4.35)
COVID_19 infection history	
Infected once	18 (78.26)
Infected twice	01 (4.35)
Never infected	04 (17.39)

f, Frequency; %, Percentage; M, Mean; SD, Standard deviation.

TABLE 3 Items of the protection motivation theory.

Constructs	Items
Severity	COVID-19 is a deadly disease
	Getting infected with COVID-19 can result in serious health issues
	One can possibly die from COVID-19
Vulnerability	I am at a constant risk of getting infected with COVID-19
	I am worried about getting infected with COVID-19
	The chances of me getting infected with COVID-19 are higher without getting vaccinated
Rewards	It is important for me to get myself vaccinated against COVID-19
	I can travel around freely after getting vaccinated against COVID-19
	Contracting COVID-19 would be a less of worry for me after getting vaccinated
	I want to get vaccinated because it's free of cost
	It is my social responsibility to get vaccinated against COVID-19
Self-efficacy	It is easy to get vaccinated against COVID-19
	I can choose to get vaccinated against COVID-19 at will
Response efficacy	Getting vaccinated can reduce the risk of getting infected with COVID-19
	Getting vaccinated can help prevent the spread of COVID-19
	Vaccine is the only effective option to prevent oneself from serious effects of COVID-19
Response cost	Getting vaccinated against COVID-19 can cause side effects
	It is time consuming to get vaccinated against COVID-19
	It is painful to get vaccinated against COVID-19

to the researchers' reflexivity. Transferability was addressed by gathering a plethora of data and presenting parsimoniously in the Results and Discussion.

2.5. Ethical considerations

Informed consent from the participants was taken. The respondents of the study were informed about the anonymity and confidentiality of their information and the correct use of the information obtained through this survey. The participant's right to privacy was also protected. The participants of the study were first elaborated on the purpose of the study to give them insight into the rationale of the research. They were given the right to withdraw from this study at any time. Moreover, enough time was given to participants to respond to each question after carefully understanding the context of the statement written and recording their true responses. The participants were not harmed in any way or form. The biases on the researcher's end were avoided and there was no discrimination made whatsoever while collecting data for this research. In addition, there was no modification of the data collected and only the responses given by participants were used to make further inferences. The study was conducted in accordance with the Declaration of Helsinki. As part of the regular ethical procedures, the study design and data collection procedures were evaluated against the Ethical Decision Tree and approved by the Local Ethics Committee of COMSATS University Islamabad, Pakistan.

3. Results

The present study was conceptualized into two phases.

3.1. Results of Phase 1

A sample of 1,736 individuals from the vaccine-eligible population (12 years and above) was selected using the convenience-sampling technique from all over Pakistan. The demographic characteristics and COVID-19-related information of the respondents are presented in Table 4. The mean age was 29.00 years (SD = 12.16), 58.9% were female, and 50% of the respondents were students. A total of 75% of respondents were not

TABLE 4 COVID-19 vaccine-related sample characteristics ($N = 1,736$).

COVID-19 related characteristics	Yes [f (%)]	No [f (%)]
Have you ever been infected with COVID-19?	428 (24.7)	1,308 (75.3)
Family member infected with COVID-19?	744 (42.9)	992 (57.1)
Closed relative infected with COVID-19?	1,152 (66.4)	584 (33.6)
Vaccinated against COVID-19	1,555 (89.6)	181 (10.4)
In favor of getting younger children/siblings vaccinated against COVID-19	1,361 (78.4)	375 (21.6)
In favor of getting vaccinated against other diseases	1,518 (87.4)	218 (12.6)

F, Frequency; %, Percentage.

affected by COVID-19 and almost 90% received the vaccination. Most (78.4%) of the respondents were in favor of getting their younger children/siblings vaccinated against COVID-19 (78.4%), whereas 87.4% were in favor of getting vaccinated against other diseases too.

Tables 5–7 reported the results of the multivariable linear regression analyses (stepwise) and examined the independent association of several determinants and the outcomes of interest. In terms of demographic variables as determinants of vaccine hesitancy, the results showed that being male, old age, not vaccinated, and not infected with COVID-19 (themselves and family members) are strongly associated with vaccination hesitancy. Individuals who received the vaccination and were infected with COVID-19 (themselves, family members, and relatives) are considered more vulnerable to the severity of the threat and are more positive toward vaccination.

3.2. Results of Phase 2

For the qualitative part, 23 in-depth interviews were conducted with vaccinated and partially vaccinated individuals from the vaccine-eligible population (12 years and above). The mean age was 35.52 years, 47.8% were female subjects and 52.2% were male subjects, and most were partially vaccinated and affected by COVID-19 infection. From interviews, protocols following major themes were generated.

3.2.1. Lack of knowledge and negative attitudes toward the COVID-19 vaccine

Most of the respondents had a vague and incorrect understanding of how a vaccine functions. According to respondent 1, "*It is important for [sic]lethal virus,[sic] because it is vital not only to keep yourself safe from this, it is also important to keep your family members and surrounding safe.*" Similarly, respondents 2 and 4 stated, "*A vaccine stops the infection in a body and the person won't be harmful anymore.*" Few of them had perceived the effectiveness of vaccine functioning due to their positive or negative post-vaccination experience along with the observation of the vaccine. Respondent 9 stated "*vaccine has no importance as I got the disease even after getting first shot.*" Respondent 14 had similar views saying, "*Vaccine has no as such importance and no vaccine has been invented which is[sic] specifically boost immunity against COVID. However, there is no harm in getting vaccinated.*" Inquiring about their attitude toward vaccination, most of the respondents reported to be forcefully vaccinated and had anti-vaccination attitudes. According to respondent 1, "*I got vaccinated against my will keeping in view the government restrictions.*" Respondent 10 said, "*I got [sic]vaccine shot due to the restriction on entry in[sic] the university without [sic]vaccine card but I am afraid that I[sic] will be bad for my health.*"

3.2.2. Religious beliefs regarding safety behaviors

One of the major causes of non-compliance toward safety behaviors is the religious perception regarding these safety behaviors. As one of the respondents reported, "*It is the will of God that decides whether I live or die, not wearing a mask or keeping [sic]distance from people.*" One of the factors that developed a negative attitude toward these safety behaviors is the restriction on large-scale religious gatherings, especially in the holy month of fasting. One of the respondents said, "*How will people refrain from going to mosques and not offer the evening prayers in Ramazan which is essential before fasting.*"

3.2.3. Fluctuating rates of infections between COVID-19 waves

The compliance to the safety measures (e.g., SOPs) was higher when mortality rate and reported cases of COVID-19 increased. Pakistan had observed four waves of COVID-19 infection where a sharp rise and decline in infection rates had been observed. The data reflect that compliance with safety behaviors correlates with fluctuating rates of reported COVID-19 cases. As one respondent said, "*I usually strictly follow safety behaviors like mask wearing and social distancing when COVID infection rates gets[sic] high or the death rate [sic]are reported to get higher. I feel this is the right attitude since you can't[sic] follow SOPs forever.*" Another respondent reported that "*Logically it is not possible to follow safety behaviors all the time. So, I just look at the situation of [sic]infection rate and adjust my behaviors accordingly. Even authorities also relax restrictions when COVID infection rates decreases[sic].*"

3.2.4. Discomfort due to harsh climate conditions

The findings revealed that safety behaviors, especially wearing masks, are not followed because of discomfort and suffocation due to harsh climate conditions. Pakistan has long and harsh summers in which the temperature increases up to 45–47°C in most of the areas of the country. In such environmental conditions, wearing a mask, which is considered to be mandatory safety behavior in public during the pandemic situation, is a challenge. The data revealed similar findings as respondents mostly complained about

TABLE 5 Multiple linear regression analysis of determinants and the outcomes of interest ($N = 1,736$).

Variables	Response cost				
	Model 1	Model 2	Model 3	95% CI	
	B	B	B	LL	UL
(Constant)	9.414	9.553	9.522	9.104	9.941
Vaccinated	−1.234	−1.195	−1.199	−1.630	−0.767
Family_Member_Infected_with_COVID-19		−0.403	−0.587	−0.887	−0.286
Infected_With_COVID-19			0.454	0.109	0.799
R^2	0.018	0.023	0.027		
F	31.289***	20.107***	15.671***		
ΔR^2		0.005	0.004		
ΔF		8.785	6.667		
Variables	**Severity**				
	Model 1	Model 2	Model 3	95% CI	
	B	B	B	LL	UL
(Constant)	11.824	10.756	10.979	10.541	11.418
Closed_Relative_Infected_With_COVID-19	0.904	0.859	0.805	0.536	1.075
Vaccinated		1.224	1.236	0.822	1.650
Gender (ref. male)			−0.481	−0.739	−0.222
R^2	0.024	0.043	0.050		
F	42.787***	38.472***	30.267***		
ΔR^2		0.018	0.007		
ΔF		33.358	13.312		
Variables	**Self-efficacy**				
	Model 1	Model 2	Model 3	95% CI	
	B	B	B	LL	UL
(Constant)	7.149	7.797	7.542	7.182	7.901
Vaccinated	1.022	1.033	0.997	0.711	1.283
Age		−0.023	−0.022	−0.029	−0.015
Closed_Relative_Infected_With_COVID_19			0.404	0.219	0.589
R^2	0.027	0.048	0.058		
F	47.693***	43.312***	35.254***		
ΔR^2		0.021	0.010		
ΔF		37.915***	18.274***		

***$p < 0.001$.

similar issues. One of the respondents said "*most people feel suffocated due to wearing masks, especially being students when we are in classrooms full of students, in such an extreme weather we can't[sic] wear masks as practically it is not possible.*" Another respondent reported "*how can we wear masks in [sic]summer time, I feel suffocated.*" One respondent acknowledged, "*mask wearing is the most important safety behavior but practical situations are also there. May be government and pharmaceutical companies should look into manufacturing masks which are according to harsh climates.*"

3.2.5. Lack of strict government regulations

Data show that the lack of strict government regulations is one of the major factors behind the lack of adherence to safety behaviors against the COVID-19 pandemic. A respondent reported, "*But generally in daily life I don't follow safety behaviors like wearing mask[sic] in public place[sic] due to the fact that the authorities don't[sic] care. For example, if you are entering a mall, the officials just check at the entrance if you are wearing a mask or not. Once you are inside, nobody cares. So there is no point in following these safety*

TABLE 6 Multiple linear regression analysis of determinants and the outcomes of interest ($N = 1,736$).

	Threat appraisal					
	Model 1	Model 2	Model 3	Model 4	95% CI	
Variables	B	B	B	B	LL	UL
(Constant)	36.552	35.393	35.355	35.697	34.454	36.939
Vaccinated	4.694	4.522	4.464	4.483	3.308	5.657
Closed_Relative_Infected_With_COVID-19		1.980	1.373	1.300	0.419	2.182
Family_Member_Infected_With_COVID-19			1.149	1.130	0.291	1.970
Gender (ref. male)				−0.737	−1.469	−0.004
R^2	0.034	0.048	0.052	0.054		
F	60.547***	43.729***	31.656***	24.755***		
ΔR^2		0.014	0.004	0.002		
ΔF		26.547	7.197	3.893		
	Vulnerability					
	Model 1	Model 2	Model 3	Model 4	95% CI	
Variables	B	B	B	B	LL	UL
(Constant)	9.260	8.953	8.923	8.488	8.032	8.945
Family_Member_Infected_With_COVID-19	0.978	0.653	0.456	0.444	0.095	0.793
Closed_Relative_Infected_With_COVID-19		0.672	0.656	0.645	0.309	0.980
Infected_With_COVID-19			0.508	0.505	0.148	0.863
Vaccinated				0.500	0.052	0.948
R^2	0.026	0.035	0.040	0.042		
F	47.614***	31.702***	23.793***	19.082***		
ΔR^2		0.009	0.004	0.003		
ΔF		15.394	7.730	4.794		

measures." Another respondent said, *"I have seen officials at airports, banks, and malls taking bribes for letting people enter without masks."* It is also highlighted in the data that in countries where strict rules were applied by the government to follow COVID-19 safety behaviors, people tend to show more adherence to safety measures willingly. One respondent said, *"I had been to a foreign country for some time during this pandemic period when travel restrictions were lifted and I had observed that there were very strict rules and implications of not following safety behaviors in public places. This shows that governments in those countries were very serious regarding [sic]COVID situation. Whereas, in Pakistan, government actions convey a non-serious attitude toward[sic] this grave health emergency. For example, during the 1st year of COVID in 2020, [sic]government relaxed shopping restrictions before [sic]Eid festival. This was insane."*

3.2.6. Social pressures toward non-compliance with safety behaviors

Another important factor that is found to be associated with adherence to safety behaviors to prevent COVID-19 infection is social pressure. It was observed that people who follow safety behaviors experience negative feedback from relatives, friends, and coworkers. Comments such as *"You are being [sic]coward"* and *"It's[sic] going to affect you more if you wear [sic]mask all the time"* reflect a discouraging attitude toward people who willingly follow safety behaviors to prevent the spread of the disease. It is also reported that following safety behaviors is considered a lack of faith in God. One of the respondents reported, *"My coworker said to me that you don't[sic] have faith in Allah and you trust these masks more."* Another respondent said *"I keep myself clean by doing wazoo before prayers five times a day. This keeps me safe from COVID. I don't[sic] need these sanitizers as this is merely a[sic] propaganda to increase [sic]sale of these products."* The most prominent aspect was social distancing in mosques during prayer times. Their peers ridiculed people who willingly offered prayers at home. One of the respondents said, *"My neighbors questioned my stance of not going to mosque due to COVID restrictions and said that this is against religion. I then started going to [sic]mosque to offer my prayers."* These accounts clearly point to the fact that social pressure is a major contributing factor toward non-compliance to safety behaviors among people.

TABLE 7 Multiple linear regression analysis of determinants and the outcomes of interest.

Variables	Model 1	Model 2	95% CI	
	Copping appraisal			
	B	B	LL	UL
(Constant)	26.315	27.574	26.759	28.389
Vaccinated	1.799	1.820	1.134	2.506
Age		−0.044	−0.061	−0.027
R^2	0.015	0.029		
F	26.089***	25.768***		
ΔR^2		0.014		
ΔF		25.084		
	Response efficacy			
Variables	Model 1	Model 2	95% CI	
	B	B	LL	UL
(Constant)	9.751	10.322	9.806	10.839
Vaccinated	2.011	2.020	1.585	2.455
Age		−0.020	−0.031	−0.009
R^2	0.045	0.052		
F	81.768***	47.596***		
ΔR^2		0.007		
ΔF		12.864		

4. Discussion

The adverse effects of the COVID-19 pandemic continue all over the world for the past 3 years. Although many vaccines have been developed to immunize people against the virus, the threat of this serious disease still lingers (40, 41). The current study was aimed at identifying the determinants of COVID-19 vaccine hesitancy and acceptance among the general population of Pakistan along with analyzing the awareness levels of vaccine effectiveness leading to SOP adherence after vaccination. The population of the study included those who were eligible to get vaccinated against COVID-19 at the time of the research, including the general population aged 12 years and above. The primary data were collected using a self-generated scale under the framework of protection motivation theory (PMT) and in-depth interviews.

In Pakistan, generally, people have COVID-19 vaccine hesitancy as there is a prevalence of mistrust in vaccines along with the belief in conspiracy theories about the vaccine. Social media, a widely available source of information, has played a role in spreading false information regarding COVID-19 (42). Narratives such as the vaccine damaging or changing the DNA of individuals has also been prevalent. Another narrative claims that the vaccine will result in the person getting affected with coronavirus rather than making a person immune to it. Besides, religious scholars have played their role in making people fearful of the vaccine and believing it will sterilize all Muslims along with other adverse side effects. These narratives are giving birth to many doubts about the safety and efficacy of the COVID-19 vaccine (43), subsequently leading to low confidence in the vaccine (1). Research highlights the low-level acceptance of the COVID-19 vaccine in many countries in Europe, Africa, and the Middle East (44) due to safety concerns and risks associated with the newly developed vaccine (45, 46). Similar results have reported that vaccine hesitancy has affected COVID-19 vaccination programs worldwide (22).

Gender, age, vaccination status, self-infection, and experience of family members' infection are the strongest predictors of vaccination hesitancy and acceptance in the current study. Elderly male participants are more reluctant whereas a positive attitude toward vaccination can be seen in female participants. Female participants, who either had COVID-19 infection or not, followed SOPs and had a favorable attitude to get vaccinated. The literature highlights that vaccine acceptance is positively associated with COVID-19 knowledge, worry/fear regarding COVID-19, higher income, younger age, and testing negative for COVID-19, whereas females and chronic illness are associated with a low rate of vaccine acceptance (47, 48). Another study highlights that females are associated with vaccine acceptance in countries such as Germany, Russia, France, and Sweden (49). The difference in findings could be impacted by several sociocultural factors. The first important finding is that most of the respondents had vague ideas about how a vaccine functions. People's knowledge, attitudes, and habits on any health behaviors are heavily influenced by their sources of information. A large proportion of respondents with higher educational levels acquired knowledge about COVID-19 from media such as TV and radio, as well as from the internet, which is consistent with previous research (50). Many scientists determined that the vaccine's effectiveness reduced with age, producing lower total body immune responses in persons aged 65 to 85 years than those aged 18 to 55 years (51).

Vaccine hesitancy is associated with a lack of trust in the vaccine's efficacy and safety, as well as unavailability of vaccination and carelessness (52). Few of the study participants had perceived the effectiveness of vaccine functioning due to their positive or negative post-vaccination experience along with the observation of the vaccine, which is coherent with another study carried out by Piraveenan et al. (53). Many religious groups, including Protestants, Catholics, Jews, Muslims, Christians, Amish, Hindus, and Sikhs, have religious reasons for their vaccine apprehension. The biggest hurdle observed in Muslim populations was the presence of porcine or non-halal substances in vaccines (54). Religious organizations were seen as conduits for the spread of false information regarding COVID-19, thus instilling distrust in health professionals and healthcare activities among religious adherents (55). Furthermore, religious meetings and rituals were responsible for the transmission of the coronavirus in other cases because religious devotees disobeyed social distancing instructions (56). According to Waris et al. (57), religious beliefs have been linked to varying degrees of compliance with COVID-19 preventive measures. One cause for this disparity could be the intensity with which religious traditions are followed.

It is necessary to evaluate the state of knowledge, beliefs, and preventive behaviors related to SOP adherence in the post-COVID-19 period, as well as to identify factors impacting post-vaccination preventive practices (58). Therefore, this research focuses on the predictors of SOP adherence post-vaccination. Fear of COVID-19 leads to people adhering to SOPs. Considering the results of the study and according to participants' responses on their knowledge, attitudes, and behaviors, there are some predictors identified that add to the lack of SOP adherence post-vaccination. Among the factors revealed, "lack of sense of fear" is one of the major predictors of reduced SOP adherence after vaccination. It leads them to feel safe from getting COVID-19. Consequently, they do not adhere to SOPs. According to research studies, the COVID-19 vaccine lowers worry as well as anxiety about becoming infected by COVID-19 (59).

Another identified predictor of lack of SOP adherence among the population is "public confidence" reported by the respondents about being protected after receiving one vaccine. In addition to this, participants do not adhere to SOPs after vaccination because of their personal experience of not being re-infected even when they did not follow SOPs. Researchers have discussed that those who cannot be immunized due to comorbidities or who do not develop personal immunity to COVID-19 infection are at risk from vaccine refusers and people who lack SOPs adherence (60).

The following limitations of this study should be kept in mind for future research. Owing to the non-availability of the national database due to security concerns, the random sampling technique was not used for the quantitative part, which affects the generalizability of the research findings. The sample collected mostly consisted of vaccinated individuals. The sample comprised mostly of those whose education level was between 13 and 16 years of education. There was less representation of those with a low educational background and socioeconomic status in the study because it was logistically difficult to collect data from such a diverse group as the population of the study was the general public of Pakistan. The verification of vaccination status was the major limitation in the qualitative part. Future researchers may improve the sampling strategy to collect data that is equally representative of all the education levels and socioeconomic groups of Pakistan. As the findings of this research conclude five major factors contributing to vaccine acceptance and one determining vaccine hesitancy, future research should be focused on social factors beyond the health sector that are contributing to the acceptance of and hesitancy toward COVID-19 vaccines under the framework of protection motivation theory.

5. Conclusion

As of January 2023, Pakistan has administered a total of 317,696,373 doses of vaccine, with 56.8% of the population fully vaccinated. The findings of the present study show that effective measures should be taken to address the problems related to vaccine acceptance and all the institutes have to play an effective role to create awareness related to the safety, efficacy, and acceptance of the COVID-19 vaccine. It is also recommended that long-term policy measures should be taken to promote the acceptance of health-related safety behaviors. Programs should be designed for communities to raise awareness of communicable diseases and their prevention.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by COMSATS University Islamabad, Pakistan. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

AI, AM, SZ, SW, MN, and HK participated in the design of the study and contributed to the data collection, data analysis, and interpretation. AI and AM the principal investigators, designed the study, were responsible for the statistical analysis and interpretation, and wrote the article. SZ wrote the introduction of the article. All authors have read and approved the final version of the manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Nigerian parents and caregivers knowledge, attitude and willingness to vaccinate their children against COVID-19

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Objectives: In order to achieve herd immunity against COVID-19, a significant proportion of the population will need to be vaccinated. Experts have recommended that African children be allowed to get vaccinated to protect them from emerging variants of COVID-19 infection. This study investigated Nigerian parents and caregivers' knowledge, attitude, and willingness to vaccinate their children against COVID-19 once the vaccines are made available to them.

Methods: A cross-sectional online survey of 500 parents/caregivers was conducted in Nigeria. Participants were asked to complete a questionnaire about their sociodemographic characteristics, knowledge of and attitude toward COVID-19 infection and vaccination, willingness to vaccinate their child and factors that could influence their decision to vaccinate their child. A scoring system was used to classify the level of knowledge and attitude of participants into 2 categories, namely poor, and good. We analyzed data obtained using SPSS Version 22.

Results: Majority of the participants were females (63.6%). Analysis of responses revealed good knowledge and attitude in 265 (53.0%) and 266 (53.2%) respondents, respectively. Overall, less than half of the parents/caregivers (48.4%) expressed intention to vaccinate their children against COVID-19. Factors associated with willingness to vaccinate children against COVID-19 included age greater than 40 years, male gender, residing in Southern Nigeria, having good knowledge, knowing an infected person or a vaccinated person, feeling they or their child is at risk of contracting COVID-19 infection, willingness to vaccinate self against COVID-19 and good attitude. Significant predictors of willingness to vaccinate their child include age greater than 40 years [AOR: 2.56; 95% CI = (1.14–5.76)], willingness to vaccinate self [AOR: 1016.81; 95% CI = (128.51–8045.60)] and good attitude [AOR: 6.21; 95% CI = (2.83–13.64)].

Conclusion: This study revealed that parental willingness to vaccinate their children against COVID-19 is low and identified factors influencing it. It is important to develop and implement health education programs iterating the risk of children getting infected with SARS-CoV-2 and its emerging variants to ensure optimal uptake of the COVID-19 vaccine in Nigerian children.

KEYWORDS
COVID-19, vaccination, children, parent, willingness, Nigeria

Introduction

The novel coronavirus disease 2019 (COVID-19) infection was first reported in December, 2019 (1). Ever since, it has continued to spread across the globe with over 680 million cases and 6 million deaths reported in 231 countries (2, 3). In Nigeria, as of March 10, 2023, the country has recorded a total number of 266,598 and 3,155 cases and deaths, respectively (4). Notably, in the past year, there have been reports of the emergence of SARS-CoV-2 variants potentially more infectious and virulent than the original strain responsible for the initial outbreak (5). At the beginning of the pandemic, public health measures were recommended to prevent and reduce the transmission of COVID-19, including frequent hand-washing, use of face masks and social distancing while vaccines were in development (1, 2).

Vaccination is a cost-effective way of boosting immunity against pathogens (2). In December 2020, the SARS-CoV-2 vaccine was rolled out with the hope that it would reduce the disease burden on healthcare systems globally and put an end to the pandemic (1). The COVID-19 vaccination program in Nigeria has been implemented in both urban and rural areas, with primary healthcare centers across all 774 local government areas providing free vaccines (6). The first batch of COVID-19 vaccines (Oxford-AstraZeneca) was received from the Japanese government in March 2021, with additional doses received from various sources throughout 2021 and 2022 (7).

As Nigeria is the most populous African country, its COVID-19 vaccination coverage will have significant subregional and regional impacts (6). Nigeria's goal was to vaccinate at least 70% of the eligible population with COVID-19 vaccines by the end of December 2022. However, as at 20th January, 2023, the country had only fully vaccinated 65,143,040 (56%) eligible individuals, while 76,957,026 (66.4%) had received at least one vaccine dose. Vaccine hesitancy due to misinformation about the vaccine's safety and efficacy poses a significant challenge to achieving this target. Vaccination is critical toward mitigating the outbreak as it ensures herd immunity (8). To achieve herd immunity for COVID-19 infection, there is a need to expand vaccine coverage to include children (1). A number of mRNA vaccines have been approved for use in children aged 18 years and below including Comirnaty (Pfizer-BioNTech's BNT162b2) and Spikevax (Moderna's mRNA-1273) (5). In 2020, the COVID-19 vaccination program in Nigeria granted a waiver for children aged 16–17 years to receive the vaccine for educational purposes, and as at February 2023, a total of 2,229,295 children had received the vaccine for this purpose (9).

Children aged 14 years and younger account for over 89 million Nigerians, almost half (44%) of the total population (10). Children and adolescents of all ages are vulnerable to SARS-CoV-2 infection. They may be at increased risk of getting infected by SARS-CoV-2 variants such as Delta and Omicron, especially if they are not vaccinated (5). COVID-19 presents with a milder course of acute illness in children compared to adults, however, there is a potential risk for severe complications that can affect their health on the long term (5). Asides these, children in LMICs like Nigeria have a higher prevalence of co-morbidities and as such, these children at increased risk of severe disease should be vaccinated against COVID-19 (11). Thus, experts have recommended that African children be allowed to get vaccinated against COVID-19 especially those with significant risk of severe disease and death, given the emerging variants of SARS-CoV-2 infection (8).

Parents significantly influence their child's vaccine uptake, and as such to increase the vaccination rate amongst children, parental hesitancy must be considered (1). Several research has been done to investigate parental willingness to vaccinate children since the vaccine was introduced. In a meta-analysis of 44 studies including 317,055 parents, parental intention to accept COVID-19 vaccine for their child ranged from 25.6 to 92.2%. However, the vast majority of the papers included were done in high-income countries, and it may be difficult to generalize their findings to Sub Saharan African population (12). In a rapid review carried out by Olu-Abiodun et al., in Nigeria in 2022, the vaccine acceptance rate among adults varied across the six geopolitical zones of the country, ranging from 20.0 to 58.2%. The non-acceptance of the vaccine was attributed to several factors such as propaganda, concerns over adverse effects, conspiracy theories, disbelief, and queries over vaccine safety (13). The factors that might be pertinent to the decision-making of parents regarding whether to vaccinate their children or not include vaccine side effects, conspiracy theories, disbelief, and fear of vaccine safety (Figure 1).

In June 2022, Nigeria reported fears of a fifth wave of COVID-19 outbreak amidst abysmally low vaccine uptake amongst adults. This poor uptake has been linked to vaccine hesitancy. A nationwide survey of 3,076 Nigerians reported a 50.7% vaccine acceptance rate (2). Reluctance to get vaccinated against COVID-19 can significantly impact outbreak control in the country. For minors aged under 18 years, parents and caregivers are the decision-makers and as such, it is important to determine their willingness to accept COVID-19 vaccination for their children and its determinants. This epidemiological landscape presents the urgent need to report determinants of parental willingness to vaccinate their children as identifying factors associated with parental acceptability will guide public health officials and other stakeholders on strategies to improve vaccination rates and achieve herd immunity. To address this gap in knowledge, the study was conducted by the Neo Child Initiative for Africa (TNCI), a non-governmental organization focused on improving the lives of Nigerian children through various initiatives that promote child health and education for sustainable development (14). The present study aimed to investigate the willingness of Nigerian parents and caregivers to vaccinate their children against COVID-19. We also compared the sociodemographic characteristics of parents and caregivers willing to vaccinate their child with those who were not willing to vaccinate their child.

Materials and methods

Study design

A country-wide cross-sectional survey was conducted, using a survey tool distributed via online media sites to all six geopolitical zones in

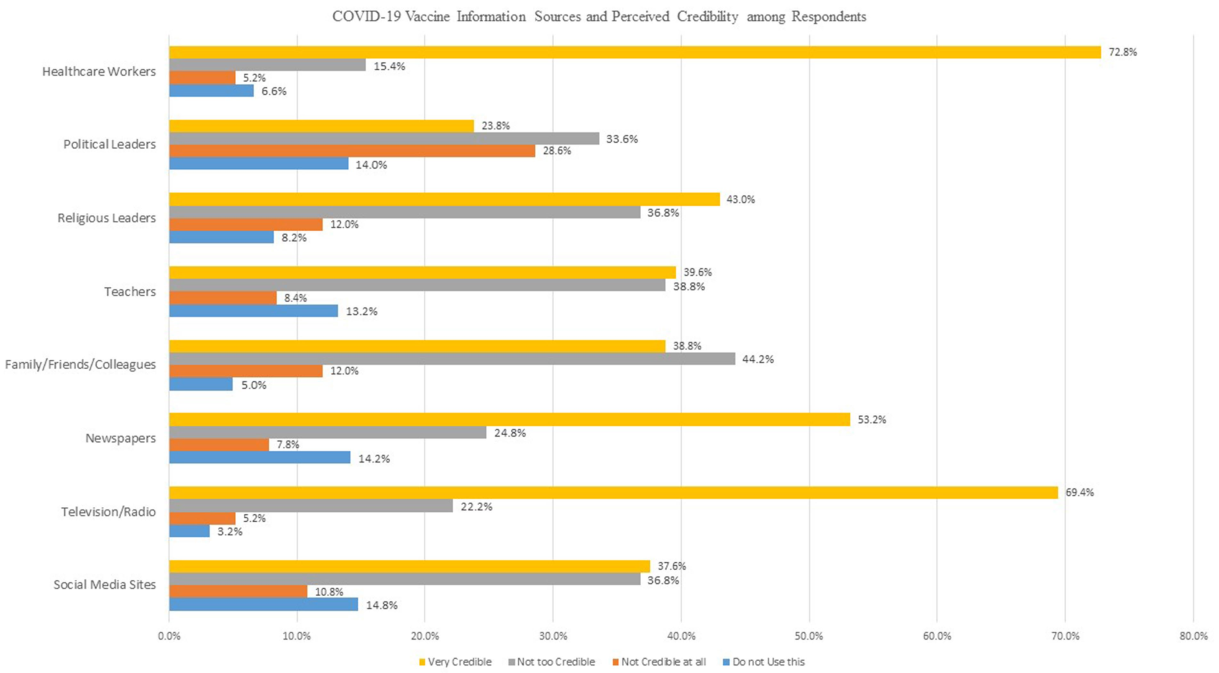

FIGURE 1
Perception of credibility of information sources regarding COVID-19.

Nigeria to assess parents and caregivers knowledge, attitude, and willingness to vaccinate their children against COVID-19 infection.

Population and sample size

Convenient sampling was utilized for this research. Minimum sampling size was determined to be 363. This was calculated by assuming a prevalence level of 72.6 from a previous study done by Zhang et al., confidence level of 95%, margin of error of 5% and a non-response rate of 20% (15, 16).

The survey was designed on Google Form and shared on social media platforms, including Twitter, Instagram, WhatsApp, Facebook over a period of 1 month social media influencers and volunteers of the Neo Child Initiative residing in the six geopolitical zones of the country were recruited to ensure dissemination in every region. The inclusion criteria of the study were as follows: participants aged at least 18 years, parent and/caregiver of at least one child, and currently residing in Nigeria, ability to read and understand English and being a user of any of the following social media platforms – Facebook, Twitter, Instagram or WhatsApp. Participants whose children were not residing in Nigeria, and those who had no digital literacy were excluded from the study.

Measures

The questionnaire used for this survey was developed with adaptations of relevant sections from previous studies that have sought to address similar objectives (17–20). It was initially piloted with 15 parents and caregivers selected from the six geopolitical zones with further refinement based on feedback gotten from these respondents and public health experts. The final questionnaire was then designed and disseminated using the application Google Form from the 1st of June 2021 to 28th of June 2021.

The questionnaire was self-administered and consisted of 47 questions divided into four sections: in the first part, socio-economic background was explored, including age, gender, educational level, occupation, marital status, and income. In the second part, knowledge of COVID-19 infection was asked. Respondents were also asked their opinion on the credibility of information sources for COVID-19. This question was collected on a 4-point Likert scale, ranging from not credible at all to very credible. In the third part, attitudes toward COVID-19 infection were asked, including perception of risk of infection for themselves and their child. In the fourth part, the respondents were asked if they had ever been diagnosed with COVID-19, or knew someone who had been diagnosed, whether they were willing to vaccinate themselves, and if they were willing to vaccinate their child, and reasons why they do not want to collect the vaccine. Knowledge and attitude variables were scored (A score of 1 was given for correct answers and a score of 0 for wrong answers). Using the mean values of the scores from all respondents, we created dichotomized measures for knowledge and attitude. Knowledge and attitude were categorized as good if the respondent had a score equal to or above the mean value and poor if score was lower than the mean value (19).

Data analysis

We analyzed survey responses using the Statistical Package for the Social Sciences (SPSS) V. 21.0 (SPSS, Chicago, Illinois, United States). Descriptive statistics, including frequency, measures of central tendency and variations were used to report information about participants socio-economic characteristics, knowledge and attitudes toward COVID-19 vaccination, willingness to vaccinate their children, and factors influencing willingness to vaccinate.

Bivariate analysis was used to compare the characteristics of parents and caregivers who were willing to vaccinate their child with those who were not willing. Associations between categorical variables were analyzed using the Chi-Square and Fisher's exact test. Bivariate logistic regression analysis was used to identify the predictors of parent and caregivers being willing to vaccinate their child and adjusted odds ratios (AORs) and 95% CIs were reported.

Ethics approval

Ethical approval for this study was obtained from the Institutional Review Board at the Lagos University Teaching Hospital with the ethical approval number ADM/DCST/HREC/APP/4200. Implicit consent to be a part of this survey was considered when participants completed the online questionnaire.

Results

A total of 500 adults filled the online form for data collection. There were no missing data. Most of the respondents were aged between 31 and 40 years (34.6%), Female (63.6%), married (79%) and from the Southern part of the country (89.4%). They were mostly parents (70.4%) and had tertiary level of education (54.8%). About one third of them knew a person that had been diagnosed with COVID-19 infection. Approximately half of them had good knowledge and attitude (53 and 53.2% respectively). Only a third of them (33.8%) perceived that they were at risk of COVID-19 infection and less than one-third of them (31.4%) felt that their child was at risk of COVID-19 infection. Almost all the parents/caregivers had previously vaccinated their child from birth (84.2%). Only one-tenth of them had previous side effects after vaccination (Table 1).

Among 500 respondents, 242 (48.4%) were willing to vaccinate their child and 285 (57%) respondents were willing to vaccinate themselves against COVID-19 disease while 23 and 18.8% were unsure of vaccinating their child and themselves against the disease (Table 1). Most parents/caregivers felt that healthcare workers were the most credible source of information regarding COVID-19, followed by mass media (Television/Radio). Social media was regarded as the least credible source of information (Table 2). Approximately half of the surveyed parents/caregivers (58.2%) knew that COVID-19 is preventable with vaccines; however, 73% believed that the COVID-19 vaccine can be used to protect oneself against severe disease. Only 56.8% of surveyed respondents believed that receiving the COVID-19 vaccine can be used to protect other family members (Table 3).

Less than half of the respondents agreed that the COVID-19 vaccine is safe and effective; however, when queried on vaccines in general, majority of them (77.6%) agreed that vaccines are generally important in children. Eighty-two respondents (16.4%) reported that they do not believe in vaccines while 231 respondents (46.2%) reported that they would not vaccinate their child as they are worried about the side effects of the vaccine (Table 4). It is noteworthy that having a good

TABLE 1 Participant's sociodemographic characteristics, overall knowledge, attitude, and willingness to vaccinate their child against COVID-19.

Variable		Frequency	Percentage
Age as at last birthday	18–20	16	3.2%
	21–30	124	24.8%
	31–40	173	34.6%
	41–50	118	23.6%
	51–60	58	11.6%
	61 and above	11	2.2%
Gender	Female	318	63.6%
	Male	182	36.4%
Marital status	Divorced	16	3.2%
	Married	395	79%
	Seperated	4	0.8%
	Single	76	15.2%
	Widowed	9	1.8%
Religion	Christianity	306	61.2%
	Islam	187	37.4%
	None	1	0.2%
	Traditional	6	1.2%
Geopolitical zones	North Central	36	7.2%
	North East	6	1.2%
	North West	11	2.2%
	South East	120	24%
	South South	62	12.4%
	South West	265	53%
Region	Northern Nigeria	53	10.6%
	Southern Nigeria	447	89.4%
Level of education	None	5	1%
	Primary level	50	10%
	Secondary level	171	34.2%
	Tertiary level	274	54.8%
Estimated monthly income	<#50,000	202	40.4%
	#50001-#100,000	145	29%
	#100001-#200,000	78	15.6%
	>#200,000	75	15%
Designation	Both	74	14.8%
	Caregiver/Guardian	74	14.8%
	Parent	352	70.4%
Total number of children	1	131	26.2%
	2	146	29.2%

(Continued)

TABLE 1 (Continued)

Variable		Frequency	Percentage
	3	115	23%
	4	60	12%
	5	30	6%
	> 5	18	3.6%
Ever been diagnosed with COVID	Yes	40	8%
	No	460	92%
Know anyone diagnosed with COVID?	Yes	143	28.6%
	No	357	71.4%
Overall knowledge	Good	265	53%
	Poor	235	47%
Do you think you are at risk of COVID-19 infection?	Yes	169	33.8%
	No	253	50.6%
	Uncertain	78	15.6%
Do you think your child is at risk of COVID-19 infection?	Yes	157	31.4%
	No	257	51.4%
	Uncertain	86	17.2%
Did you previously vaccinate your child from birth	Yes	421	84.2%
	No	79	15.8%
Do you know anyone who has gotten the COVID-19 vaccine?	Yes	269	53.8%
	No	231	46.2%
Overall attitude	Good	266	53.2%
	Poor	234	46.8%
Previous bad experience with vaccination?	Yes	54	10.8%
	No	446	89.2%
Are you willing to accept COVID-19 vaccine for yourself?	Yes	285	57%
	No	121	24.2%
	Uncertain	94	18.8%
Are you willing to accept COVID-19 vaccine for your child?	Yes	242	48.4%
	No	143	28.6%
	Uncertain	115	23%

attitude toward COVID-19 vaccination was significantly associated with willingness to vaccinate oneself against the disease ($p<0.001$). Likewise, respondents who had a good attitude toward COVID-19 vaccination were also found to be six times more likely to be willing to vaccinate their child compared to those who had a poor attitude toward COVID-19 vaccination, and this relationship was statistically significant.

TABLE 2 Information sources about COVID-19 and COVID-19 vaccine.

Source of information	Do not use this	Not credible at all	Not too credible	Very credible
Social media (Facebook/ Instagram/ WhatsApp)	74 (14.8%)	54 (10.8%)	184 (36.8%)	188 (37.6%)
Television/Radio	16 (3.2%)	26 (5.2%)	111 (22.2%)	347 (69.4%)
Newspapers	71 (14.2%)	39 (7.8%)	124 (24.8%)	266 (53.2%)
Family/Friends/ Colleagues	25 (5.0%)	60 (12.0%)	221 (44.2%)	194 (38.8%)
Teachers	66 (13.2%)	42 (8.4%)	194 (38.8%)	198 (39.6%)
Religious leaders	41 (8.2%)	60 (12.0%)	184 (36.8%)	215 (43.0%)
Political leaders	70 (14.0%)	143 (28.6%)	168 (33.6%)	119 (23.8%)
Healthcare workers	33 (6.6%)	26 (5.2%)	77 (15.4%)	364 (72.8%)

Willingness to vaccinate self was strongly associated with willingness to vaccinate their child ($p<0.001$). Only 0.5% of those who did not want to vaccinate themselves were willing to vaccinate their children while 84.6% of those willing to vaccinate themselves were willing to vaccinate their children. Good knowledge and attitude were also strongly associated with willingness to vaccinate children ($p<0.001$ and $p<0.001$ respectively) (Table 5).

Willingness to vaccinate self was strongly associated with willingness to vaccinate their child. Only 0.5% of those who did not want to vaccinate themselves were willing to vaccinate their children while 84.6% of those willing to vaccinate themselves were willing to vaccinate their children. Good knowledge and attitude were also strongly associated with willingness to vaccinate children (Table 5).

Univariate analysis also showed that age greater than 40 years, male gender, knowledge of a person previously diagnosed with COVID-19, being from Southern Nigeria, having good knowledge of COVID-19 disease and vaccine, having good attitude toward COVID-19 vaccination, presence of perceived risk of COVID-19 infection for themselves and risk of infection for their child, knowledge of someone who had gotten vaccinated and willingness to vaccinate self were significantly associated with higher odds of parental vaccine acceptability. After adjusting for covariates, willingness to vaccinate self, good attitude and age greater than 40 years were still associated with higher odds of vaccine acceptance. Compared to those unwilling to vaccinate themselves, those who were willing to receive the vaccine were a thousand times more likely to vaccinate their child [AOR: 1016.81; 95% CI = (128.51–8045.60)]. People aged greater than 40 years and those with good attitude were twice more likely and six times more likely to accept the vaccine than those aged younger than

TABLE 3 Participant's knowledge about COVID-19 and COVID-19 vaccine.

Variable		Frequency	Percentage
COVID-19 is a Respiratory Infection?	Yes	358	71.6%
	No	30	6%
	I do not know	112	22.4%
COVID-19 can be transmitted via respiratory droplets and contact with infected persons	Yes	392	78.4%
	No	24	4.8%
	I do not know	84	16.8%
Symptoms of COVID-19 include fever, cough, chest pain and fatigue?	Yes	381	76.2%
	No	28	5.6%
	I do not know	91	18.2%
All patients have symptoms	Yes	137	27.4%
	No	232	46.4%
	I do not know	131	26.2%
COVID-19 develops within 2-14 days	Yes	263	52.6%
	No	62	12.4%
	I do not know	175	35%
Children cannot get COVID-19	Yes	85	17%
	No	279	55.8%
	I do not know	136	27.2%
COVID-19 is preventable with the use of vaccines	Yes	291	58.2%
	No	65	13%
	I do not know	144	28.8%
COVID-19 vaccine can be used to protect oneself	Yes	365	73%
	No	37	7.4%
	I do not know	98	19.6%
COVID-19 vaccine is used by government to steal money	Yes	56	11.2%
	No	260	52%
	I do not know	184	36.8%
COVID-19 vaccine can be used to protect family from the disease	Yes	284	56.8%
	No	59	11.8%
	I do not know	157	31.4%

TABLE 4 Participants attitude toward COVID-19 and COVID-19 vaccine.

Variable		Frequency	Percentage
COVID-19 vaccine is safe and effective?	Agree/Strongly agree	220	44%
	Disagree/Strongly Disagree	61	12.2%
	Neutral	219	43.8%
Are you scared of contracting COVID-19 disease?	Agree	147	29.4%
	Disagree	226	45.2%
	Neutral/Uncertain	127	25.4%
Vaccines are important in children	Agree	388	77.6%
	Disagree	34	6.8%
	Neutral/Uncertain	78	15.6%
I trust vaccines and health workers	Agree	337	67.4%
	Disagree	46	9.2%
	Neutral/Uncertain	117	23.4%
I do not believe in vaccines generally	Agree	82	16.4%
	Disagree	323	64.6%
	Neutral/Uncertain	95	19%
I do not want my child to get the vaccine	Agree	366	73.2%
	Disagree	76	15.2%
	Neutral/Uncertain	58	11.6%
I do not trust the vaccine	Agree	119	23.8%
	Disagree	217	43.4%
	Neutral/Uncertain	164	32.8%
The vaccine is from the devil	Agree	33	6.6%
	Disagree	347	69.4%
	Neutral/Uncertain	120	24%
The vaccine is a micro-chip to control the world	Agree	49	9.8%
	Disagree	313	62.6%
	Neutral/Uncertain	138	27.6%
I will vaccinate my child to protect him/her	Agree	259	51.8%
	Disagree	95	19%
	Neutral/Uncertain	146	29.2%

(Continued)

TABLE 4 (Continued)

Variable		Frequency	Percentage
I will vaccinate my child to protect other family members	Agree	271	54.2%
	Disagree	97	19.4%
	Neutral/Uncertain	132	26.4%
I will vaccinate my child because of school	Agree	263	52.6%
	Disagree	101	20.2%
	Neutral/Uncertain	136	27.2%
I will not vaccinate my child as I am worried about the side effects of vaccine	Agree	231	46.2%
	Disagree	96	19.2%
	Neutral/Uncertain	173	34.6%
I believe the vaccines are fake	Agree	59	11.8%
	Disagree	233	46.6%
	Neutral/Uncertain	208	41.6%

40 years [AOR: 2.56; 95% CI = (1.14–5.76)], and those with bad attitude, respectively [AOR: 6.21; 95% CI = (2.83–13.64)] (Table 6).

Discussion

Our study showed that less than half of Nigerian parents are willing to vaccinate their children against COVID-19. This is much lower than what obtains in high income countries (21, 22). Bianco et al. (21) found that 82% of parents surveyed in Italy were willing to vaccinate their children against COVID-19 while Goldman et al. (22) found that 61.1% of parents surveyed in Canada were willing to vaccinate their child. We found that willingness to vaccinate self was a strong predictor of willingness to vaccinate their children, which is similar to previous findings (1, 23–25). However, more than one-tenth of respondents who were willing to vaccinate themselves were still not willing to vaccinate their children, alluding to the need for intensified parental education about COVID-19 vaccine's safety and efficacy in children to ensure uptake when it is rolled out. We also found that having good attitude toward COVID-19 vaccination and good knowledge of COVID-19 disease was associated with willingness to vaccinate their child. This is in line with findings from a similar study by Hunyh et al. that examined vaccine hesitancy amongst the general population and parents (23).

In our study, older parents/caregivers aged greater than 40 years were more likely to vaccinate their child against COVID-19, similar to previous findings (2, 26). In a scoping review that summarized the evidence on vaccine hesitancy in Africa, it was reported that being a male was associated with positive attitude toward the vaccine (27). Our study also showed that men were more likely to vaccinate their child, similar to previous studies that have reported women to be less likely to be willing to vaccinate their child (1, 28). Gender disparities across various sectors of the economy in Nigeria, characterized by lower rates of female labor force participation and inadequate investment in women's human capital, may account for the greater likelihood of men vaccinating their children compared to women (29). This disparity translates to men having enhanced access to healthcare information, and as such, may be a key factor responsible for their increased inclination toward vaccinating their children. In order to convince men who are disinclined to vaccinate their children, healthcare providers should be encouraged to employ diverse strategies such as targeted educational interventions via social media and inclusive involvement of fathers in the vaccination decision-making process for children from infancy. We believe this may be due to fear of adverse side effect of the virus amongst women. Further research to investigate specific cause of this gender difference should be done and public health professionals should develop gender-specific messages to promote vaccine acceptance amongst women.

Interestingly, the present study did not find a significant relationship between level of education, marital status, and willingness to vaccinate children. This contrasts with previous findings that identified that parents with secondary or lower education and those who were single were more willing to vaccinate their child against COVID-19 (21, 30). Padhi et al. (25) in their study reported conflicting findings that people with higher levels of education were more willing to vaccinate their child (25). However, this was not observed in our study; this may be because our surveyed population mainly consisted of young parents age less than 40 years. This inconsistency has been previously reported when evaluating the educational level of parents and intention to vaccinate; hence it is possible that education may not always be a key determinant of willingness to accept vaccine (19).

In addition to the previously discussed sociodemographic factors related to parental willingness to vaccinate their child, we also investigated the role of the perceived risk of COVID-19 infection. Past research has shown that people who perceived they or their child were at risk of getting infected with COVID-19 were more likely to be willing to vaccinate their child (31, 32). In this present study, we also found that parents who perceived themselves or their child could get infected with the SARS-CoV-2 virus were more willing to accept the vaccine. Majority of our respondents found healthcare workers to be the most credible source of information regarding COVID-19. Public health campaigns aiming to improve willingness need to find ways to tailor their message using healthcare workers for community outreaches and campaigns on mass media platforms. Future research should investigate the impact of information sources on parental vaccination intention.

Strength and limitations

The strength of this study is that it was a nationwide survey of parents and caregivers with children in Nigeria. The COVID-19 vaccine was recently approved for use among 16- and 17-year-old Nigerian children for educational and travel purposes, and it is likely that in the light of the recent fear of the fifth wave of the virus, the

TABLE 5 Factors associated with willingness to vaccinate child against COVID-19.

Variables		Willing to vaccinate child (n = 242)	Unwilling to vaccinate child (n = 262)	Total (n = 500)	X^2	p value
Age	>40 years	107 (57.2%)	80 (42.8%)	187 (100%)	9.303	0.002
	<=40 years	135 (43.1%)	178 (56.9%)	313 (100%)		
Gender	Male	112 (61.5%)	70 (38.5%)	182 (100%)		<0.001
	Female	130 (40.9%)	188 (59.1%)	318 (100%)	19.779	
Marital status	Married	192 (48.6%)	203 (51.4%)	395 (100%)		0.857
	Others	50 (47.6%)	55 (52.4%)	105 (100%)	0.032	
Religion	Christian	142 (46.4%)	164 (53.6%)	306 (100%)	1.257	0.262
	Others	100 (51.5%)	94 (48.5%)	194 (100%)		
Geopolitical zone	North Central	9 (25.0%)	27 (75.0%)	36 (100%)	14.655	0.0093*
	North East	4 (66.7%)	2 (33.3%)	6 (100%)		
	North West	5 (45.5%)	6 (54.5%)	11 (100%)		
	South East	50 (41.7%)	70 (58.3%)	120 (100%)		
	South South	30 (48.4%)	32 (51.6%)	62 (100%)		
	South West	144 (54.3%)	121 (45.7%)	265 (100%)		
Region	Southern Nigeria	224 (50.1%)	223 (49.9%)	447 (100%)	4.948	0.026
	Northern Nigeria	18 (34%)	35 (66%)	53 (100%)		
Highest level of education	Tertiary Level	141 (51.5%)	133 (48.5%)	274 (100%)	2.273	0.132
	Others	101 (44.7%)	125 (55.3%)	226 (100%)		
Monthly income	>$100	148 (49.7%)	150 (50.3%)	298 (100%)	0.472	0.492
	<=$100	94 (46.5%)	108 (53.5%)	202 (100%)		
Number of children	>2	108 (48.9%)	113 (51.1%)	221 (100%)	0.035	0.852
	<=2	134 (48%)	145 (52%)	279 (100%)		

(Continued)

TABLE 5 (Continued)

Variables		Willing to vaccinate child (n = 242)	Unwilling to vaccinate child (n = 262)	Total (n = 500)	X^2	p value
Previous COVID-19 infection	Yes	21 (52.5%)	19 (47.5%)	40 (100%)	0.293	0.589
	No	221 (48%)	239 (52%)	460 (100%)		
Know anyone diagnosed with COVID-19	Yes	81 (56.6%)	62 (43.4%)	143 (100%)	5.449	0.020
	No	161 (45.1%)	196 (54.9%)	357 (100%)		
Overall, knowledge	Good	168 (61.5%)	105 (38.5%)	273 (100%)	41.562	<0.001
	Poor	74 (32.6%)	153 (67.4%)	227 (100%)		
Feeling at risk of COVID-19	Yes	117 (69.2%)	52 (30.8%)	169 (100%)	44.355	<0.001
	No	125 (37.8%)	206 (62.2%)	331 (100%)		
Feeling child is at risk of COVID-19	Yes	109 (69.4%)	48 (30.6%)	157 (100%)	40.516	<0.001
	No	133 (38.8%)	210 (61.2%)	343 (100%)		
Previously vaccinated child	Yes	208 (49.4%)	213 (50.6%)	421 (100%)	1.08	0.299
	No	34 (43%)	45 (57%)	79 (100%)		
Know COVID-19 vaccinated person	Yes	156 (58%)	113 (42%)	269 (100%)	21.453	<0.001
	No	86 (37.2%)	145 (62.8%)	231 (100%)		
Willingness to vaccinate self	Yes	241 (84.6%)	44 (15.4%)	285 (100%)	347.034	<0.001*
	No	1 (0.5%)	214 (99.5%)	215 (100%)		
Attitude	Good	202 (76%)	64 (24%)	266 (100%)	172.6	<0.001
	Poor	40 (17.1%)	194 (82.9%)	234 (100%)		
Previous bad experience with vaccination	No	167 (49.7%)	169 (50.3%)	336 (100%)	0.829	0.363
	Yes	73 (45.3%)	88 (54.7%)	161 (100%)		

vaccine may soon be expanded to include other children older than 12 years. Hence, the findings of our survey will be useful to guiding public health professionals and other stakeholders on targeted campaigns to promote vaccine uptake amongst Nigerian children.

However, our findings should be interpreted in the light of certain limitations. Firstly, it was an internet-based survey and, as such is subject to selection bias. People who may have participated are internet-savvy and are likely to be more educated than the average Nigerian and as such, the generalizability of our findings is limited. Further research using the identified factors related to vaccine acceptability should consider targeting people with no access to the internet. Secondly, this was a cross-sectional survey, and we cannot infer causality for the reported associations. Third, according to the data collected, respondents that took this survey were mostly from southern Nigeria. Northern Nigeria was the least represented and seeing as vaccine hesitancy is rifer in that region, it is possible that

TABLE 6 Bivariate logistic analysis of factors associated with willingness to vaccinate child.

Characteristics	Adjusted odds ratio (95% CI)	*p* value
Age greater than 40 years	2.56 (1.14 to 5.76)	**0.023**
Male gender	1.98 (0.94 to 4.2)	0.073
Residing in Southern Nigeria	1.47 (0.45 to 4.8)	0.520
Knowing an infected person	0.45 (0.18 to 1.08)	0.075
Good knowledge	0.65 (0.25 to 1.67)	0.371
Feeling at risk of COVID-19 Infection	1.96 (0.72 to 5.33)	0.185
Feeling child is at risk of COVID-19 Infection	1.23 (0.45 to 3.4)	0.686
Knowing a vaccinated person	0.69 (0.27 to 1.81)	0.455
Willingness to vaccinate self	1016.81 (128.51 to 8045.6)	**<0.001**
Good attitude	6.21 (2.83 to 13.64)	**<0.001**

*Bold here refers to those values that were statistically significant.

our findings may not be applicable to parents and caregivers in that part of Nigeria. Further research to investigate their willingness to accept COVID-19 vaccine for their children and associated factors is recommended. Fourth, our study did not explore the impact of co-morbidities on parental willingness. Studies investigating the role of co-morbidities as a determinant in vaccine acceptance have reported conflicting findings. While some have shown that parents were less willing to vaccinate a child with co-morbidities (23), others have shown parent's being more willing to vaccinate a child with co-morbidities (33). These studies have mostly been done in high income countries and as such, there is a need to replicate it in the African population. Lastly, our study did not investigate the impact of the various types of information sources on parental vaccination intention and as such, we cannot determine whether it influences parental decision.

Conclusion

The present study investigated the knowledge, attitude, and willingness of Nigerian parents to vaccinate their children against COVID-19 disease. It was shown that less than half of parents were willing to vaccinate their child. We found that willingness to vaccinate self, being aged greater than 40 years and a good attitude toward COVID-19 vaccine were significant predictors of vaccine acceptability. In the context of expanding COVID-19 vaccine access to children in the future, the results point to the importance of considering these factors in the design of evidence-based vaccine promotion campaigns targeted toward improving uptake.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

AA, CA, AI, TD, TK, BR, MA, OO, YS, and AR: idea, design, and editing. AA, CA, AI, TD, and AR: prepared the questionnaires. AA, CA, and AI: analyzes. All authors collected the data, wrote the draft, and approved the final draft.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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