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Reviews in vaccination programmes

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Table of contents

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Two centuries of vaccination: historical and conceptual approach and future perspectives

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Over the past two centuries, vaccines have been critical for the prevention of infectious diseases and are considered milestones in the medical and public health history. The World Health Organization estimates that vaccination currently prevents approximately 3.5–5 million deaths annually, attributed to diseases such as diphtheria, tetanus, pertussis, influenza, and measles. Vaccination has been instrumental in eradicating important pathogens, including the smallpox virus and wild poliovirus types 2 and 3. This narrative review offers a detailed journey through the history and advancements in vaccinology, tailored for healthcare workers. It traces pivotal milestones, beginning with the variolation practices in the early 17th century, the development of the first smallpox vaccine, and the continuous evolution and innovation in vaccine development up to the present day. We also briefly review immunological principles underlying vaccination, as well as the main vaccine types, with a special mention of the recently introduced mRNA vaccine technology. Additionally, we discuss the broad benefits of vaccines, including their role in reducing morbidity and mortality, and in fostering socioeconomic development in communities. Finally, we address the issue of vaccine hesitancy and discuss effective strategies to promote vaccine acceptance. Research, collaboration, and the widespread acceptance and use of vaccines are imperative for the continued success of vaccination programs in controlling and ultimately eradicating infectious diseases.

KEYWORDS

vaccines, history of vaccines, vaccinology, types of vaccines, vaccine development, health literacy, vaccine hesitancy

1 Introduction

Over the past century, a significant number of infectious diseases have been prevented, primarily due to advancements in science and technology. Among these breakthroughs, vaccines stand out as one of the most pivotal achievements in medicine and public health (Box 1). More than two centuries have passed since Benjamin Jesty and Edward Jenner laid the groundwork for vaccinology with their observations and experiments on smallpox and cowpox. Their pioneering efforts paved the way for the development of effective strategies for controlling and eradicating infectious diseases, many of which were considered invincible at the time.

A century ago, infectious diseases were the primary cause of death worldwide. In 1900, the average life expectancy at birth in the United States was ∼47 years, and children under five accounted for 30.4% of all deaths (1, 2). Survivors of these infections often suffered severe complications and disabilities such as paralytic poliomyelitis (3), osteomyelitis variolosa (4), and neurological and vision impairments, among others (5, 6). However, there was a significant decline in the mortality rate from infectious diseases throughout the 20th century, from 797 deaths per 100,000 in 1900 to 59 deaths per 100,000 in 1996 (7). By the late 1990s, chronic diseases like cardiovascular disorders, stroke, and cancer had become the leading causes of death (7). Currently, the average life expectancy at birth in the United States is ∼78 years, marking an impressive 30-year increase (8). This trend is similarly observed in most middle- and high-income countries (9, 10).

The increase in life expectancy and the decline in mortality from infectious diseases can be attributed to various factors. Key among these is the reduction in disease transmission and host susceptibility, a consequence of improved housing, enhanced hygiene and sanitation, secure food and water supplies, and the widespread use of safe, effective, and affordable vaccines. Additionally, significant advances in medical treatments, including antimicrobial and antiviral agents, have contributed substantially (11).

Collectively, these advances in public health have markedly contributed to the eradication of important pathogens, such as smallpox virus and wild poliovirus types 2 and 3 (with wild polio type 1 close to eradication) (12–14). Several vaccine-preventable diseases, including diphtheria, measles, mumps, rubella, and pertussis, are now largely under control. Nonetheless, the path toward a world free of these infectious diseases is complex and faces significant challenges, making it essential to maintain adequate vaccination coverage to avoid resurgences (15–17).

Numerous infectious diseases continue to afflict humanity, and while significant progress has been made in some areas, notable gaps remain in our vaccine arsenal. One of the most prominent examples is HIV/AIDS, a global pandemic that has persisted for decades. Despite extensive research, concerted efforts, and numerous clinical trials, an effective HIV vaccine remains elusive (18). This scenario underscores the complexity and challenges of vaccine development against certain pathogens, even with advances in modern science. These challenges highlight the urgent need for continued support for research and innovation in vaccinology.

It is worth noting that some of the leading causes of child mortality, such as malaria and respiratory syncytial virus (RSV), are soon to be tackled with prevention strategies that will include new vaccines (19–21). Additionally, the persistent threat of emerging and reemerging diseases, as demonstrated by the recent COVID-19 pandemic, further accentuates the need for advancements in vaccinology. These advancements, supported by cutting-edge genetic engineering, molecular biology, and structural biology, have expedited the development of several innovative vaccines against SARS-CoV-2.

However, the challenges we face are not purely biological. During the COVID-19 pandemic, an "infodemic" occurred, characterized by the spread of false, misleading, or biased information related to vaccines (22). In this context, it becomes imperative to promote accurate and evidence-based information to achieve broad acceptance and understanding of vaccines within communities.

This narrative review aims to trace the path of historical milestones in the development and progress of vaccines, recognizing pioneers with global impact in this field. We will briefly explain the principles and mechanisms of action of the main types of vaccines, highlighting their characteristics, advantages, and limitations. Additionally, we analyze the impact of vaccines, emphasizing their contribution to reducing morbidity and mortality, as well as their economic and social benefits. Finally, we address the issue of vaccine hesitancy and underscore the importance of effective communication to promote vaccination acceptance.

Aimed primarily at non-expert audiences in the healthcare field, this review seeks to provide useful information to improve health literacy and better address the growing threat of vaccine misinformation. Ultimately, the acceptance and widespread use of vaccines are *sine qua non* conditions for further progress in controlling and eradicating infectious diseases.

2 Methodology

For this narrative review, a comprehensive literature search was carried out in the PubMed, Science Direct, and Google Scholar databases. The search strategy was formulated using a combination of keywords: "vaccine development history," "vaccine types," "immune response to vaccines," "vaccine public health impact," and "vaccine hesitancy." This set of keywords was selected to ensure the inclusion of a broad range of relevant articles covering various aspects of vaccinology. The abstracts of the articles were then reviewed to evaluate their relevance and eligibility based on the inclusion criteria. Selection criteria were defined to include articles that described historical milestones in vaccine development, addressed the immunological basis of vaccination, or discussed the origin, causes and mitigation strategies of vaccine hesitancy. Articles that met these criteria were reviewed in their entirety. In addition to database searches, the reference lists of the selected articles were hand searched to identify further relevant studies that may not have been included in the database searches. This literature search and article selection approach was designed to ensure that the review was comprehensive and unbiased, providing

BOX 1 What is a vaccine?

A vaccine is defined as a biological product designed to stimulate the immune system to generate antigen-specific immunity against a pathogen, thereby preventing the disease it causes. Typically, vaccines are formulated from attenuated or inactivated versions of the pathogen, or derived components such as proteins and polysaccharides. The addition of an adjuvant in many vaccine formulations serves to enhance the adaptive immune response.

Upon administering a vaccine, the immune system identifies some components of the pathogen (antigens) present in the vaccine producing a specific immune response. Thus, the vaccine "trains" and prepares the immune system to respond effectively to the pathogen upon exposure; this phenomenon is known as immunological memory. Therefore, when a vaccinated individual is later exposed to the same pathogen, their immune system will be prepared to generate an effective defense, preventing the development of the disease, or reducing its severity.

Each vaccine is meticulously designed and rigorously tested to ensure it elicits a specific immune response that is both safe and protective. This underscores the intricate balance and interaction between the vaccine composition and the dynamics of the immune system.

a well-rounded perspective on the history, development, and impact of vaccines on public health.

3 History of vaccines and vaccination

Most stories in microbiology usually begin with the first observation of microorganisms. Microorganisms were absent from human knowledge until 1674, when the Dutch merchant Antonie van Leeuwenhoek, a self-taught scientist, and naturalist, discovered the microscopic world (23, 24).

Leeuwenhoek, employing refined lenses of his own manufacture, meticulously documented the existence of "animalcules", now known as bacteria and protozoa. His detailed observations, written and drawn in numerous letters addressed (almost always) to the Royal Society of London, provided the first images of cells and organisms that cannot be seen with the naked eye (23). These findings were foundational, paving the way for the emergence of scientific disciplines like cell biology and microbiology, which have their roots in understanding the microscopic world.

As we delve into the following sections, the fundamental role of the discovery of microorganisms in the field of vaccinology will become increasingly evident. However, to fully understand this impact, it is necessary to take a journey to an era before the invention of vaccines.

This historic analysis reveals a chronicle marked by perseverance, innovation, defeats, and triumphs, which collectively summarize the evolution of vaccines. This history not only deserves celebration but also serves as an axis that connects our past understandings, current knowledge, and projections in the fields of immunization and disease prevention.

3.1 Variolation, the ancient method of immunization

As we look through the annals of medicine, we encounter a period before the development of vaccines, a time when rudimentary methods by today's standards were used to fight infectious diseases. One such method was variolation, the practice of inoculating healthy individuals, either through the nose or a scratch in the skin, with material obtained from smallpox pustules to confer immunity (25, 26).

Smallpox, caused by the Variola virus, was a highly contagious disease, transmitted primarily through direct contact and respiratory droplets. The disease presented in two clinical forms. Variola major, the more common and severe form, was characterized by an extensive rash and high fever, and an overall mortality rate close to 30%. Variola minor was less prevalent and exhibited a milder manifestation, with mortality rates of 1% or less (27).

Variolization was practiced in Asia, particularly in China and India, as early as the 17th century AD, although it probably originated centuries earlier. Lu, a renowned Chinese physician, provided the first detailed description of variolation in a book published in 1695 (28). He described three main methods: the first involved inserting a piece of cotton soaked in pus from fresh pustules into the nostrils; the second consisted of inhalation of dried and powdered scabs; the third involved exposing a healthy individual to clothing worn by an infected individual. Each method induced a mild form of smallpox and subsequent immunity, with variolation being considered more effective and safer compared to natural infection exposure. The Chinese also distinguished between variola major and minor, extracting smallpox material from people affected by the latter. However, despite its relative efficacy, variolation was not without significant risks, including the possibility of suffering severe smallpox, and even death (26, 29).

In India, the variolation method was different; it involved inoculating individuals with smallpox material through a scratch in the skin (cutaneous inoculation). This method was recognized as safer than the Chinese practices and spread to the Middle East through merchant caravans (30–33).

In the 18th century, variolation found its way to Europe, mainly due to the efforts of Lady Mary Wortley Montague, the wife of the British ambassador to the Ottoman Empire. During her stay in Constantinople, Lady Montague learned about variolation. Having herself suffered from smallpox, she became a strong advocate for this preventive method. In 1721, after returning to London, she decided to variolate her 3-year-old daughter in the presence of the English court physicians. The successful protection of her daughter against smallpox, coupled with her strong advocacy for variolation, stimulated the adoption of this method throughout Europe (32, 34).

In North America, the promotion of variolation was notably led by Reverend Cotton Mather and Dr. Zabdiel Boylston, who fervently advocated for its use (35). Their advocacy was particularly crucial during a smallpox epidemic in Boston in 1721, which claimed hundreds of lives. Data from the United States

National Library of Medicine indicates that 0.5–3% of those variolated died, compared to 9.5–30% dying from smallpox after natural exposure (36). Despite presenting comparative analyses of mortality rates pointing to its efficacy, proponents of variolation faced considerable opposition.

Benjamin Franklin, who was also personally affected by smallpox, joined the defense of variolation after losing his son to the disease in 1736. He deeply regretted not having variolated his son and conveyed his experience to other parents, urging them to choose variolation as the safest way to protect their children (37).

Despite its associated risks, variolation was an important step toward comprehending and developing techniques to prevent smallpox. Adopting and promoting this method through the efforts of prominent figures like Lady Montague, Reverend Mather, and Dr. Boylston, marked a significant advance in the history of public health. Although safer and more effective immunization strategies eventually replaced variolation, its historical significance is indelible. It represents the persistent search for strategies to fight infectious diseases.

3.2 Benjamin Jesty, Edward Jenner, and the foundation of vaccinology

In an era when smallpox ravaged populations, there was a desperate search for preventive methods more reliable and safer than variolation. In this historical context, vaccinology has its roots not only in the well-documented work of the English physician Edward Jenner but also in the lesser-known but significant contributions of the farmer Benjamin Jesty.

Jesty made the critical observation, as Jenner would years later, that milkmaids who had contracted cowpox (a disease similar but milder to human smallpox) did not contract smallpox, even after close contact with infected individuals. In 1774, during a smallpox outbreak in England, Jesty adeptly applied this observation and inoculated his wife and two sons with material from a cowpox pustule using a stocking needle. Jesty did not inoculate himself because he had previously contracted cowpox and was confident that he was already protected (38). This event is considered the first recorded vaccination. The successful result of this method was evidenced by the fact that his family never suffered from smallpox, even when they were subsequently exposed to the disease. Moreover, Jesty extended his efforts to vaccinate other individuals in his community (39, 40).

While Jesty's efforts were pioneering, Jenner's systematic experiments and published works earned him a unique place in history, as the "father of vaccinology". As mentioned above, Jenner also noted apparent immunity to smallpox among individuals who had contracted cowpox. Prompted by this observation, Jenner performed a series of experiments involving the inoculation of material from cowpox pustules. In 1796, he inoculated James Phipps, an 8-year-old boy, with material from a fresh cowpox lesion obtained from a milkmaid named Sarah Nelms. Subsequently, when Jenner exposed the boy to material from a human smallpox lesion, Phipps did not become ill, demonstrating the protective capacity of this method (41, 42). Jenner compiled the findings of this experiment, along with sixteen additional case histories, into his publication "An inquiry into the causes and effects of the *variolae vaccinae*" (43). The success of these experiments demonstrated that cowpox minimally affected humans while generating protection against smallpox.

However, at the time, Jenner was unable to elucidate why his method provided protection, owing to an incomplete understanding of the causal relationship between microorganisms and diseases. As knowledge in microbiology and immunology advanced, later scientists adapted and expanded his fundamental work (34, 44, 45). Furthermore, the insights of Jenner into the essential role of animals in vaccinology were truly ahead of his time, foretelling the future use of cows, guinea pigs, rabbits, and even chicken eggs in vaccine development (46). However, the use of cows in Jenner's method made many people wary and sometimes hostile to the idea of inoculating foreign animal products into their own bodies. Initially, Jenner encountered satirical ridicule in the popular press and opposition from eminent physicians. Yet, as word of his breakthrough spread, his work gradually became accepted, acknowledged, and celebrated (46, 47).

Jenner's work based on scientific methods of observation and experimentation led to the formulation of the vaccine concept. The terms "vaccine" and "vaccination" originate from "*variolae vaccinae*", a phrase coined by Jenner to literally refer to smallpox of the cow. In 1881, Louis Pasteur, known as the "father of microbiology," in recognition of Jenner's legacy, proposed extending these terms to the new protective immunizations that were being developed at that time. Thus, the terms vaccine and vaccination transcended their origin and began to be applied to all biological products and methods used to confer immunity against infectious diseases (41, 48).

Importantly, the discoveries of Jenner revolutionized prevention of infectious diseases, influencing the development of all subsequent vaccines (29, 48). Therefore, while Jesty is recognized as the first vaccinator, it was Jenner who laid the foundations for the establishment of vaccinology as a scientific discipline. Table 1 presents a select list of vaccines developed after Jenner's seminal discovery.

In 1980, the World Health Organization (WHO) declared the eradication of smallpox. This is one of the most outstanding achievements of all time in public health and science, demonstrating the power of vaccination in the fight against infectious diseases. In addition, it underscored the relevance of cooperation between scientists, institutions, and governments in providing extraordinary outcomes for the benefit of humankind (34, 88).

3.3 The contribution and impact of Louis Pasteur

Between the 1850s and 1860s, the French chemist Louis Pasteur conducted a series of groundbreaking experiments that substantiated the Germ Theory. He conclusively demonstrated that food spoilage was due to the presence and contamination of organisms that cannot be seen with the naked eye

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TABLE 1 Outstanding examples of vaccines developed*.

Pathogen	Disease	Year	Developer(s)	Vaccine type	References
Variola virus	Smallpox	1796	Edward Jenner	Vaccine based on bovine smallpox virus	(43)
Rabies virus	Rabies	1885	Louis Pasteur and Émile Roux	Attenuated vaccine	(49)
Salmonella enterica Serovar Typhi	Typhoid fever	1896	Richard Pfeiffer and Almroth Wright	Inactivated vaccine	(50)
Vibrio cholerae	Cholera	1896	Wilhelm Kolle	Inactivated vaccine	(51)
Yersinia pestis	Bubonic plague	1897	Waldemar Haffkine	Inactivated vaccine	(52)
Mycobacterium tuberculosis	Tuberculosis	1921	Albert Calmette and Camille Guérin	Attenuated vaccine based on *Mycobacterium bovis*	(53)
Corynebacterium diphtheria	Diphtheria	1923	Gaston Ramon	Toxoid vaccine that protects against the toxin	(54)
Clostridium tetani	Tetanus	1925	Gaston Ramon	Toxoid vaccine that protects against the toxin	(55)
Bordetella pertussis	Pertussis	1930s	Pearl Kendrick and Grace Eldering	Whole-cell inactivated vaccine	(56)
Yellow fever virus	Yellow Fever	1937	Max Theiler	Attenuated vaccine (17D strain)	(57)
Polio virus	Poliomyelitis	1955	Jonas Salk	Inactivated vaccine that protects against all 3 serotypes	(58)
Polio virus	Poliomyelitis	1960	Albert Sabin	Oral attenuated vaccine that protects against all 3 serotypes	(59)
Measles virus	Measles	1954–1960	John F. Enders and Samuel L. Katz	Attenuated vaccine; part of the MMR vaccine	(60)
Mumps virus	Mumps	1967	Maurice Hilleman	Attenuated vaccine; part of the MMR vaccine	(61)
Rubella virus	Rubella	1969	Stanley Plotkin	Attenuated vaccine (RA 27/3 strain); part of the MMR vaccine	(62)
Varicella-Zoster virus	Varicella	1974	Michiaki Takahashi	Attenuated vaccine (Oka strain)	(63)
Neisseria meningitidis serogroups A, C, W, and Y	Meningitis	1981		Polysaccharide vaccine	(64, 65)
Hepatitis B virus	Hepatitis B	1982	Baruch Blumberg and Irving Millman	Subunit vaccine based on viral surface protein	(66)
Streptococcus pneumoniae	Pneumonia	1983	Robert Austrian et al.	Polysaccharide vaccine against 23 serotypes	(67)
Haemophilus influenzae type b	Pneumonia, meningitis, and other illnesses	1985	David H. Smith, Porter Anderson, et al.	Polysaccharide vaccine	(68)
Haemophilus influenzae type b	Pneumonia, meningitis, and other illnesses	1987		Conjugate polysaccharide vaccine	(69)
Vibrio cholerae	Cholera	1991	Jan Holmgren et al.	Vaccine containing killed whole cell of *V. cholerae* O1 and cholera toxin B subunit	(70)
Bordetella pertussis	Pertussis	1992	Rino Rappuoli et al.	Acellular vaccine	(71)
Hepatitis A virus	Hepatitis A	1990s	Various developers	Inactivated vaccines	(72)
Neisseria meningitidis serogroup C	Meningitis	1999		Conjugate polysaccharide vaccine	(73)
Streptococcus pneumoniae	Pneumonia	2000		Conjugate polysaccharide vaccine against seven serotypes	(74)
Neisseria meningitidis serogroups A, C, W, and Y	Meningitis	2005		Conjugate polysaccharide vaccine	(65)
Rotavirus	Gastroenteritis	2006	Various developers	Attenuated vaccine against rotavirus and reassortant vaccine	(75)
Human Papillomavirus (HPV)	Human papillomavirus-associated cancers	2006	Ian Frazer and Jian Zhou	Subunit vaccine based on viral proteins; protects against cervical cancer and other HPV-associated cancers	(76)

(Continued)

TABLE 1 (Continued)

Pathogen	Disease	Year	Developer(s)	Vaccine type	References
Neisseria meningitidis serogroup B	Meningitis	2013		Subunit vaccine plus outer membrane vesicles.	(77)
SARS-CoV-2	COVID-19	2020–2021	Various developers	Various technologies: inactivated vaccines, mRNA vaccines, and non-replicating viral vector vaccines.	(78–85)
Respiratory syncytial virus (RSV)	Cold-like symptoms, pneumonia.	2023		Subunit vaccine based on the prefusion F protein.	(86, 87)

*For a historical context, the first vaccines to be licensed or those that marked a milestone in the management of a specific disease are highlighted. The approximate year of development or licensure and the main developers are indicated. The optimization of many of these vaccine formulations has led to their replacement by others that have proven to be safer and more effective. The names of the main developers of the vaccine are indicated. In some cases, the vaccines were developed by pharmaceutical companies and therefore their names are omitted. For more information refer to the text.

(microorganisms), thereby discrediting the idea of spontaneous generation (89).

His investigations also led to the development of experimental techniques to mitigate the deleterious effects of microorganisms in foods and beverages. From 1860 to 1864, he worked on the pasteurization method, which involves heating liquids to a specific temperature for a defined period to eliminate or significantly reduce the presence of harmful microorganisms (89–91). Initially applied to wine and beer, this method not only extended their shelf life but also ensured their safety for consumption. The adaptation of the pasteurization method to milk significantly reduced the transmission of milk-borne diseases (91).

In 1864, Pasteur proposed the "Germ Theory of Disease", postulating that infectious diseases were caused by microorganisms (92). This theory laid the foundations for understanding how infectious diseases spread among people through the transmission of pathogenic microorganisms. However, this approach was subject to intense debate during the following decades, and various versions of the germ theory of disease continued to circulate (93).

It was not until the late 19th century, with Robert Koch, that consensus was reached for this theory. Koch identified the causative agent of anthrax and later tuberculosis (see below). Based on his findings, he established the criteria (Koch's postulates) as a requirement to establish a causal relationship between a microorganism and the development of a specific disease (94).

In 1877, Pasteur began studies on avian cholera (also called fowl cholera), identifying *Pasteurella multocida* as the bacterium that causes this disease. In 1879, he accidentally discovered that cultures of this bacterium experienced a decrease in virulence over time (95). In a serendipitous twist of events, Pasteur, before leaving for vacation, instructed an assistant to inject some chickens with fresh cultures of *P. multocida*, but the assistant forgot to do so before leaving for vacation. Upon return, the assistant inoculated the chickens with the cultures that had been left in the laboratory for a month in glass tubes sealed only with a cotton plug. Contrary to expectations, the chickens developed mild symptoms and fully recovered. Intrigued, Pasteur injected the recovered chickens with an inoculum of fresh culture of *P. multocida* awaiting for the development of the disease. Observing that the birds remained healthy, he deduced that exposure to oxygen caused the loss of virulence. To validate this hypothesis, a series of controlled experiments were conducted. As a result, it was observed that *P. multocida* cultures that were tightly sealed and isolated from air maintained their virulence. In contrast, those exposed to air for varying durations exhibited a consistent and predictable decline in their virulent nature. Pasteur named this reduction in virulence "attenuation", a term that remains today (95). Pasteur also observed that some infected albeit healthy chickens excreted virulent *P. multocida*, indicating the existence of healthy carriers, a key concept for explaining the spread of germs during epidemics (90).

In 1880, Pasteur in France and George Miller Sternberg in the United States simultaneously isolated *Streptococcus pneumoniae*. This bacterium is responsible for various human diseases, including pneumonia, bacteremia, meningitis, empyema, and endocarditis (96).

The following year, Pasteur, with his colleagues Charles Chamberland and Emile Roux, developed an attenuated vaccine against *Bacillus anthracis*, a serious threat to the sheep industry. In contrast to the *P. multocida* cultures, *B. anthracis* cultures transformed into highly virulent spores when exposed to air. However, *B. anthracis* strains grown at a temperature of 42–43°C did not form spores. Although these non-sporulated cultures remained live at these temperatures for a month, a pronounced reduction in virulence was observed following administration to animals (95, 97). Another key finding by Pasteur and colleagues in their research on chicken cholera and anthrax was that repeatedly transferring (serial passage) a microorganism through the same or a different animal species could change its ability to cause disease, either increasing or reducing its virulence (89, 98).

During the 1880s, Pasteur achieved another breakthrough in vaccinology by developing the rabies vaccine. Rabies is a zoonotic disease that primarily affects mammals, including humans, and is transmitted mainly through the bite of infected animals. The rabies virus attacks the central nervous system, causing encephalitis with a very high lethality rate (99).

At the time, the Latin-derived term "virus", which means "poison", was employed to denote any agent that caused infectious disease. The ability to visualize viruses did not emerge until the invention of the electron microscope 50 years later in the 1930s (100). Notwithstanding the lack of clarity on the distinction between bacteria, fungi, and viruses, Pasteur made substantial advancements through his nuanced understanding of disease-causing agents and immunity. Notably, fine filtration techniques devised by Pasteur allowed for the differentiation between microbes. Those of larger size that could be cultivated outside the body (*in vitro*) and observed to form colonies visible to

the naked eye were classified as bacteria. By contrast, pathogens that passed through these smaller filters and were not cultivable outside of living cells became known as viruses. This provided a working definition for viruses, valid until the mid-20th century when the electron microscope facilitated their visualization (89).

For the rabies vaccine, Pasteur recognized that the virus could not be cultivated *in vitro* as it was an actual virus and not a bacterium; thus, the method of atmospheric attenuation could not be used. Instead, he relied on his understanding of the serial passage of microorganisms from one animal to another. In collaboration with his students, Pasteur developed the rabies vaccine by desiccating nervous tissue from rabbits infected with rabies. The virulence of the pathogen decreased progressively during 14 days of desiccation and through successive passages. This led Pasteur to discover that this attenuated virus could protect animals (rabbits or dogs) against a challenge with the wild-type virus without inducing severe disease (89).

In 1885, a 9-year-old boy named Joseph Meister was bitten by a rabid dog and brought to Pasteur's laboratory. Even though the vaccine had not been tested in humans, Pasteur decided to administer it to the child due to the gravity of the situation (29, 49). It is important to note that the rabies virus has a prolonged and variable incubation period that ranges from 4 to 12 weeks or more. Thus, in the case of a bite from an infected animal, the virus does not immediately cause the disease (101). This time between virus entry and symptom onset (today known as the incubation period) provides a window for vaccine administration and the generation of protection. Following this rationale, Meister received a vaccination series during the incubation period. The child did not develop the disease and fully recovered. This marked the birth of the first successful vaccine against rabies and the beginning of a new era in preventing infectious diseases (29). Following this pioneer rabies vaccine, carbolic acid-inactivated nerve tissue-derived vaccines were introduced, followed by phenol-inactivated versions in 1915. These vaccines were used until the mid-1950s when tissue culture-derived inactivated rabies vaccines were first developed, which remain in use today (89, 99, 102).

It should be noted that Pasteur conducted his entire vaccine research without an understanding of the biological processes involved in the protection of vaccinated animals and individuals. However, his work represents the development of the first laboratory-created vaccines, leading to the "isolate, inactivate, and inject" principle that underpinned vaccine development for the next century (95, 103–105).

The legacy of Pasteur goes beyond his revolutionary scientific discoveries, toward an institutional influence. In 1888, the Pasteur Institute was founded, a center dedicated to rabies, as well as research and training in infectious diseases (106). Named after Pasteur, the institute continues its mission to prevent and treat diseases through research, education, and public health intervention.

The last decade of the 19th century marked the beginning of an era in which vaccine development was supported by more solid scientific principles. This progress was led by eminent scientists from Great Britain, Germany, the United States, and Pasteur's laboratory in France. Key achievements of this decade included techniques for inactivating whole bacteria and their use as vaccines (killed vaccines; see below), the discovery of bacterial toxins, and of immune serum containing antibodies capable of neutralizing toxins, denominated antitoxins (103).

During this period, inactivated whole-cell vaccines against diseases such as typhus, cholera, and plague were developed and successfully tested (50–52, 107, 108). Emil von Behring, Shibasaburo Kitasato, Émile Roux, Alexandre Yersin, Almwroth Wright, and Paul Ehrlich are a few of the leading researchers in the field of serum antibodies. Ehrlich, in particular, expanded understanding of antibodies as complementary entities to antigens. Additionally, Roux and Yersin demonstrated that diphtheria bacilli produced an exotoxin, and von Behring and Kitasato verified that antitoxin antibodies could be induced in animal sera exposed to sublethal doses of toxin (103, 109–111).

3.4 The dawn of the 20th century, the discovery of toxoids, and the development of a vaccine for tuberculosis

Before the 20th century, diseases such as diphtheria, tetanus, pertussis, and tuberculosis were major causes of morbidity and mortality, and effective treatments or adequate preventative measures were unavailable.

Diphtheria, a potentially fatal disease, is caused by the bacterium *Corynebacterium diphtheriae*. This pathogen primarily affects the upper respiratory tract and produces a toxin (diphtheria toxin) that disrupts cellular function causing exudative pharyngitis followed by systemic involvement (112). Tetanus is a severe nervous system infection caused by the bacterium *Clostridium tetani*, commonly found in the soil. This bacterium produces a neurotoxin (tetanus toxin) which can cause muscle contractions, including violent spasms, leading to death in severe cases (113).

In 1923, Alexander Glenny and Barbara Hopkins made a significant scientific breakthrough by demonstrating that diphtheria toxin could be inactivated into a toxoid using formalin. Although the toxicity of the toxin was significantly reduced, it was not abolished, and in order to be well-tolerated, it required administration with an antitoxin serum (109, 114). Later, Gaston Ramon was able to produce a stable and non-toxic diphtheria toxoid through the action of formalin and subsequent incubation at 37°C for several weeks. Immunization with this toxoid generated protective antibodies against the diphtheria toxin, laying the foundation for an effective vaccine. This same procedure was used to prepare the tetanus toxoid and several other toxoids (54, 55, 109, 115).

Pertussis, also known as "whooping cough," is caused by the bacterium *Bordetella pertussis*. This infection affects people of all ages, potentially causing severe disease in infants and death. In the early efforts against pertussis, the work of Thorvald Madsen in the 1920s led to a formalin-inactivated whole-cell vaccine that provided a degree of protection, but it was the work of Pearl Kendrick and Grace Eldering in the 1930s which finally provided an effective vaccine against whooping cough (56, 116). In 1948, vaccines against diphtheria, tetanus, and whooping cough were combined into the DTP vaccine, leading to a significant decrease

in associated illnesses and deaths (117, 118). Due to pertussis toxin content, the vaccine was associated with considerable side effects such as fever, inflammation at the injection site, and in rare cases, severe neurological disorders, including encephalopathy (17, 119). Concerns about the safety of this vaccine led in the following decades to the development of less reactogenic formulations through endotoxin removal in acellular formulations as reviewed further down.

One of the "global killers" has been and continues to be tuberculosis (TB), named by Johann Schonlein in 1834, and referred throughout history as: "phthisis" in ancient Greece, "tabes" in ancient Rome, and "schachepheth" in ancient Hebrew. In the 18th century, it was denominated "the white plague" due to the characteristic pallor of affected individuals. Although Schonlein had already named it tuberculosis, in the 19th century, it was also called "consumption". During this period, TB acquired the grim nickname of "Captain of all these men of death" (120, 121).

TB primarily affects the lungs but can also affect other organs. It is transmitted airborne when a person with active TB coughs, sneezes or speaks (122). In 1882, Robert Koch identified *Mycobacterium tuberculosis* as the bacterium responsible for TB (123). TB was one of the leading causes of death at that time, affecting one out of seven individuals in the United States and Europe (120).

Years later, in 1921, Albert Calmette and Camille Guérin developed the Bacille Calmette-Guérin (BCG) vaccine based on an attenuated strain of *Mycobacterium bovis*, a bacterium closely related to *M. tuberculosis* (53). This vaccine was developed in a remarkable effort through 230 serial passages of *M. bovis* in medium containing bile, over a period of 13 years (124, 125). This rigorous procedure allowed for the selection of avirulent strains lacking the ability to cause disease. Later work by Calmette and Guérin demonstrated that their vaccine protected animals and infants against *M. tuberculosis* (103, 125).

Although the BCG vaccine offers critical protection against severe forms of TB in children, such as military tuberculosis and tuberculous meningitis, its efficacy against pulmonary TB in adults has been inconsistent (126). The genetic variability between different BCG vaccine strains and the variable protection observed in different populations and geographic regions further underscore the complexities of tuberculosis immunity (125). Moreover, there is a pressing call within the scientific community for the development of new TB vaccines. However, this endeavor has been hampered by a myriad of challenges, including our limited understanding of the correlates of protective immunity against TB (127), the pathogen's sophisticated immune evasion strategies, and the multifaceted nature of the disease itself (128).

Despite the availability of BCG vaccine and several antibiotics, the control of TB is currently hindered by the emergence of multidrug-resistant strains of *M. tuberculosis*, especially in vulnerable populations such as immunocompromised individuals (129). This persistent challenge underscores the urgent need for novel TB vaccine candidates and advanced therapeutic approaches. Global initiatives focusing on prevention, early detection, and effective treatment are essential to reduce the burden of TB and advancing toward the potentially achievable, albeit difficult goal of eradication (130).

During the 1930s, the serial passage technique, either *in vitro* or in unusual hosts, was continually employed to attenuate various pathogens. For example, Max Theiler and Hugh Smith attenuated the yellow fever virus by serial passage in mice and chicken embryo tissues, respectively (57, 131, 132).

3.5 Second half of the 20th century and the eradication of poliomyelitis

In the second half of the 20th century, vaccinology made considerable achievements, mainly due to the introduction of novel methodologies for vaccine development. Among these, tissue culture methods allowed the controlled growth of bacteria and replication of viruses in the laboratory. This advancement significantly accelerated the large-scale production of vaccines (133).

These advances were complemented by improvements in storage and distribution systems, highlighted by applying preservatives and incorporating the cold chain. This ensured the quality and viability of vaccines during their storage and transport. Importantly, these advances facilitated the distribution of vaccines, providing access to an ever-increasing number of individuals worldwide (134).

A hallmark achievement during this period of rapid scientific evolution was the successful control and near-eradication of poliomyelitis. This viral disease, known to cause paralysis and permanent disability, affected hundreds of thousands of individuals annually at the time. Two significant contributors to this effort were Jonas Salk and Albert Sabin. In 1955, Salk developed the first inactivated polio vaccine (IPV), formulated with chemically inactivated viral particles encompassing all three poliovirus types (58, 135). However, IPV had inherent limitations, such as the need for administration via injection and booster doses owing to its reduced potency (136). Moreover, IPV faced some initial setbacks, including contamination of two production batches with viable viral particles, which led to serious health problems among those vaccinated and product recalls, and raised significant public doubts regarding its use. The production of IPV was resumed after stringent improvements in quality control measures and supervision (35).

A few years later, in 1961, Sabin developed an oral polio vaccine (OPV) based on attenuated viruses (59). This vaccine exhibited advantages over IPV in terms of ease of administration, cost-effectiveness, and provision of long-lasting immunity limiting the need for booster doses. Nevertheless, OPV was not without risks. On rare occasions, vaccination with the live attenuated virus could result in paralytic poliomyelitis—a condition termed vaccine-associated paralytic poliomyelitis (VAPP) or mutate to a more virulent strain causing small outbreaks of vaccine-derived poliovirus (VDPV). Despite these potential risks, the benefits of OPV resulted in its widespread adoption in Western regions, and it was instrumental in extensive vaccination campaigns that significantly decreased the global incidence of polio (12, 13).

By the end of the 1990s, the challenge was to balance the benefits and risks associated with OPV and IPV in a global plan for poliovirus eradication requiring the vaccination of the

world population. As polio cases markedly declined, the relatively minor yet substantial risk of VAPP came into sharp focus, prompting recommendations for IPV usage in polio-free nations. In contrast, OPV continued to be used for routine immunization in regions where the disease remained more prevalent (137, 138). This transition illuminates a broader trend in the evolution of vaccinology: recognizing and addressing the inherent limitations and risks of vaccines to maximize their potential benefits.

In 2016, a global coordinated shift occurred from trivalent OPV (tOPV), containing Sabin strain types 1, 2, and 3, to bivalent OPV (bOPV), containing Sabin strain types 1 and 3. Remarkably, clinical cases of wild poliovirus have decreased by over 99% since 1988, with an estimated 350,000 cases in more than 125 endemic countries compared to only 6 cases reported in 2021 (12, 13, 138). Today, wild poliovirus type 1 is endemic only in Afghanistan and Pakistan, but there has been a rise in circulating vaccine-derived poliovirus type 2 outbreaks since 2017. In response to these outbreaks, in 2020, the WHO granted Emergency Use Listing for the novel oral poliovirus type 2 (nOPV2; genetically stabilized) to be used in a limited number of countries. The Polio Eradication Strategy for 2022–2026 outlines the wider use of nOPV2 to progress toward total eradication (12). The success of polio vaccines exemplifies the triumphs and challenges of modern vaccinology, reflecting the continuing importance of technological, logistical, and ethical considerations in the drive toward global health improvement. However, one of the main challenges will be to ensure optimal coverage of these vaccines, especially after the COVID-19 pandemic, in which coverage has decreased in many regions of the planet (139).

During the 1960s, important vaccines against prevalent viral diseases such as measles, rubella, and mumps were developed. Measles, a highly contagious infection, can be fatal by causing pneumonia and neurological complications (140). Although mumps is generally less lethal, it can cause severe complications, such as aseptic meningitis and encephalitis (141). On the other hand, rubella, while often mild in children, can have devastating effects on pregnant women and neonates (142).

The first approaches to developing vaccines against these pathogens focused on developing formalin-inactivated viruses. However, these vaccines failed to provide full and long-lasting immunity, so efforts turned to the development of attenuated vaccines (35). These vaccines were developed by weakening the viruses through their passage in embryonated eggs or cell cultures, making the attenuated viruses safe, and less reactogenic while retaining immunogenic capacity (62, 142, 143).

The first attenuated measles vaccine was developed by John Enders between 1954 and 1960 and later licensed in 1963 (60, 144, 145). At the same time, Maurice Hilleman and colleagues developed an attenuated mumps vaccine, approved in 1967 (61). Regarding rubella, Paul Parkman, and Harry Meyer Jr. developed the first attenuated vaccine in 1965, known as HPV-77 (143, 146). However, Hilleman developed a more effective vaccine, the RA 27/3 (62), which by the late 1970s became the only rubella vaccine used worldwide, except in Japan (147). Live attenuated rubella vaccine strains Takahashi, Matsuura, and TO-336 were licensed in Japan in 1969-1970 and continue to be used today (148, 149).

The 1970s ushered in the era of combination vaccines, particularly the combination of live vaccines into a single formulation offering protection against measles, mumps, and rubella (MMR vaccine) (150). MMR vaccine simplified immunization schedules and reduced the number of inoculations. Importantly, it exhibited substantial efficacy, resulting in a marked decline in the global incidence of these diseases (151). Before widespread vaccination against measles in 1980, this disease caused ∼2.6 million annual deaths worldwide (152). After mass vaccination, measles deaths have drastically reduced, to ∼140,000 deaths in 2018 (153).

In the same decade, Michiaki Takahashi developed the vaccine against the varicella-zoster virus by cultivating it serially in human embryonic lung cells and then in guinea pig embryo cells (63). However, this vaccine was not licensed until 1987 in Japan and Korea and not until 1995 in the United States and other countries (154).

A breakthrough in vaccinology has been the prevention of infection-associated cancers, for which the hepatitis B vaccine was the pioneer (155). In 1982, using molecular biology techniques, the first subunit vaccine against hepatitis B was developed. This vaccine is based on the production and purification of a surface protein from the virus and has been essential in reducing the transmission of this hepatotropic infection and preventing hepatocellular carcinomas (66, 156). This vaccine is currently part of the infant immunization regimen in most WHO member countries (133).

In the 1980s, there was significant progress in the implementation of new strategies for vaccine design. During this period, vaccines against the three main bacterial "killers" in children, *Haemophilus influenzae* type b (Hib), *Streptococcus pneumoniae* and *Neisseria meningitidis* advanced albeit with differences, using a similar strategy. The first approach was the development of capsular polysaccharides vaccines. In 1981, the strategy partially worked for *N. meningitidis* serogroups A, C, W, and Y (64), but not for serogroup B due to the molecular mimicry between the pathogen capsule of this serogroup and lipids of the human central nervous system (157, 158). In 1983, a 23-valent vaccine against *S. pneumoniae* was licensed (74). Concomitantly, in 1985, the polysaccharide vaccine against Hib was licensed (68). However, subsequent trials revealed that these polysaccharide vaccines were insufficient in eliciting adequate protection in infants (159–161).

Consequently, polysaccharide-protein conjugation strategies, originally conceived in the 1930s, were applied to enhance the immunogenicity of these vaccines (133, 162, 163). In 1987, the first Hib conjugate vaccine was licensed (69, 164). In 1999, the first *N. meningitidis* serogroup C conjugate polysaccharide (MenC) vaccine became available (73, 163, 165), and in 2005, a conjugated vaccine for serogroups A, C, W, and Y (MenACWY) was licensed (166). In 2000, the first *S. pneumoniae* conjugate vaccine (PCV) was licensed including seven serotypes (PCV7), progressing to PCV10 and PCV13, and, more recently, PCV15 and PCV20 (74).

In 1991, licensing the first inactivated oral cholera vaccine (OCV) was a significant milestone (70). This vaccine has been instrumental in controlling cholera, a diarrheal disease caused by

the bacterium *Vibrio cholerae*. The OCV has been especially useful in cholera-endemic regions, during outbreaks, and emergencies, such as armed conflicts and natural disasters, where sanitation conditions may deteriorate, increasing the risk of spreading cholera (167).

A year later, in 1992, the recombinant acellular vaccine against whooping cough was developed. Providing a safer and less reactogenic alternative to the preceding whole-cell pertussis vaccine, it has since replaced the latter in many countries (71). Additionally, this year marked another milestone with the licensing of the first inactivated vaccine against hepatitis A (168), followed by the licensing of several subsequent hepatitis A vaccines (72).

3.6 21st-century vaccines and emerging technologies

In the 21st century, the development of new vaccines has continued to progress, leading to vaccines against rotavirus and human papillomavirus (HPV). Globally, rotavirus is the predominant cause of acute diarrhea in children under five. Two rotavirus vaccines, one based on virus attenuation and the other on the novel virus reassortment technique (allowing the expression of a specific gene in a selected animal rotavirus strain as the backbone), were licensed in 2006. These vaccines and few others that have followed have since been adopted in over 100 countries (75, 169). Responding to the significant rotavirus disease impact during childhood, the WHO recommended including an oral rotavirus vaccine in routine childhood immunization programs in 2009. As a result, countries that adopted rotavirus vaccines have reported a 40% reduction in hospitalizations due to rotavirus in children under five. At the same time, annual deaths worldwide from rotavirus-induced diarrhea have decreased by 25% (170).

A breakthrough in cancer prevention was the development of first HPV vaccine, which was licensed in 2006. This vaccine includes specific attenuated oncogenic types, and has proven to be highly effective in protecting against cervical cancer and other HPV-associated cancers in females and males (76, 171). HPV vaccines have been incorporated into immunization programs in many countries. The immunization strategy notably emphasizes the application of this vaccine in women during early adolescence. However, it is worth noting that the vaccine is also effective for men and is recommended for the prevention of anal cancer, penile cancer, and other HPV-associated cancers (171). Furthermore, it should be noted that HPV vaccines are a preventive measure, they do not serve as a cure for these cancers, nor do they protect against all types of HPV. However, they do offer protection against the most common oncogenic HPV types, which vary among different commercial vaccines (172).

The advent of reverse vaccinology (RV) has substantively modified our understanding and approaches to vaccine research, especially for the development of *N. meningitidis* serogroup B (MenB) vaccine. Unlike classical methods based on Pasteur's "isolate, inactivate, and inject" principle, RV employs whole genome sequencing (WGS) and robust bioinformatic analysis to predict the antigenic repertoire of a pathogen. This innovative approach is essential for pathogens such as MenB, for which conventional approaches have been ineffective (173).

As discussed previously, antigenic mimicry between the MenB capsular polysaccharide and human glycoproteins leads to poor immunogenic responses and raises concerns about autoimmunity (158). In 2000, the complete genome sequence of MenB MC58 was published (174). Using bioinformatics tools, a comprehensive analysis of this genome revealed 570 proteins that were predicted to be either surface-exposed or secreted. Of these, 350 were successfully cloned and expressed in *Escherichia coli*. These recombinant proteins were injected into mice, showing a promising finding, as 91 exhibited immunogenic properties and 28 triggered the production of bactericidal antibodies, suggesting their potential in vaccine development (175). The identification of these novel bactericidal antigens marked a significant advance in the field, given that only a few such antigens had been identified until then (77).

The increased availability of MenB genomes facilitated a comprehensive analysis of globally circulating MenB strains, offering insights into the diversity and conservation of meningococcal antigens. This analysis resulted in the identification of three conserved and bactericidal antigens: Neisseria Heparin Binding Antigen (NHBA), *N. meningitidis* adhesion A (NadA), and factor H binding protein (fHbp). These antigens, formulated with detergent-extracted outer membrane vesicles from a New Zealand MenB epidemic isolate, culminated in the development of the first MenB vaccine, denominated 4CMenB (176, 177). This multicomponent vaccine received approval in 2013 in Europe and Canada, and in 2015 in the United States, among other countries (77). Concurrently, a second MenB vaccine was developed, known as the rLP2086 vaccine. This vaccine, which contains two variants of the fHbp protein, was approved in the United States in 2014 and in Europe in 2017(178). In 2017, a clinical trial was initiated to evaluate the immunogenicity and safety of a pentavalent meningococcal ABCWY vaccine that combines two licensed vaccines, the MenACWY vaccine and the rLP2086 vaccine (179).

Currently, the pace of vaccine development continues to accelerate impressively, a trend fueled by the COVID-19 pandemic. This pandemic underscored the importance of centuries of accumulated knowledge in vaccinology, including technologies that had not been widely applied, but that seemed promising. As a result, an unprecedented number of different types of vaccines aimed at containing SARS-CoV-2 were developed in record time. Existing infrastructure for new vaccine platforms, such as mRNA- and DNA-based vaccines, vector-based delivery systems, as well as extensive previous work with related coronaviruses, namely SARS-CoV-1 and MERS, were critical for the rapid development of these vaccines. This previous knowledge enabled a rapid transition from preclinical evaluation to Phase I clinical trials for some of the leading vaccine candidates (180).

Among the most innovative vaccine development technologies that emerged during this pandemic are those based on mRNA, which is introduced into human cells either through viral vectors or encapsulated in liposomes. These novel vaccines have proven to be safe and effective against SARS-CoV-2 and have decisively contributed to resolving the global health emergency caused by this pathogen

BOX 2 Basic concepts of immunology and vaccines.

Antigens: Molecules, typically proteins or polysaccharides, present on the surface of pathogens. Antigens are recognized by the immune system as foreign and trigger an immune response.

Adjuvants: In the context of vaccinology, they are components capable of enhancing and/or shaping antigen-specific immune responses. The use of adjuvants makes it possible to reduce the amount of antigen needed in a vaccine and improve the duration and magnitude of the immune response (187). Commonly incorporated adjuvants in human vaccines include aluminum salts, oil-in-water emulsions (such as MF59 and AS03), and bacterial derivatives (such as monophosphoryl lipid A) (188).

Innate response: The first line of defense of the immune system, acting quickly but lacking specificity. It involves activating cells such as macrophages, dendritic cells, and neutrophils, and, which recognize and eliminate pathogens through processes such as phagocytosis and the release of antimicrobial substances.

Antigen presentation: Process in which specialized cells, such as dendritic cells, capture, process, and present antigens on their surface along with major histocompatibility complex (MHC) molecules. This allows the T lymphocytes to recognize part of the antigen and subsequently become activated.

Adaptive response: Second line of defense of the immune system, characterized by its specificity and memory. It involves the activation of T lymphocytes and B cells in response to specific antigens, leading to a more precise and lasting immune response.

T Lymphocytes: Classified into two main types: CD4 and CD8. CD4 T lymphocytes, also called "helper" cells, recognize antigens presented by class II MHC molecules and aid in activating and regulating the immune response. CD8 T lymphocytes, known as "cytotoxic", recognize antigens presented by class I MHC molecules and directly eliminate pathogen-infected cells.

B cells: Lymphocytes that differentiate into antibody-producing plasma cells upon being activated by an antigen. The antibodies produced are specific for the antigen that activated the B cell.

Antibodies: Also known as immunoglobulins, these are specialized proteins that bind to their target antigen and can directly neutralize pathogens and/or mark them to facilitate their elimination through other effector functions.

Effector functions: Actions performed by immune cells to eliminate pathogens and protect the organism. These functions include phagocytosis by innate cells, releasing cytokines and chemokines that promote inflammation and activation of immune cells, the production of antibodies by B cells, and elimination of infected cells by cytotoxic T lymphocytes.

Immune memory: Key feature of the adaptive immune system that allows for a faster and more efficient response to future exposures to the same antigen. Immune memory is due to the generation of memory B and T cells, which persist in the body after the resolution of an infection or the administration of a vaccine.

Primary and secondary response: Primary response is the initial immune response to an antigen, characterized by activating naïve B and T cells and producing specific antibodies. Although this response can effectively control an infection, it tends to be slower and less efficient than a secondary response. The secondary response occurs when the immune system reencounters the same antigen, and due to immune memory, memory B and T cells are rapidly activated, producing a faster, more robust, and lasting response.

(181, 182). In a later section, we will delve deeper into these vaccine types.

In 2023, the first vaccines against Respiratory Syncytial Virus (RSV) were approved in the United States and Europe. The journey to develop an effective vaccine against RSV was marked by significant challenges. In the 1960s, a formalin-inactivated RSV vaccine, rather than conferring protection, exacerbated severe lung inflammatory responses during natural RSV infections in children. Consequently, safety concerns profoundly delayed RSV vaccine development for decades (21).

However, the landscape of RSV vaccine research changed due to increased understanding in the biology of this virus and its structure (183, 184). The RSV surface is decorated with proteins, including the fusion protein (F), which is a major target for vaccine development due to its essential role in viral entry and to its sequence conservation. The F protein has two complex structural conformations, the prefusion and postfusion states. The antigenic complexity and conformational dynamics of this protein underscore the intricate challenges in RSV vaccine development. Notably, prefusion F protein is present in infectious RSV but absent on the surface of formalin-inactivated RSV (185).

The first licensed RSV vaccine, denominated RSVPreF3 OA, contains the prefusion F protein and the AS01 adjuvant. This vaccine is approved for use in adults over the age of 60 (86). The second licensed RSV vaccine, denominated RSVPreF, is a bivalent vaccine containing equal amounts of the prefusion F protein from the two predominant RSV subgroups (RSV A and RSV B). This later vaccine is also approved for use in adults over the age of 60 (186), and in pregnant women between 32- and 36-weeks of gestation, to protect infants up to the age of 6 months (87).

4 Immunological basis of vaccination

The functionality of vaccines can only be fully appreciated by exploring some fundamental immunological concepts (see Box 2 for a summary of these key concepts).

The immune system is our defense mechanism against bacteria, fungi, parasites, and viruses and it has traditionally been divided into two broad components: innate and adaptive immune systems. The innate immune response serves as the first line of defense, acting quickly albeit lacking specificity. In contrast, the adaptive immune response, although slower, acts with specificity, recognizing and remembering specific pathogens to generate faster and more efficient responses upon subsequent exposures (189). Both types of immune responses actively coordinate with one another, as will be described further below.

Vaccination is possible because of adaptive immunity, with the capacity to "remember" and respond to specific pathogens. Taking advantage of this natural capacity, vaccines include the pathogen, either in live attenuated or inactivated form, or components derived from the pathogen, such as antigens or nucleic acids.

When the immune system encounters an antigen, either through infection or vaccination, it triggers a series of events

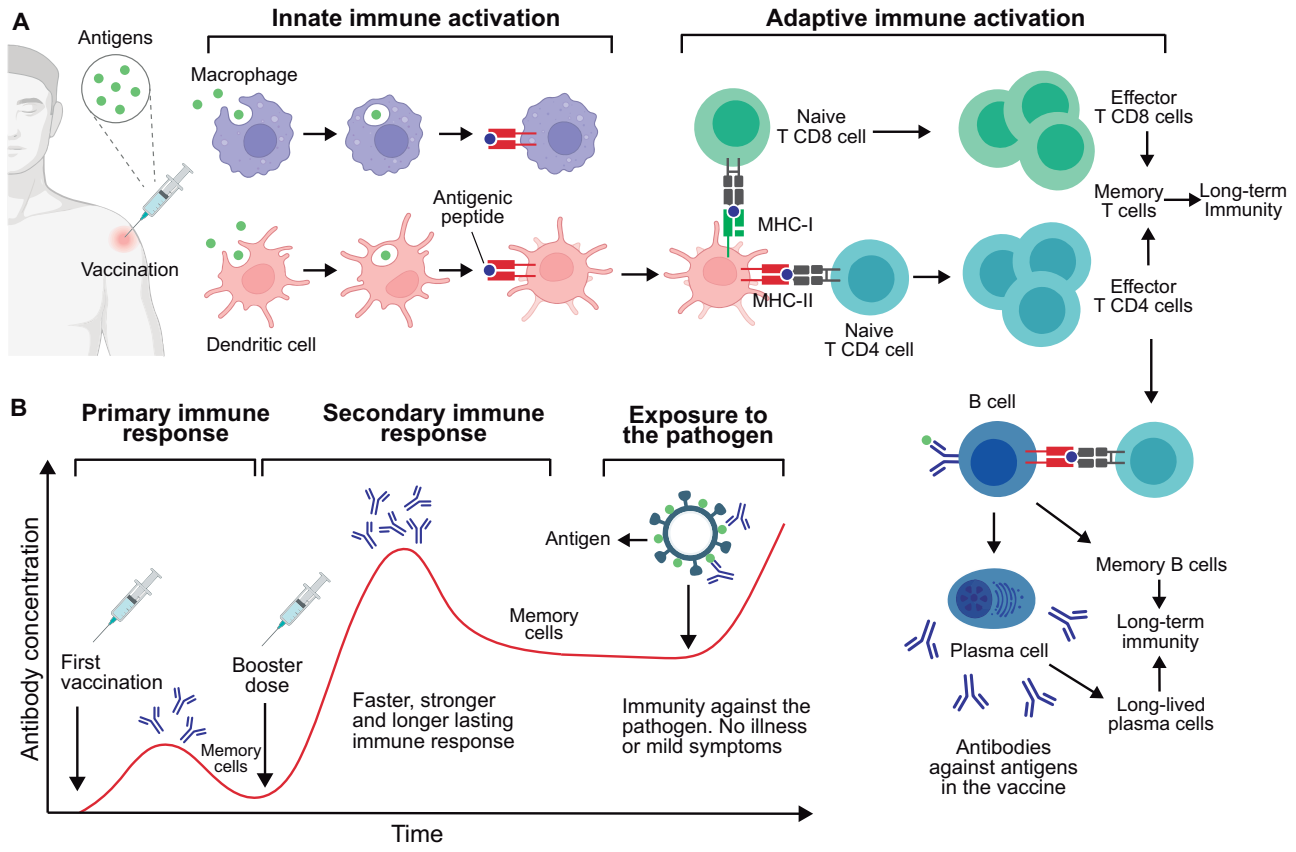

FIGURE 1
Immune response to vaccination and acquisition of immunity. **(A)** Immune response post-vaccination. This process is initiated by the activation of innate immune cells including macrophages and dendritic cells, which engulf and process antigens, leading to the presentation of antigenic peptides (epitopes) via class I or II major histocompatibility complex (MHC-I or MHC-II). These activated innate cells present antigens to CD4 and CD8 T lymphocytes, leading to their activation. Once activated, these T cells proliferate and exercise their effector functions; notably, CD4 T cells stimulate B lymphocytes specific to the antigen. These B cells proliferate and mature into plasma cells, producing antigen-specific antibodies. Of note, a number of memory T and B cells persist in the body to provide long-term immunity. Also, plasma cells can become long-lived plasma cells and secrete antibodies for months or years. **(B)** Timeline of antibody production post-vaccination. Primary and secondary immune responses are shown following the initial vaccination and subsequent booster dose, respectively. These generated antibodies and memory cells provide protective immunity against future exposure to the target pathogen. This figure was created using BioRender.com.

involving several cells and molecules of the immune system (Figure 1A). A heterogeneous group of innate cells, collectively called antigen-presenting cells (APCs), including macrophages and dendritic cells, engulf the pathogen (or antigens) and present antigenically relevant structures (epitopes) on their surface to "alert" the adaptive immune system (190, 191).

T cells, important components of the adaptive immune system, recognize the epitopes presented by APCs, leading to their activation and proliferation. This generates a specialized cell population prepared to eliminate both the antigen and the corresponding pathogen. T lymphocytes are categorized into two main types: CD4 and CD8. CD4 T cells, also called helper T cells, stimulate the function of other immune system cells such as macrophages and B cells. In the case of B cells, CD4 T cells stimulate their differentiation into plasma cells, which produce and secrete antibodies. These antibodies are specialized proteins that specifically bind to antigens and aid in neutralizing or marking the pathogen for subsequent destruction by immune cells (192). CD8 T lymphocytes, also called cytotoxic T cells, can directly destroy cells infected by pathogens, thus preventing the pathogen from multiplying and spreading to other cells (193).

During this process, immune and/or infected cells release inflammatory molecules called cytokines, which are essential for coordinating the immune response. Cytokines are small proteins that serve as chemical messengers that modulate the activity of immune cells, promoting inflammation and aiding in the recruitment of additional immune cells to the site of vaccination or infection.

CD4 and CD8 T cells, B cells, antibodies, and cytokines operate synergistically to form a complex network focused on the elimination of specific pathogens and/or pathogenic molecules. Depending on the nature of the vaccine, both cellular and antibody responses can be triggered, albeit with varying degrees of potency and phenotypic differentiation. Consequently, this leads to differentiated levels of protection against specific pathogens (194).

A key feature of the adaptive immune system is immune memory. The primary immune response is triggered upon the initial encounter with a pathogen (or antigen), taking weeks to fully develop. During this response, a subset of T and B cells become memory cells that persist in the body for a prolonged period, from years to decades (195). These memory cells acquire the ability to recognize the pathogen and are quickly activated. Thus, in subsequent encounters with the same pathogen, memory cells activate rapidly, in days, triggering a secondary immune response that is faster and more efficient (196–198).

Vaccine boosters aim to induce secondary responses that enhance the immunological memory generated by the primary vaccination (Figure 1B). Typically, booster doses may increase the quantity and quality of the immune response involving memory cells. While a single vaccine dose can confer temporary protection, booster doses may extend this immunity. The need for one or more booster doses is determined in the preclinical and clinical evaluations carried out for any new vaccine candidate, as will be discussed further bellow.

5 Vaccine safety and protective efficacy/effectiveness assessment

The evaluation of the safety and efficacy/effectiveness of vaccines is a rigorous and meticulous process requiring both preclinical and clinical studies (Figure 2).

Before a vaccine is tested in humans, preclinical studies are performed in the laboratory, and animals, such as mice or primates, aiming to assess whether the vaccine is safe and capable of producing an effective immune response. If results obtained during this phase are promising, the vaccine can progress to clinical trials (199).

Clinical trials are studies conducted in various phases, all of which must be completed before the vaccine can be approved for public use. However, during health emergencies, such as the COVID-19 pandemic, the process can be expedited without significantly compromising safety (accepting a somewhat lower threshold for the "emergency use" restriction of these pandemic vaccines). In these situations, phases of clinical trials may overlap or be conducted simultaneously (180, 200), and regulatory agencies can advance the emergency authorizations based on interim analyses (201). It is essential to highlight that, even under expedited timelines, the risk-benefit balance is critically evaluated, ensuring that the potential benefits of vaccines used in the face of a high-impact public health crisis outweigh the potential risks.

During Phase 1 clinical trials, the vaccine is tested in a small group of people to evaluate its safety, determine the appropriate dosage, and monitor the induced immune response. Phase 2 expands the trial to hundreds of people, providing additional information on vaccine safety, its ability to generate an immune response, and a first evaluation of its protective efficacy (PE) against the main outcomes to be prevented (199, 202).

In Phase 3 trials, the vaccine is tested on thousands of people to evaluate its PE against primary and secondary outcomes and monitor side effects in a more extensive and more diverse population. Protective efficacy of a vaccine can be determined through criteria such as infection prevention and/or prevention of moderate to severe disease, including deaths if feasible (202, 203).

If the vaccine proves to be safe and effective in Phase 3 clinical trials, health regulatory entities, such as the United States Food and Drug Administration (FDA), the European Medicines Agency (EMA), and others, can proceed to its approval, an essential step for vaccine licensing and use.

Once approved and distributed, the vaccine enters what is known as Phase 4 evaluations, or post-marketing surveillance (a term coined for non-case-control trials). During this stage, the safety and effectiveness of the vaccine continue to be evaluated in a real-world setting, with broader and more diverse population tracking. Phase 4 enables the collection of long-term data on the efficacy of vaccines, their effects on disease incidence, hospitalizations, and fatalities in various age groups and health conditions. It also allows monitoring for unforeseen and/or rare adverse effects that may arise when the vaccine is used in a much larger and diverse group of people (202).

Adverse effects, which both healthcare professionals and vaccinated individuals can report, are recorded, and carefully analyzed. These reports are vital for ensuring the ongoing safety of the vaccine and allow regulators and vaccine manufacturers to quickly detect and respond to any safety signal that may arise.

It is important to note that vaccine efficacy/effectiveness can be influenced by various factors such as the endogenous microbiota, genetic traits, age, and nutritional status of the individual, presence of chronic or immunosuppressive disease, among others (204). These factors must be considered when designing and implementing vaccination programs to ensure optimal safety and protection of the population.

6 Types of vaccines

In this section, we will explore the different types of vaccines (Figure 3), their main characteristics, advantages, and limitations (Table 2). From attenuated vaccines that use weakened pathogens to nucleic acid vaccines that encode specific antigens, vaccine design has evolved with advancing technology to improve safety, efficacy, production efficiency, and stability.

6.1 Live attenuated vaccines

These vaccines employ microorganisms weakened through various processes, such as serial passage in cell cultures or unconventional hosts. Essentially, by continually propagating the pathogen in an atypical environment, the microorganism accumulates genetic mutations and/or loses virulence genes, leading to its attenuation and therefore its ability to cause disease in the original host. Additionally, advancements in genetic engineering have provided faster and more reliable methodologies to delete or modify genes with the aim of attenuation (205).

However, attenuating a pathogen to produce a vaccine can be complicated and expensive, being especially challenging for bacteria, structurally more complex than viruses, with a larger

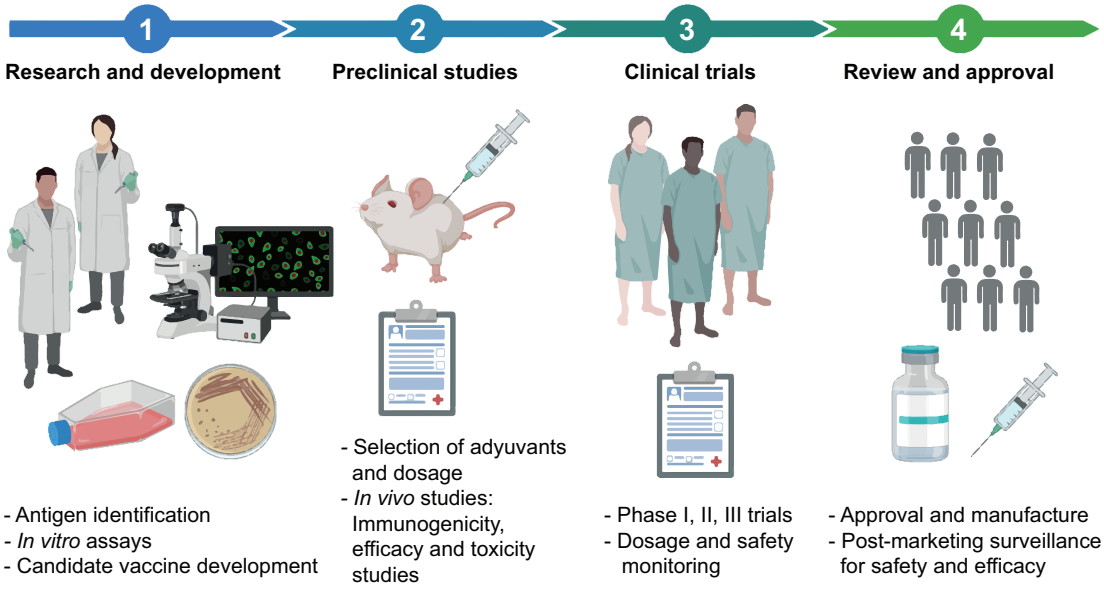

FIGURE 2
General description of the vaccine development pipeline. The process of designing, developing, and testing a vaccine involves a series of steps. It begins with the Research and development stage, where potential vaccine candidates are identified. Subsequently, preclinical studies with animals are carried out to evaluate the efficacy and safety of the vaccine candidates. The process advances to the Clinical Studies stage after a successful proof of concept of the vaccine candidate. This stage is divided into Phase I (safety and dosing), Phase II (efficacy and side effects), and Phase III (monitoring for adverse reactions in a larger population) trials. Upon successful completion of these clinical trials, the process moves to the Post-Manufacturing Approval and Phase IV, surveillance studies. Here, vaccines undergo a strict approval process to receive regulatory sanction for public use, along with ongoing surveillance to track long-term effectiveness and possible side effects. The main activities within each stage are detailed. This figure was created using BioRender.com.

number of genes and various virulence mechanisms. As a result, few live attenuated bacterial vaccines are commercially available (206).

Attenuation allows the pathogens to retain their ability to replicate in the host, allowing them to mimic a natural infection to some extent but without causing the disease. This characteristic allows these vaccines to induce a comprehensive and long-lasting immune response, generating both humoral and cell-mediated immunity (205).

Prominent examples of live attenuated vaccines include vaccines for tuberculosis (BCG), poliovirus (OPV), measles, mumps, and rubella viruses (MMR), rotavirus, and yellow fever (205). These vaccines are generally safe and effective; however, they may present risks under specific circumstances. The attenuated pathogen could potentially cause disease or adverse effects for immunocompromised individuals or pregnant women. Also, although extremely rare, there is a chance that the attenuated pathogen could revert to a virulent form and cause disease (207).

Limitations of these vaccines compared to other types of vaccines include lower stability with a shorter shelf life often requiring refrigeration, which can complicate storage and transport, particularly in resource-limited regions (208).

6.2 Inactivated vaccines

Inactivated vaccines, also referred "killed vaccines", are among the earliest vaccines developed. These vaccines are manufactured from microorganisms that, after being subjected to chemical or physical treatments, lose their ability to replicate, thus eliminating their potential to cause disease in any host. Despite inactivation, the remaining pathogen structures retain the ability to be recognized by the immune system, triggering an immune response, most commonly humoral, thereby conferring immunity (209, 210).

Inactivation can be achieved through chemical or physical processes. In the former, agents such as formaldehyde/formalin or β-propiolactone are used. Formalin generates cross-links between amino acid molecules, a process known as fixation. This process can stabilize the three-dimensional structure of the proteins, conserving their conformation but abolishing their biological functions. Additionally, these chemical agents can damage the integrity of nucleic acids, rendering the pathogen unable to replicate (209, 211). Physical inactivation can be achieved by heat, often at high temperatures (>60°C). However, this approach is frequently accompanied by a chemical treatment to ensure thorough pathogen inactivation (209, 212).

Inactivated vaccines have several advantages. They are safe and well-tolerated, even among immunocompromised individuals or pregnant women, as the inactivated pathogen cannot replicate or revert to a virulent form (213). Additionally, they are economically feasible and relatively straightforward to produce.

However, they also have limitations. Inactivation methods can eventually alter the structure of some relevant antigens, reducing

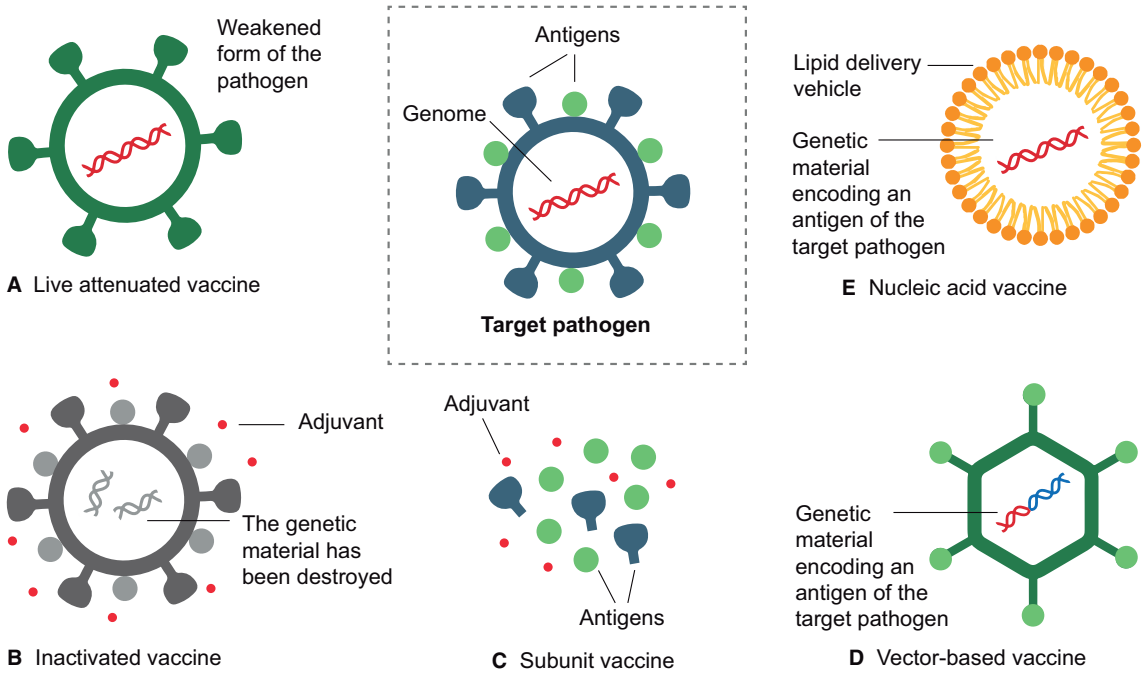

FIGURE 3
Main types of vaccines. **(A)** Live attenuated vaccines use a weakened form of the pathogen. **(B)** Inactivated vaccines contain a killed version of the pathogen, with surface antigens intact but the genome inactivated. **(C)** Subunit vaccines include only selected antigens from the pathogen. **(D)** Vector-based vaccines use a harmless vector to carry a fragment of the genome of the target pathogen. **(E)** Nucleic acid vaccines use the genetic material from the pathogen, either DNA or RNA, encapsulated within a delivery mechanism, such as liposomes or introduced through electroporation (DNA). All these types of vaccines aim to stimulate the immune response to a specific pathogen, although they may have different mechanisms of action. This figure was created using BioRender.com.

TABLE 2 **Main characteristics, limitations, and disadvantages of available vaccines.**

Type of vaccine	Characteristics	Limitations and disadvantages
Live attenuated	Weakened version of the pathogen. Provides durable immunity, often with a single dose. Although for several vaccines, repeated doses are also required.	Not recommended for immunocompromised individuals. Small risk of the pathogen reverting to its virulent form.
Inactivated	Inactivated pathogens, which cannot replicate, ensure safety even for individuals with compromised immune systems.	Requires multiple doses. Protection tends to be less durable than live attenuated vaccines.
Subunits	Purified parts (antigens) of the pathogen. Safe for immunocompromised individuals.	Requires multiple doses. Protection tends to be less durable than live attenuated vaccines.
Toxoids	Non-toxic derivatives of toxins (toxoids). Triggers an immune response against the toxin, not the pathogen itself.	Requires multiple doses. Some individuals may have allergic reactions to the toxins.
Vector-based	Carrier microorganism (vector) transporting genetic sequences encoding for a relevant antigenic protein of the target pathogen. The vector may or may not be replicative.	Potentially reduced efficacy among individuals with pre-existing immunity to the vector. Replicative vectors are not suitable for immunocompromised individuals.
Nucleic acids	Genetic material (mRNA and, less commonly, DNA) encoding a relevant virulence protein, which is encapsulated in a lipid vesicle or introduced by electroporation. Can be rapidly developed and produced.	Requires extremely low storage temperatures. Long-term effects under study.

the neutralizing capacity of induced antibodies. Moreover, as they do not mimic a natural infection, the immune response may be of shorter duration and magnitude compared to attenuated vaccines. Repeated booster doses are usually required to maintain long-term protection. Additionally, the majority of these vaccines require the incorporation of adjuvants to increase immunogenicity (211). Advances in new adjuvants, for which extensive developments have occurred in the past decades, improve the effectiveness of these vaccines (214, 215).

Among the potential risks associated with inactivated vaccines is the possibility of incomplete pathogen inactivation, which could cause post-vaccination outbreaks. Although this situation has occurred, current rigorous regulations and stringent quality controls have substantially reduced this risk (216).

Prominent examples of inactivated vaccines include vaccines for poliovirus (IPV), hepatitis (HepA), influenza, and rabies (211, 217). In addition, inactivated whole-cell vaccines have been used for bacterial diseases, such as pertussis (whooping cough) and cholera (167, 210). In the recent COVID-19 pandemic, several inactivated vaccines against SARS-CoV-2 were developed (78–80).

6.3 Subunit and conjugate vaccines

These vaccines contain only specific fragments (subunits) of the pathogen they are intended to protect against, rather than the entire pathogen. The subunits can be peptides, proteins, or polysaccharides derived from the pathogen. Although not infectious, these subunits are still capable of triggering an immune response; in other words, they are immunogenic (218).

Developing these vaccines requires identifying, producing, and purifying the antigenic components of the pathogen that can induce an effective protective immune response. In this process, the nature of the antigen used is a key factor. For instance, protein antigens tend to be more potent immunogens than polysaccharides, triggering responses from both B and T cells (207). An example is the hepatitis B vaccine, which employs a protein from the surface of the virus as a subunit (156). Another example is the acellular pertussis vaccine, which uses several purified proteins from *B. pertussis* (219).

In contrast, polysaccharide subunit vaccines induce B cell responses, albeit they typically do not activate T cells, nor do they usually generate immunological memory. Therefore, conjugate vaccines have been developed to enhance the immunogenicity of polysaccharide antigens. This approach links a polysaccharide to a carrier protein, allowing a more effective T cell response. This method increases the immunogenicity of polysaccharides, especially in infants <2 years of age. Polysaccharide-protein conjugation allows the immune system to recognize and respond more effectively, producing polysaccharide-specific antibodies and generating memory cells (219). The pneumococcal, meningococcal, and *H. influenza* type b conjugate vaccines are successful examples of this type of vaccine (220).

Subunit vaccines present several advantages. They are generally safe and well-tolerated, given that they lack live microorganisms that can cause disease. Furthermore, their high specificity generates a more targeted immune response, thereby circumventing potential adverse effects of a broader immune response (more intense inflammation, fever, malaise, among others). Production of these vaccines is straightforward and adaptable, and their lyophilization facilitates transport and storage without the need for refrigeration (221, 222).

Subunit vaccines are not without challenges. Although they are less reactogenic, their ability to stimulate robust and lasting immune responses is usually inferior to that of attenuated vaccines, more similar to inactivated vaccines. Thus, adjuvants and multiple doses are often required to achieve a long-term protective response (221, 222).

Furthermore, developing these vaccines requires a deep understanding of the components of the pathogen that trigger protective immunity, as well as an understanding of the immune responses necessary to protect against specific pathogens. This knowledge guides the choice of the antigenic components to be incorporated into the vaccine and the methods required to evaluate immunogenicity (207, 218). This can be challenging, as promising results in preclinical trials do not always translate into success in clinical trials due to various factors, including variability in immune responses between different species and the possible insufficiency of adjuvant potency (218).

6.4 Toxoid vaccines

Inactivated bacterial toxins are called toxoids. In general, the manufacturing process of these vaccines involves bacterial culture in a laboratory environment, purification, and inactivation of the toxin with formalin or another chemical agent. This inactivation aims to eliminate toxicity while preserving the ability to induce a specific immune response against the toxin (223).

Once the vaccine is administered, the immune system identifies the toxoid as a foreign antigen and produces specific antibodies called antitoxins. Consequently, in the event of future exposure to this toxin-producing bacteria, these antitoxins can neutralize the toxins, preventing damage to cells and tissues (224). Toxoid vaccines do not contain live microorganisms and thus cannot revert to virulent forms. However, these vaccines may also require adjuvants and booster doses to maintain long-term protection, as the immunity may decrease over time (223).

Classic examples of toxoid vaccines include vaccines against diphtheria and tetanus. These are often administered in combination with the pertussis vaccine in the combined DTP and DTaP (diphtheria, tetanus, and acellular pertussis) vaccines (225, 226), a more recently in the hexavalent DTaP5-IPV-Hib-HepB vaccine (227).

6.5 Vector-based vaccines

These vaccines are a recent breakthrough in vaccinology, based on the use of no pathogenic microorganisms, known as vectors, acting as a "Trojan horse". Genetic engineering techniques modify these vectors, incorporating a DNA or mRNA fragment that encodes for a specific antigen from a pathogen. Thus, the vector can express this genetic material and produce the desired antigen within host cells, leading to its recognition by the immune system (228, 229).

Prominent viral vectors currently in use include adenovirus, measles virus, influenza virus, and poxvirus. These vectors can be replicative (attenuated) or can be genetically modified to be non-replicative (inactivated), a measure that enhances the safety profile of these vaccines (81).

The development of vector-based vaccines has challenges, as the genetic manipulation of the vectors requires a high degree of precision and control to ensure the safety and effectiveness of the vaccine. Additionally, pre-existing immunity to the vector within the population or provided by primary vaccination could potentially compromise vaccine efficacy/effectiveness (82).

Before the COVID-19 pandemic, the licensure of vector-based vaccines was limited to ebola virus (83). However, the pandemic

required a rapid response that led to the development of several vaccines based on viral vectors that express the SARS-CoV-2 spike protein. These include the ChAdOx1 vaccine, which uses a modified chimpanzee adenovirus (84); the Ad26.COV2-S vaccine, which uses a type 26 adenovirus (85); the Sputnik V vaccine, which uses two adenoviral vectors, type 26 (prime) and type 5 (booster); and the Ad5-nCOV vaccine, which uses adenovirus type 5 (78, 228).

Recently, vector-based vaccines against RSV have also been developed, which are under clinical evaluation with promising results. These include the Ad26.RSV.preF vaccine, with a recombinant adenovirus serotype 26 vector encoding the prefusion F protein (230), and the MVA-BN RSV vaccine, with a modified vaccinia Ankara virus vector encoding Ga, Gb, F, and M2 proteins (231).

The mechanism of action of these vaccines is genuinely innovative. Taking the ChAdOx1 vaccine as an example, the genetically modified adenovirus (vector) enters the cell, transporting the Spike protein gene into the cell nucleus of various host cells. This gene is then transcribed into mRNA, which subsequently migrates to the cytoplasm. Within the cytoplasm, the ribosomes use the mRNA as a template to produce the Spike protein. Once produced, this protein is presented to the immune system, triggering an immune response against SARS-CoV-2 (228).

The successful outcome of vector-based vaccines during the pandemic suggests that they may play an increasingly pivotal role in the future. Their ability to generate robust and long-lasting immune responses, added to the versatility to be adapted against a variety of viral infections, establishes these vaccines as a powerful and relevant tool in vaccinology.

6.6 Nucleic acid vaccines

Nucleic acid vaccines will most likely become a turning point in vaccinology. Like vector-based vaccines, nucleic acid vaccines use DNA or RNA molecules that encode for pathogen-specific antigenic proteins. The former use a plasmid as the vehicle for the genetic material, while the latter have mostly used encapsulation in lipid nanoparticles (232, 233).

There are two categories of nucleic acid vaccines: DNA and RNA. When a DNA vaccine is administered, mainly through electroporation, the DNA enters host cells and is transported to the nucleus, where it is transcribed into mRNA. The mRNA is transported out of the nucleus, to the ribosomes responsible for synthesizing the desired antigen. This antigen undergoes processing and presentation to immune cells, thus eliciting a specific immune response (234). Unlike DNA vaccines, RNA vaccines allow direct translation of the antigen within the cytoplasm. As with DNA vaccines, the result is a specific immune response against the target pathogen (235).

This technology has been particularly relevant in the context of the COVID-19 pandemic (236). The BNT162b2 and the mRNA-1273 vaccines are notable examples of mRNA-based vaccines encoding the spike protein (237). In light of their safety and efficacy, they received emergency use authorizations and approvals in numerous countries, enabling the implementation of widespread vaccination (236). Importantly, these mRNA vaccines have demonstrated over 90% efficacy in preventing symptomatic COVID-19 disease in clinical trials. Most important, they proved to provide significant protection against severe forms of the disease and hospitalizations (238).

Nucleic acid vaccines are a versatile platform offering flexibility in design and scalability in production. Due to its adaptability, it is feasible to adjust the genetic sequence of the antigen, which allows the rapid adaptation of vaccines to new variants of the pathogen. This prompt adjustment could potentially enhance the accuracy and efficacy of the immune response against the circulating variants (239). This platform could also be employed to design vaccines against multiple pathogens (240, 241).

Limitation of mRNA vaccines include the fragile nature of the mRNA, prompting the need for cold storage at exceedingly low temperatures to maintain their stability, which can represent significant logistical challenges, especially in underdeveloped regions (238). Additionally, although rare, allergic reactions to mRNA vaccines have been reported (242), as well as uncommon severe side effects such as Bell's palsy (243), Guillain Barré syndrome (244), and myocarditis/pericarditis (245).

Beyond vaccines, mRNA technology is also being implemented for a variety of other medical applications, such as gene therapy and immunotherapy for the treatment of genetic diseases and cancer, respectively. These applications reflect the broad potential of mRNA-based therapeutics in the near future (246).

7 Public health and economic impacts of vaccination

Health professionals and biomedical researchers tend to measure the benefits of vaccines in terms of disease prevention and mortality reduction. However, it is also important to recognize and quantify the economic and social benefits of vaccines and immunization programs at both the individual and community levels. It is equally important to effectively communicate these benefits to the general public and policymakers to promote vaccination acceptance, increase immunization coverage, and encourage investments in novel vaccine development (247). In this section, we will briefly examine the impact of vaccines on public health and their economic and social benefits.

7.1 The public health value of vaccination

The most significant impact of vaccines has been their role in decreasing morbidity and mortality caused by infectious diseases that in the past were disabling or fatal (248). People today live more and better due to the control of threatening infections. For instance, in the United States, a historical comparative study by Roush et al. (118) highlighted the transformative impact of immunization on the incidence of infectious diseases. This research analyzed morbidity and mortality data associated with 13 vaccine-preventable diseases (VPDs), demonstrating a reduction of over 90% following the implementation of vaccination programs compared to rates before these programs were established. This

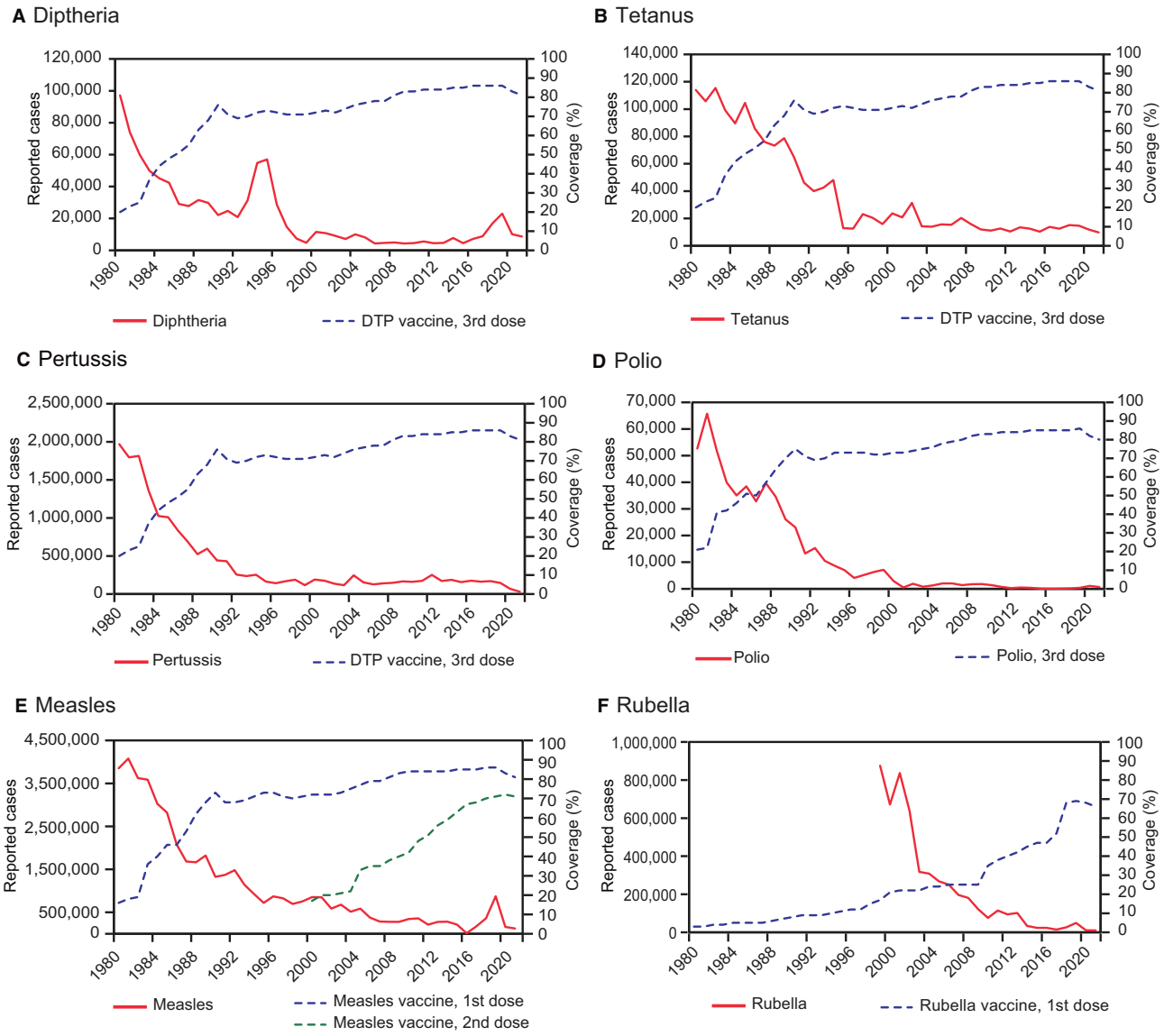

FIGURE 4
Global impact of vaccination on selected infectious diseases (1980–2021). This figure illustrates the number of reported cases for selected vaccine-preventable diseases (VPDs), including Diphtheria **(A)**, Tetanus **(B)**, Pertussis **(C)**, Polio **(D)**, Measles **(E)**, and Rubella **(F)**, from 1980 through 2021. The data was submitted to the World Health Organization (WHO) annually via the WHO/UNICEF Joint Reporting Form on Immunization (JRF). The most recent WHO/UNICEF Estimates of National Immunization Coverage (WUENIC) for these specific VPDs on a global scale are presented. Notably, the increase in vaccination coverage led to a marked decrease in the number of cases reported annually for each of these diseases. Data were sourced from the World Health Organization's immunization data portal, accessible at: https://immunizationdata.who.int/.

remarkable achievement was possible due to high coverage for vaccines such as polio, DTaP, and MMR (247).

Vaccine distribution poses a considerable challenge in low- and middle-income countries (LMICs). Nevertheless, over the past 40 years, the increase in global vaccination rates has led to a significant decrease in the number of annually reported cases of VPDs. Figure 4 shows the worldwide impact of vaccination on select VPDs from 1980 to 2021.

Current vaccines are an efficient tool for preventing diseases related to climate change, such as cholera, yellow fever, and dengue. These diseases are expanding to new regions of the world due to floods, temperature fluctuations, or changes in disease vectors (e.g., mosquitoes) (167, 249). Alongside other public health strategies, vaccines have played a key role in controlling outbreaks, epidemics, and pandemics. Examples include the cholera epidemic in Haiti from 2010 to 2019 (250), the ebola epidemic in the Democratic Republic of Congo from 2018 to 2019 (251), and the recent COVID-19 pandemic (236, 252).

In the current public health landscape, many diseases caused by pathogenic bacteria can be prevented with vaccines. This prevention strategy reduces the need for antibiotics, thereby decreasing the selective pressure that leads to the development of resistance to these drugs. This is critical to address the growing threat of multidrug resistance in

bacteria, which could be responsible for future pandemics (253, 254).

Notably, vaccines can prevent diseases beyond the specific pathogen for which they were designed. Infections, particularly caused by viruses, can predispose to secondary bacterial infections. For instance, influenza virus infection often leads to complications like bacterial pneumonia and acute otitis media (AOM) (255, 256). Indeed, vaccination against influenza can result in a modest yet significant reduction in AOM cases (257). Another noteworthy example is the impact of the introduction of the measles vaccine in the 1960s, which led to a significant reduction in child morbidity and mortality, not only associated with measles, but also with other diseases (258, 259). Measles causes immunosuppression, increasing susceptibility to secondary bacterial infections for several weeks to months, particularly those caused by *S. pneumoniae* and Hib (259, 260). Thus, measles vaccination has been proposed as a preventive measure against these secondary bacterial infections (258, 261).

The scope of vaccines goes beyond the prevention of diseases at the individual level, as they also protect communities through herd or collective immunity. When a significant portion of the population acquires immunity against a pathogen that is readily transmissible from person to person, either through vaccination or by having overcome the infection, the spread of the pathogen decreases considerably. This protects even those who cannot receive the vaccine due to age or medical conditions. This indirect protection is especially crucial for safeguarding vulnerable individuals, such as newborns, older adults, and people with weakened immune systems (262, 263).

7.2 Economic and social benefits of vaccination

Vaccines, beyond their direct impact on health, offer substantial economic benefits and contribute to poverty reduction. In many LMICs, where healthcare coverage often remains inadequate, people commonly must face high out-of-pocket (OOP) medical expenses. Econometric studies estimate that increasing vaccination coverage in LMICs can save billions in OOP expenses, thus preventing millions of people from facing catastrophic health expenses. These are defined as a significant proportion (usually 10–25%) of household income or expenditures (264). Consequently, by preventing disease, vaccines represent a cost-effective strategy that mitigates the financial burden on both families and health systems. This reduction in expense is seen through the avoidance of costly and time-consuming medical tests, procedures, and treatments.

Vaccines also play an important role in mitigating productivity losses associated with absenteeism and presenteeism (265). Absenteeism refers to instances where employees are unable to work due to illness. On the other hand, presenteeism reflects a scenario where employees continue to work while sick, resulting in suboptimal productivity levels due to illness-related impairments. By preventing disease, vaccinations can enhance overall workforce productivity, whether employees operate in traditional office settings or from remote environments, thereby stimulating economic growth. Moreover, reducing childhood disease incidence decreases parental absenteeism, as parents would otherwise need to take days off to care for their sick children. This dynamic has a significant economic impact, further underscoring the comprehensive value of vaccination (266).

The socio-educational benefits of childhood vaccination merit emphasis. Vaccination allows children to attend school and participate in community activities without interruption from debilitating diseases (267). Studies conducted in LMICs reveal that childhood vaccination, by preventing diseases, can boost physical and cognitive development, improve educational performance, and increase lifetime earnings.

Such studies consistently associate childhood vaccination with an additional 0.2–0.3 years of education in various countries. This impact is even more evident in economically disadvantaged groups, highlighting the social and economic value of childhood vaccination (268).

In this context, vaccines are a tool, in universal programs, that promote equity and social benefits in healthcare. By mitigating the burden of infectious diseases that disproportionately affect the most vulnerable, vaccines enhance the quality of life and healthcare accessibility for everyone, regardless of their economic or social situation (269, 270).

The Expanded Program on Immunization (EPI), implemented in 1974 as a WHO initiative, is an example of how vaccines can reduce healthcare disparities. This initiative increased vaccination coverage in developing countries from 5 to 80%, significantly improving children's life opportunities and health equity (270).

Finally, vaccines promote a safer and more efficient exchange of people and goods internationally by contributing to controlling outbreaks. This effect drives trade and tourism, which in turn promotes economic growth (248, 271). Thus, vaccines play a key role not only in individual and collective health, but also in global social and economic development.

8 Origin, impact, and mitigation of vaccine hesitancy

Vaccine hesitancy is characterized by a delay in acceptance or outright refusal to vaccines despite the availability of vaccination services (272). Several models have been proposed to elucidate the nature of vaccine hesitancy. For instance, the "Three C's" model proposed by MacDonald et al. (273), identified complacency, convenience, and confidence as influential factors. Additionally, Hagood and Herlihy (274), classified individuals into four groups: vaccine-acceptor, vaccine-hesitant, vaccine-resisting, and vaccine-rejecting. Meanwhile, the Sage Working Group proposed the Vaccine Hesitancy Continuum, which describes a spectrum ranging from unconditional acceptance of all vaccines to complete refusal. Individuals who are vaccine-hesitant fall somewhere in between these two extremes, forming a diverse group (272). It is important to note that while these classifications provide valuable insight into the various attitudes toward vaccination, they will not be used explicitly in this review. However, recognizing this spectrum of vaccine-hesitant individuals is important to understanding this phenomenon.

8.1 Origin of vaccine hesitancy

The phenomenon of vaccine hesitancy has been present since the introduction of vaccination. Its history, as old as that of vaccines themselves, is marked by persistent resistance through several milestones in medical advancement. For a comprehensive historical analysis of vaccine hesitancy, the reader is referred to previous extensive reviews (275–277).

The origin of vaccine hesitancy date back to the late 18th century. The introduction of the smallpox vaccine by Jenner in 1796 elicited both admiration and criticism. As discussed in a preceding section, Jenner inoculated individuals with material from cowpox lesions, raising fears and misconceptions (47). This unfamiliar method, combined with religious beliefs and distrust in medicine, planted the initial seeds of hesitation. Some individuals feared that the procedure would lead to "bovine" characteristics in humans, while others believed it went against God's will (31, 278).

Despite these concerns, the effectiveness of the smallpox vaccine was undeniable, leading to its rapid adoption and spread throughout Europe and the United States. Nonetheless, a segment of the population consistently opposed vaccination. In the mid-19th century, some Western countries instituted mandatory vaccination laws, imposing stringent penalties for non-compliance, to safeguard public health (279).

These mandatory vaccination policies often met with public opposition, being perceived as violations of personal freedoms, and gave rise to anti-vaccine groups and major legal battles (280). These groups, later termed as "Anti-vaxxers" in contemporary discourse, were driven by a variety of factors ranging from concerns about vaccine safety and efficacy to broader socio-political motivations (277). One of the most notable of these legal confrontations reached in the United States Supreme Court in 1905. In a landmark judgment, the court reaffirmed the authority of the state to mandate vaccinations to protect the public from communicable diseases (281).

The 20th century saw an increase in both the number of available vaccines and the intensity of opposition. In the United Kingdom and the United States between the 1960s and 1980s, concerns emerged regarding potential adverse effects and neurological complications associated with the DTP vaccine. Although initial studies suggested potential risks, subsequent research refuted any link between the vaccine and neurological damage (117, 280). Nonetheless, public skepticism led to decreased vaccination rates, resulting in disease outbreaks in numerous countries (282–284).

In more recent times, the infamous and now discredited 1998 study linking the MMR vaccine to autism stands out as the best example of the impact of misinformation (285, 286). The extensive media coverage of this study, even after its retraction, left a lasting mark on public perception, reducing MMR vaccination rates and leading to measles outbreaks in many parts of the world (287). This incident underscores the enduring effects of misinformation on public health.

A focal point in vaccine hesitancy has been concerns related to the safety of additives, or excipients, in vaccine formulations. These additives include a range of substances that enhance the immune response (adjuvants), stabilize (stabilizers) and preserve the vaccine (preservatives) (288). Critics argue that these substances, potentially harmful in large doses, pose health risk when included in vaccines. Nevertheless, scientific research has consistently demonstrated the safety of these additives in the trace amounts used in vaccines (289–291). The removal of thimerosal, a mercury-containing compound, from most vaccines in Europe in 1992 and in the United States in 2001 exemplifies the evolution of vaccine technology and regulations in response to public concerns (286, 292).

8.2 Vaccine hesitancy in digital era

In the digital era, the internet and social networks have revolutionized information dissemination and consumption, profoundly impacting public health communication, particularly regarding vaccine acceptance (275). The easy access to a broad spectrum of information has empowered individuals to seek health-related knowledge. However, it has also facilitated the rapid proliferation of both accurate and inaccurate information. Specifically, social networks have become hubs for spreading misinformation and creating echo chambers, where individuals predominantly encounter information that reinforces their pre-existing beliefs (293). This dynamic has significantly contributed to vaccine resistance, as misinformation about vaccine safety and efficacy can spread widely, be amplified, and prove resistant to correction (294).

The COVID-19 pandemic exemplifies these challenges. Vaccines against SARS-CoV-2 were developed, tested, and approved at an unprecedented pace, attracting attention and scrutiny. These rapid vaccine developments resulted from a global effort and substantial resource allocation, all while maintaining rigorous vaccine development standards. The COVID-19 vaccine clinical trials were conducted with a meticulous risk-benefit balance, involving overlapping or consecutive phases, guaranteeing the safety and effectiveness of the vaccines (180).

Nonetheless, the accelerated pace of vaccine development generated misconceptions and hesitancy, contributing to an "infodemic" characterized by an overwhelming flood of both information and disinformation across various media channels. Social media platforms played a central role in disseminating both accurate information and misinformation, leading to public confusion and skepticism (295). The predominant reasons for refusing COVID-19 vaccines included general opposition to vaccines, concerns about the safety of rapidly developed vaccines, potential unknown short- and long-term adverse effects, and perceptions of COVID-19 as being relatively harmless (296). Notably, these claims have been actively debated and refuted with clinical and experimental evidence, highlighting the safety and protective efficacy of vaccines against severe COVID disease (see previous sections).

8.3 Impact of vaccine hesitancy

The consequences of vaccine hesitancy are multiple, serving to undermine the public health benefits and economic benefits associated with vaccines, which were discussed in the previous section.

From the perspective of public health, such hesitancy affects vaccine coverage, which can directly lead to the resurgence of diseases that are preventable through vaccination. This situation poses a risk not only to unvaccinated individuals but also jeopardizes herd immunity, thereby endangering communities at large. In 2019, for instance, a decline in MMR vaccine coverage, attributed to vaccine hesitancy, resulted in a resurgence of measles in numerous high-income countries (297). Furthermore, unvaccinated children face an elevated risk of contracting diseases that vaccines can prevent and may experience severe complications associated with these diseases. Glanz et al. (298) conducted a study demonstrating that children who were delayed in receiving one or more doses of the DTaP vaccine were 4.4 times (2.23–8.55) more likely to be diagnosed with pertussis compared to their peers who were vaccinated in accordance with the recommended schedule.

From an economic standpoint, outbreaks and resurgences of vaccine-preventable diseases put pressure on vulnerable families and health systems. These situations also redirect essential resources away from other critical health services (299).

8.4 Mitigation of vaccine hesitancy

Addressing vaccine hesitancy requires a comprehensive, evidence-based approach that incorporates a variety of strategies (Figure 5). This process begins with clearly defining the extent of vaccine hesitancy, distinguishing it from other factors that may cause people to be unvaccinated or under-vaccinated. It is important to differentiate hesitancy from other barriers to vaccination, such as access issues or lack of awareness. Understanding this distinction is key to determining whether interventions specifically targeting vaccine hesitancy are required to enhance vaccine uptake rates (272).

Following this initial clarification, it is essential to identify the causes of vaccine hesitancy and thus implement programs designed to effectively address these barriers. Diagnostic tools, such as the Parent Attitudes about Childhood Vaccines (PACV) (300) survey and the Behavioral and Social Drivers (BeSD) of Vaccine Uptake model (301, 302), can be employed to assess vaccine acceptance and identify potential barriers.

Developing targeted interventions to mitigate vaccine hesitancy has key components, including building trust, providing accurate and understandable information, and actively engaging with communities. These and other strategies will be discussed below.

Directly confronting concerns, misconceptions, and fears is crucial for fostering trust. Transparency in scientific communication is of paramount importance. The rapid development and approbation of COVID-19 vaccines underscored the need for a "radical transparency" approach in vaccine communication. Transparency, even when disclosing potential negative aspects of vaccines, fosters trust in health authorities, despite potentially impacting vaccine acceptance negatively in the short term. A recent study by Petersen et al. (303), showed that transparent communication of negative vaccine information enhances trust in health authorities. Conversely, vague, and overly reassuring communication strategies fail to increase vaccine acceptance and, in fact, result in diminished trust and increased endorsement of conspiracy theories.

Communication approaches include broad community vaccine campaigns and tailored communication programs designed for specific cultural groups and communities (304). The role of effective communication between healthcare workers and patients, using techniques such as presumptive language and motivational interviewing, cannot be underestimated (305). Furthermore, risk communication tools, including visual aids like icon arrays, bar graphics, and images, enhance health literacy and support informed decision-making (306, 307).

Community engagement plays a key role in this process. Trained vaccine champions, such as health workers, community leaders, faith leaders, and industry influencers, can provide clear, transparent, and consistent information, share personal positive vaccination experiences, and act as influential role models (308–310). These individuals, by actively participating in community dialogues and addressing questions and concerns empathetically and respectfully, contribute significantly to building trust and supporting vaccination within their communities. Activities and programs that actively involve parents in discussions and decision-making about vaccines, rather than merely being recipients of directives, further promote vaccine acceptance (311).

In the digital era, fight misinformation and disinformation require the implementation of social listening systems or infoveillance. These systems monitor social media channels for emerging trends, enabling the timely identification and address of biased or non-evidence-based information before it gains widespread traction (312). Complementing these systems, it is imperative to ensure that accurate and reliable information is consistently accessible to the public (306).

Although coercive strategies, such as financial incentives, positive reinforcement, and vaccine mandates, have proven effective in increasing vaccination rates in certain contexts (313, 314), their application requires careful consideration of cultural and regional nuances (315, 316).

9 Conclusions and perspectives

Since the development of the first vaccine against smallpox, vaccines have emerged as one of the most effective strategies in preventing infectious diseases and promoting public health globally. Through vaccination, pathogens such as smallpox virus and wild poliovirus type 2 and 3 have been eradicated, and many others controlled, several of which are close to eradication.

The development of a myriad of vaccine platforms, each with specific advantages and limitations, has allowed us to prevent infections caused by a wide range of pathogens and protect different target populations. The COVID-19 pandemic has catalyzed rapid progress in vaccinology, culminating in the development and approval of an array of vaccines, including several based on novel technologies, in less than a year.

Looking ahead, vaccine research is expected to advance in several directions. First, current vaccine platforms will likely be refined to improve their efficacy, safety, and responsiveness to different pathogens and populations. Adjuvants will continue to be

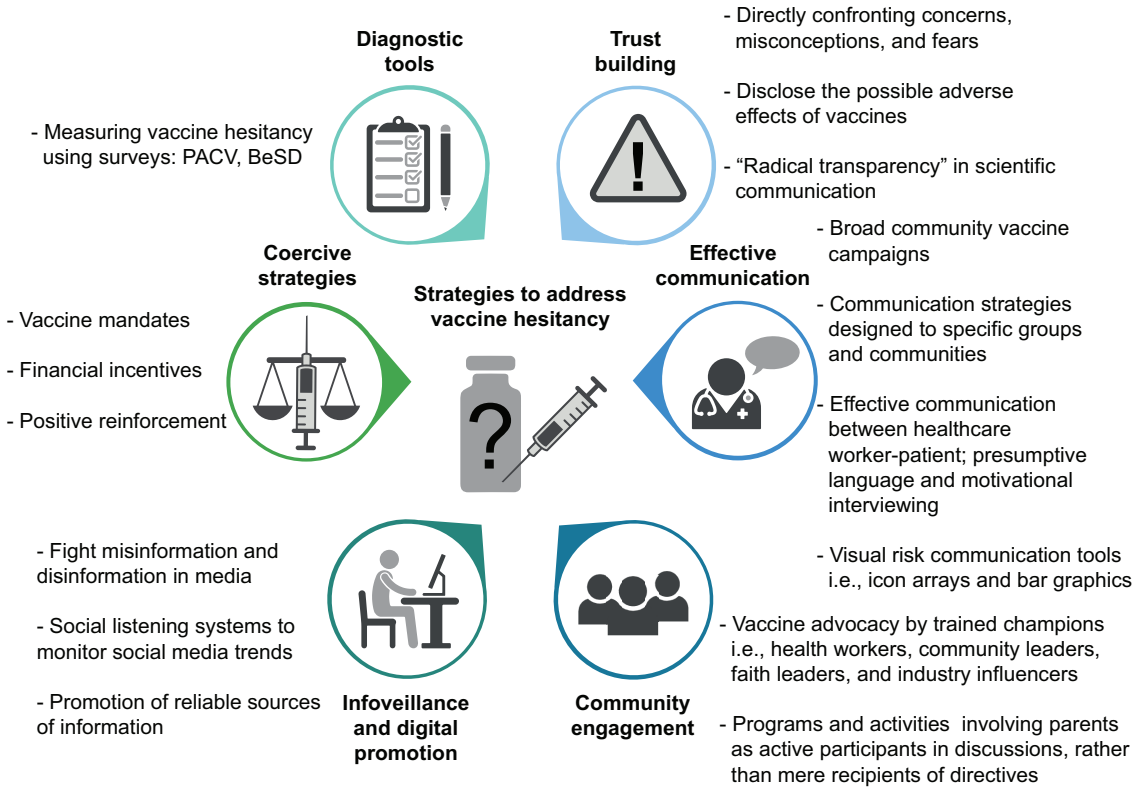

FIGURE 5
Multifaceted approach to mitigate vaccine hesitancy. Diagnostic tools, such as surveys, can be utilized to identify potential barriers to vaccination. Building trust necessitates an active approach to addressing public concerns, misconceptions, and fears, while advocating for "radical transparency" in science communication. To ensure effective communication about vaccines, comprehensive campaigns targeting both the general population and specific groups and communities are imperative. Enhancing communication between healthcare workers and patients is key, requiring the adoption of presumptive language and motivational interviewing techniques to build trust and facilitate informed decision-making. Vaccine advocates, including community leaders and healthcare workers, play a crucial role. Programs that engage parents as active participants are equally significant. In the digital age, infoveillance is crucial for monitor trends on social media platforms and counteracting misinformation and disinformation about vaccines. Lastly, while coercive strategies, such as vaccination mandates and financial incentives can be effective, their implementation must be judiciously considered and culturally and regionally adapted. PACV, parent attitudes about childhood vaccines. BeSD, behavioral and social drivers of vaccine uptake model. This figure was created using BioRender.com.

refined to enhance the immunogenicity of inactivated and subunit vaccines (215).

Second, the development of mRNA vaccines for a broad range of pathogens beyond SARS-CoV-2 is anticipated. Its rapid, scalable, and adaptable production make it a breakthrough technology that could aid in controlling neglected, emerging, and re-emerging infectious diseases (317, 318).

Third, progress in immunology and a deeper understanding of host factors influencing immunity development, such as comorbidities, nutrition, and the microbiota, are expected to yield insights into the mechanisms driving vaccine effectiveness (319, 320). This knowledge could be used to design more precise and personalized vaccines.

Fourth, innovations in vaccine delivery technology could improve the efficacy and acceptance of vaccines. For instance, novel administration methods, such as microneedle patches or intranasal delivery, could simplify vaccination and enhance the immune response compared to traditional intramuscular injection. Additionally, these methods could reduce pain and anxiety associated with vaccinations, facilitating their acceptance (208, 321).

Fifth, international cooperation and investment in vaccine development are expected to continue growing, especially in the face of the threat of emerging and re-emerging infectious diseases. Partnerships among governments, international organizations, the pharmaceutical industry, and academia will be essential for ensuring equitable vaccine access and expedited global distribution.

Sixth, enhancing health literacy and effective vaccine communication will be pivotal in increasing vaccine uptake and trust. While vaccine hesitancy is not a new phenomenon, it is a recurring challenge that has waxed and waned in parallel with advances in vaccinology. History has demonstrated that vaccines are one of the most powerful tools in humanity's arsenal against infectious diseases. Their continued success depends not only on scientific innovation but also on maintaining public trust and acceptance. As we move forward, it is imperative to learn from past experiences, both triumphs and setbacks, to ensure safe and effective vaccines are accessible for all.

Author contributions

DM: Formal analysis, Investigation, Writing – original draft. RV: Formal analysis, Investigation, Writing – original draft. JV: Formal analysis, Investigation, Writing – original draft. LC: Formal analysis, Investigation, Writing – original draft. JT: Formal analysis, Investigation, Writing – review & editing. MB: Formal analysis, Investigation, Writing – original draft. Y-YT-R: Formal analysis, Investigation, Writing – original draft. AO: Formal analysis, Investigation, Writing – original draft. MO'R: Formal analysis, Writing – review & editing.

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In memoriam

This paper is dedicated to the memory of Carmenza Forero (1955–2020), beloved mother and greatest teacher.

Conflict of interest

MO'R participates in a rotavirus vaccine phase III Trial from Bharat laboratories and was principal investigator for the COVID-19 vaccine from Janssen.

The remaining authors declare that they have no commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Otorhinolaryngologic complications after COVID-19 vaccination, vaccine adverse event reporting system (VAERS)

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Background: There have been reports of otolaryngological adverse event following immunization (AEFI) such as instances of olfactory and gustatory dysfunction following COVID-19 vaccination. This study aimed to analyze otolaryngological AEFIs following COVID-19 vaccination.

Methods: This study was conducted with a secondary data analysis that the Vaccine Adverse Events Reporting System (VAERS) and the COVID-19 Data Tracker, which are both administered by the Centers for Disease Control and Prevention in the US. Using Medical Dictionary for Regulatory Activities (MedDRA) concepts, AEFIs included: Considering the overall frequency and similarity of symptoms in the first 153 PTs, they were grouped into major 19 AEFIs groups. The incidence rates (IRs) of AEFIs per 100,000 were calculated on individual and cumulative AEFIs levels, involving people who received complete primary series and an updated bivalent booster dose with one of the available COVID-19 vaccines in the US. The proportions of AEFIs by age, sex, and vaccine manufacturer were reported. We also calculated the proportional reporting ratio (PRR) of AEFIs.

Results: We identified 106,653 otorhinolaryngologic AEFIs from the VAERS database, and a total of 226,593,618 people who received complete primary series in the US. Overall, the IR of total Otorhinolaryngologic AEFIs was 47.068 of CPS (completed primary series) and 7.237 UBB (updated bivalent booster) per 100,000. For most symptoms, being female was associated with statistically significant higher AEFIs. Upon examining the impact of different vaccine manufacturers, the researchers found that Janssen's vaccine exhibited higher IRs for hearing loss (5.871), tinnitus (19.182), ear infection (0.709), dizziness (121.202), sinusitis (2.088), epistaxis (4.251), anosmia (5.264), snoring (0.734), allergies (5.555), and pharyngitis (5.428). The highest PRRs were for Anosmia (3.617), Laryngopharyngeal Reflux - Acid Reflux (2.632), and Tinnitus -Ringing in the ears (2.343), in that order, with these three significantly incidence than other background noises.

Conclusion: This study, utilizing an extensive sample sizes, represents a significant step toward comprehensively characterizing the otolaryngological AEFIs associated with COVID-19 vaccinations. This large-scale analysis aims to move beyond isolated case reports and anecdotal evidence, providing a robust

and detailed portrait of the otolaryngological AEFIs landscape in response to COVID-19 vaccinations.

KEYWORDS

COVID-19 vaccines, drug-related side effects and adverse reactions, otolaryngological adverse events, COVID-19, vaccines

1 Introduction

The COVID-19 pandemic, caused by the SARS-CoV-2 virus, has had a profound global impact, leading to significant morbidity and mortality rates (1). In response to this unprecedented health crisis, an intense global effort was made to develop vaccines to prevent COVID-19. In December 2020, the US Food and Drug Administration (FDA) granted Emergency Use Authorization (EUA) for the COVID-19 mRNA vaccine developed by Pfizer-BioNTech (2). Subsequent authorizations were granted for the mRNA-1273 vaccine developed by Moderna (3), and the Ad26.COV2 vector-based vaccine developed by Janssen Johnson & Johnson (3).

The EUAs issued by the FDA facilitated rapid deployment of these vaccines based on promising preliminary data, a pivotal decision considering the urgent need to curb the spread of the virus. However, this expedited the authorization process without extensive clinical trials typically required for full approval, thereby necessitating rigorous post-authorization safety monitoring.

Several case reports have been published detailing instances of olfactory and gustatory dysfunction following the COVID-19 vaccination (4, 5). However, the potential for broader otolaryngological adverse event following immunization (AEFI)—encompassing the ear, nose, and throat regions—associated with COVID-19 vaccination remains largely unexplored. According to the definition of the World Health Organization (WHO), AEFI is defined as any untoward medical occurrence following immunization which does not necessarily have a causal relationship to the vaccine. Given that these areas are frequent sites of viral infection and are also involved in immune responses, it is plausible that they may be vulnerable to AEFIs. Furthermore, the potential AEFIs associated with COVID-19 vaccination, studies have shown a waning immune response post-vaccination influenced by factors such as immunosenescence, gender-related hormonal differences, and pre-existing comorbidities (6–8).

To address this knowledge gap, this study conducted an analysis of otolaryngological AEFI reported after COVID-19 vaccination using the Vaccine VAERS data (9). The VAERS database is a national early-warning system designed to detect possible safety problems in US-licensed vaccines and plays a critical role in post-authorization safety monitoring (9).

This study aims to characterize the nature and prevalence of otolaryngological AEFIs with COVID-19 vaccines. The researchers further examined the demographic distribution of these AEFIs in terms of gender and age and evaluate the variation in these AEFIs among the different vaccine manufacturers (Pfizer-BioNTech, Moderna, and Janssen Johnson & Johnson). Ultimately, this study provides a basis for uncovering mechanisms and improving the understanding of the safety profile of COVID-19 vaccines through reporting of AEFIs following vaccination.

2 Materials and methods

This study followed the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) (10) reporting guidelines (Supplementary Table 1), and was conducted after receiving approval from the institutional review board of Konyang University (KYU-2023-09-002).

2.1 Study design

This study was conducted through secondary data analysis, collecting VAERS data from December 2020 to August 2023 to analyze otolaryngologic AEFIs associated with the COVID-19 vaccines authorized in the United States.

2.1.1 Data source

The VAERS was developed in 1990 as a US vaccine safety surveillance program by the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA) (9). It collects information regarding adverse event (AE)s to serve as an early-warning system for potential safety issues regarding US-licensed vaccines. Vaccine recipients, health care providers, and vaccine makers can openly report side effects to VAERS (9). The VAERS data and individual reports without personally identifiable information were available to the public on the VAERS[1] and CDC WONDER[2] websites (all accessed through August 31, 2023). The details of the survey including the questionnaires, methodology, and description of the dataset were available on the aforementioned websites.

2.1.2 Measurement

Since VAERS does not provide data on the entire vaccinated US population, the researchers used data from the CDC Data Tracker,[3] which collected information from people who received complete primary series and an updated bivalent booster dose, by age, sex, and manufacturer. The CDC calculates rate and percentage in relation to vaccination among the entire population and selected demographic groups (e.g., individuals aged 65 or older). The data used for these calculations is from the US Census Bureau's Annual Estimates of the Resident Population for the United States[4] (Figure 1). The researchers then collected the reports of AEFIs incurred by 1 or 2 doses of the

1 https://vaers.hhs.gov/data.html
2 https://wonder.cdc.gov/vaers.html
3 https://covid.cdc.gov/covid-data-tracker/#datatracker-home
4 https://www.census.gov/newsroom/press-kits/2020/population-estimates-detailed.html

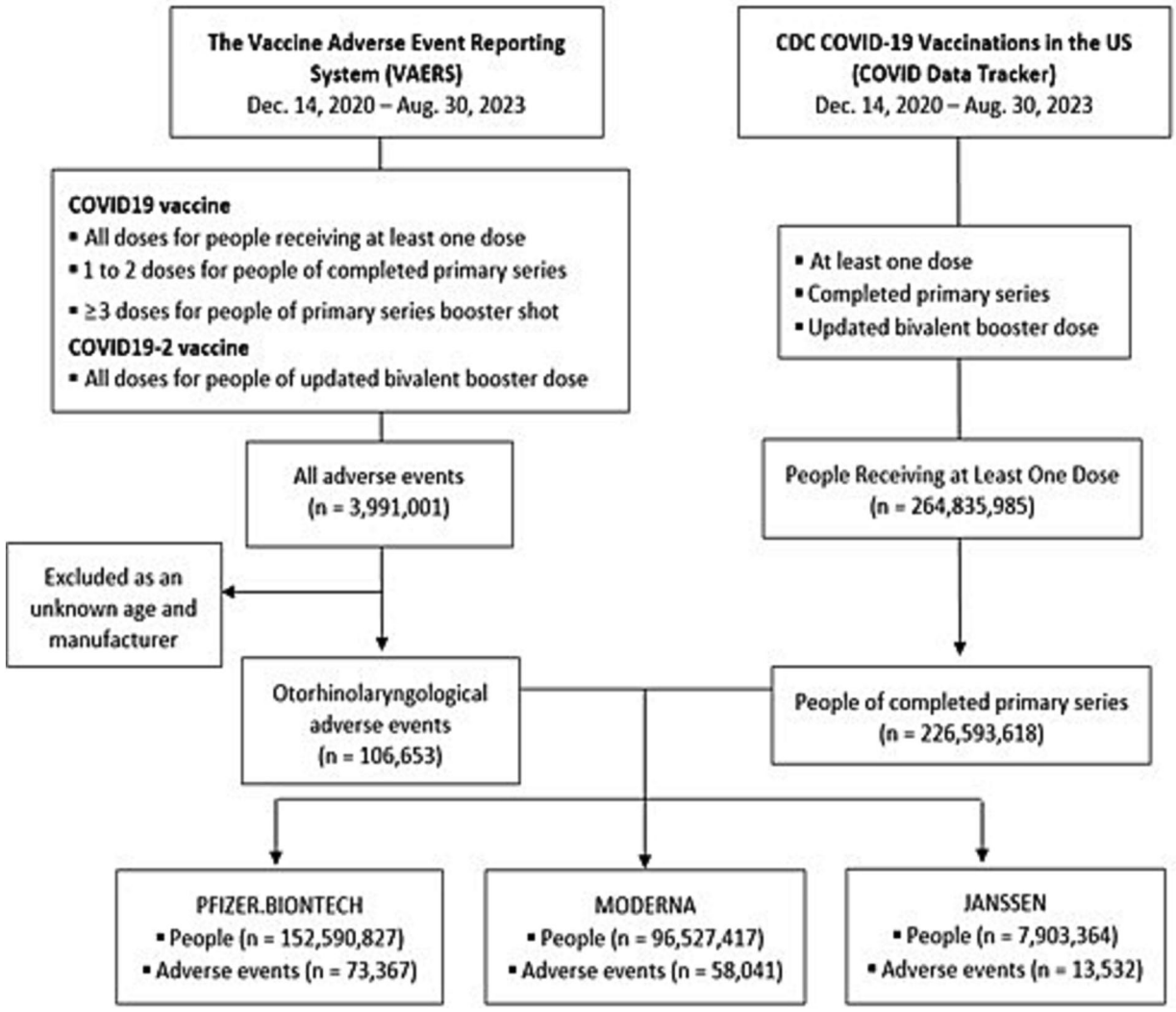

FIGURE 1
Flow diagram. People receiving completed primary series, the total number of people who received completed primary series of COVID-19 vaccine approved or authorized for use in the United States. Data are from the vaccine adverse event reporting system (VAERS) and CDC Covid-19 vaccinations data tracker from December 14, 2020 to August 30, 2023.

COVID19 vaccine, from people that received complete primary series. The AEFIs related to all number of doses of the COVID19-2 vaccine were collected from people who received an updated bivalent booster dose.

Age group was divided into five levels as: 0–17, 18–49, 50–64, and 64 or above using VAERS and CDC. The researchers compared the AEFIs incidence that incurred after the vaccination of the two mRNA vaccines (mRNA-1273, Moderna; and BNT162b2, Pfizer-BioNTech) or one viral vector vaccine (JNJ-78436735, Janssen/Johnson and Johnson), as reported in VAERS data. As the CDC did not provide the number of complete primary series of manufacturers, substituted the item with "At Least One Dose." The CDC did not provide the number of updated bivalent booster made by Jassen because it was not used as an updated bivalent booster in the US.

2.1.3 Adverse event

The otorhinolaryngologic AEFIs following the COVID-19 vaccination were based on the Medical Dictionary for Regulatory Activities (MedDRA) concepts at the preferred term (PT) level (11). In this study, 153 PTs were considered to be related to otolaryngology AEFIs through a meeting of otolaryngologists and all researchers (Supplementary Table 2). Considering the overall frequency and similarity of symptoms in the first 153 PTs, they were grouped into major 19 AEFIs groups (Supplementary Table 3).

Two researchers (JY Kim and JE Shin) independently screened the descriptions in the database to ensure the reliability of the Otorhinolaryngologic PTs. One author (JY Kim), a specialist in otorhinolaryngology, confirmed the retrieved terms and term groupings. The authors also examined all narrative text of coexisting current illnesses and comorbidities in VAERS. If they disagreed with the judgment of the description, the final PTs were determined by consensus of the researchers.

2.1.4 Analyses of PRR

The proportional reporting ratio (PRR) is a commonly used method to assess the significance of AEFIs. It is a fundamental measure of disproportionality utilized by the FDA for data mining in the FAERS database (12), which analyzes drug-related data, including

COVID-19 vaccines (13). To calculate the PRR, the ratio of the total cases for a specific AEFI associated with COVID-19 vaccines is divided by the ratio of the same AEFI for all other vaccines in the VAERS database. This calculation is akin to determining the relative risk of a drug. The PRR formula is as follows:

$$PPR = \frac{m}{n}\left[\frac{M-m}{N-n}\right]$$

m represents the number of cases for the specific AEFI of the COVID-19 vaccines.

n represents the total number of AEFI of the COVID-19 vaccines.

M represents the total number of cases for the specific AEFI in the VAERS database.

N represents the total number of all AEFI in the VAERS database.

The PRR serves as a valuable tool in evaluating the potential significance of AEFIs associated with COVID-19 vaccines and other drugs. A value of ≥2 indicates a signal that is greater than background noise (14–16).

2.2 Statistical analysis

The incidence rates (IRs) of AEFIs per 100,000 were calculated on individual and cumulative AEFIs levels, involving people who received complete primary series and an updated bivalent booster dose with one of the available COVID-19 vaccines in the US. The proportions of AEFIs by age, sex, and vaccine manufacturer were reported. Pearson's chi-squared tests or Fisher's exact tests were carried out to determine statistically significant differences between categories. The importance of AEFIs was assessed by calculating PRR.

All statistics were two-tailed, and p values <0.05 were considered statistically significant. R version 4.3.1 was used for all statistical analyses (R Foundation for Statistical Computing, Vienna, Austria).

3 Results

3.1 Characteristics of the study sample

The initial search identified a total of 106,653 otorhinolaryngologic AEFIs from the VAERS database, and a total of 226,593,618 people who received complete primary series in the US, based on the CDC Data Tracker between January 1, 2020 and August 30, 2023. Since the COVID-19 vaccine was first approved in the United States in December 2020, actual data were collected from December 2020 to August 2023. Of those reporting AEFIs, the number of AE reports from Pfizer-BioNTech, Moderna, and Janssen groups were 73,367 (50.6%), 58,041 (40.0%), and 13,532 (9.3%), respectively (Figure 1).

3.2 Comparison of AEFIs by sex group

The IRs of AEFI types per 100,000 people who received complete primary series with COVID-19 vaccines are presented in Figure 2 and Table 1. Overall, the IR of total Otorhinolaryngologic AEFIs was 47.068 of CPS (completed primary series) and 7.237 UBB (updated bivalent booster) per 100,000. For most symptoms, being female was associated with statistically significant higher AEFIs (Table 1).

In CPS, females showed a higher IR of hearing loss (2.158), tinnitus (6.221), ear infections (0.317), and dizziness with a notable IR of 43.108 for dizziness in the ear region. In the nasal region, epistaxis (1.168), anosmia (2.036), snoring (0.177), and allergies (4.017) were higher IR among females, while in the throat area, females were more likely to experience laryngitis (0.094), laryngopharyngeal reflux (0.248), and pharyngitis (2.168).

The UBB dataset similarly demonstrated higher IRs for dizziness (3.697), sinusitis (0.623), anosmia (0.535), allergies (0.508), and pharyngitis (1.581) among females.

3.3 Comparison of AEFIs by age group

The CPS dataset revealed varying age-based trends for different otolaryngological AEFIs in Figure 2 and Table 2. For symptoms related to the ear, the 50–64 age group demonstrated the highest IR of hearing loss (1.678), tinnitus (6.417), ear infections (0.186), and dizziness (22.715). Anosmia (1.174) also recorded the highest IR in the 50–64 age group. Conversely, the 65 and older age group showed the highest IR for sinusitis (0.557), rhinitis (0.051), epistaxis (0.682), snoring (0.257), and allergies (1.956). In the throat region, laryngitis (0.068) and laryngopharyngeal reflux (0.157) were most common among the 50–64 age group, whereas pharyngitis (1.505) was most prevalent among those 65 and older.

In the UBB dataset, the highest IRs for tinnitus (0.593) and ear infections (0.154) were observed in the 50–64 age group, while dizziness (2.294), sinusitis (0.564), anosmia (0.419), snoring (0.303), allergies (0.286), and pharyngitis (1.897) were more frequent among those aged 65 and older.

3.4 Comparison of AEFIs by vaccine manufacturer

Upon examining the impact of different vaccine manufacturers, the researchers found that Janssen's vaccine exhibited higher IRs for hearing loss (5.871), tinnitus (19.182), ear infection (0.709), dizziness (121.202), sinusitis (2.088), epistaxis (4.251), anosmia (5.264), snoring (0.734), allergies (5.555), and pharyngitis (5.428) when compared to other vaccines in the "At Least One Dose" analysis in Figure 2 and Table 3.

In the UBB group, higher IRs for dizziness (3.328) and pharyngitis (1.759) were observed for the Moderna vaccine compared to the Pfizer-BioNTech vaccine. Conversely, Pfizer-BioNTech exhibited a higher IR for snoring (0.341) compared to Moderna.

3.5 Proportional reporting ratio compared with other AEFIs

The highest PRRs were for Anosmia (3.617), Laryngopharyngeal Reflux - Acid Reflux (2.632), and Tinnitus -Ringing in the ears (2.343), in that order, with these three significantly incidence than other background noises (PRR >2) in Table 4. Hearing Loss(PRR:1.554), Ear Infectios (Otitis Me-dia; PRR:0.227), Meniere's Disease (PRR:1.945), Dizziness or Vertigo (PRR:1.629), Sinusitis (PRR:0. 832), Rhinitis (Allergic and Non-allergic; PRR:0.056),

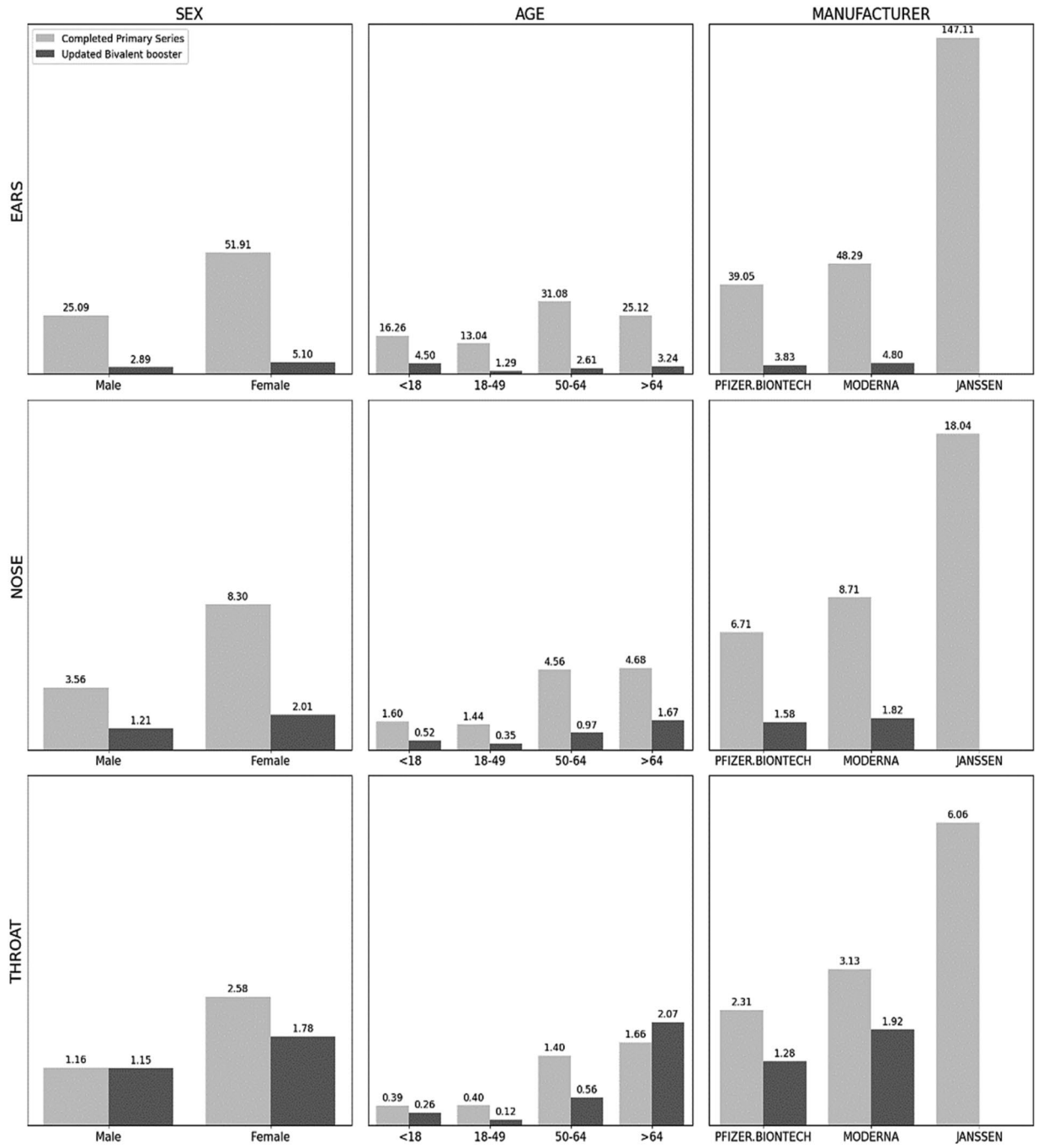

FIGURE 2
Incidence rates of adverse events by sex, age, and manufacturers. Note: Per 100,000 persons. Data are from the vaccine adverse event reporting system (VAERS) and CDC Covid-19 vaccinations data tracker from December 14, 2020 to August 30, 2023. In manufacturer, the CDC did not provide the number of Completed Primary Series, so we substituted At Least One dose. Ears (Hearing Loss, Tinnitus, Ear Infections, Meniere's Disease, Vestibular Neuronitis, Dizziness or Vertigo); Nose (Sinusitis, Rhinitis, Epistaxis, Anosmia, Nasal Polyps, Snoring or Difficulty Breathing through the Nose and Sleep Apnea, Allergies); Throat (Tonsillitis, Laryngitis, Vocal Cord Polyps and Nodules, Laryngopharyngeal Reflux, Epiglottitis, Pharyngitis). All adverse events by sex, age, and manufacturer have statistically significant differences between categories using $\chi 2$-test or Fisher's exact test.

Epistaxis (PRR:1.605), Snoring or Difficulty Breathing through the Nose and Sleep Ap-nea (PRR:0. 205), Allergies (PRR:0.251), Tonsillitis (PRR:0.491), Layryngitis (PRR:0.332), Epiglottitis (PRR:0.348), Pharyngitis (0.573) were statistically significant but did not show clinically significant incidence when compared to other AEFIs (PRR <2; Table 4).

4 Discussion

In the context of the global rollout of COVID-19 vaccinations, understanding potential AEFIs is of paramount importance. Previous studies have mainly focused on general systemic or localized AEs, leaving otolaryngological AEFIs relatively unexplored (17–19). This

TABLE 1 Otorhinolaryngologic adverse effects of COVID-19 vaccination in the United States.

Adverse effects	Completed primary series							Updated bivalent booster						
	Sum		Male		Female		*P* value	Sum		Male		Female		*p* value
	n(%)	IR	n(%)	IR	n(%)	IR		n(%)	IR	n(%)	IR	n(%)	IR	
Hearing loss	4,319(4.05)	1.906	1,759(5.46)	1.629	2,560(3.44)	2.158	<.0.001	19(64.86)	0.352	70(5.3)	0.278	126(4.65)	0.413	0.413
Tinnitus (Ringing in the ears)	12,338(11.57)	5.445	4,960(15.41)	4.593	7,378(9.91)	6.221	<.0.001	381(9.45)	0.684	146(11.05)	0.579	235(8.67)	0.771	0.771
Ear infections (Otitis Media)	563(0.53)	0.248	187(0.58)	0.173	376(0.5)	0.317	<.0.001	81(2.01)	0.145	24(1.82)	0.095	57(2.1)	0.187	0.187
Meniere's disease	82 (0.08)	0.036	25(0.08)	0.023	57(0.08)	0.048	0.002	3(0.07)	0.005	1(0.08)	0.004	2(0.07)	0.007	0.007
Vestibular neuronitis	98 (0.09)	0.043	35(0.11)	0.032	63(0.08)	0.053	0.018	11(0.27)	0.02	4(0.3)	0.016	7(0.26)	0.023	0.023
Dizziness or vertigo	71,255(66.81)	31.446	20,126(62.53)	18.637	51,129(68.66)	43.108	<0.001	1,610(39.94)	2.89	483(36.56)	1.915	1,127(41.59)	3.697	<0.001
Sinusitis	1,333(1.25)	0.588	346(1.07)	0.32	987(1.33)	0.832	<0.001	270(6.7)	0.485	80(6.06)	0.317	190(7.01)	0.623	<0.001
Rhinitis (Allergic and Non-allergic)	126(0.12)	0.056	49(0.15)	0.045	77(0.1)	0.065	0.049	8(0.2)	0.014	2(0.15)	0.008	6(0.22)	0.02	0.02
Epistaxis	2,085(1.95)	0.92	700(2.17)	0.648	1,385(1.86)	1.168	<0.001	45(1.12)	0.081	15(1.14)	0.059	30(1.11)	0.098	0.098
Anosmia	3,652(3.42)	1.612	1,237(3.84)	1.146	2,415(3.24)	2.036	<0.001	227(5.63)	0.408	64(4.84)	0.254	163(6.01)	0.535	<0.001
Nasal polyps	15(0.01)	0.007	7(0.02)	0.006	8(0.01)	0.007	0.939	2(0.05)	0.004	1(0.08)	0.004	1(0.04)	0.003	0.003
Snoring or difficulty breathing through the nose and sleep apnea	494(0.46)	0.218	284(0.88)	0.263	210(0.28)	0.177	<0.001	152(3.77)	0.273	84(6.36)	0.333	68(2.51)	0.223	0.223
Allergies	5,983(5.61)	2.64	1,219(3.79)	1.129	4,764(6.4)	4.017	<0.001	213(5.28)	0.382	58(4.39)	0.23	155(5.72)	0.508	<0.001
Tonsillitis	73(0.07)	0.032	20(0.06)	0.019	53(0.07)	0.045	0.001	4(0.1)	0.007	1(0.08)	0.004	3(0.11)	0.01	0.01
Laryngitis	135(0.13)	0.06	23(0.07)	0.021	112(0.15)	0.094	<0.001	54(1.34)	0.097	11(0.83)	0.044	43(1.59)	0.141	0.141
Vocal cord polyps and nodules	27(0.03)	0.012	6(0.02)	0.006	21(0.03)	0.018	0.008	0	0	0	0	0	0	
Laryngopharyngeal reflux (acid reflux)	337(0.32)	0.149	43(0.13)	0.04	294(0.39)	0.248	<0.001	21(0.52)	0.038	6(0.45)	0.024	15(0.55)	0.049	0.049
Epiglottitis	8(0.01)	0.004	3(0.01)	0.003	5(0.01)	0.004	0.565	0	0	0	0	0	0	
Pharyngitis	3,730(3.5)	1.646	1,159(3.6)	1.073	2,571(3.45)	2.168	<0.001	753(18.68)	1.352	271(20.51)	1.075	482(17.79)	1.581	<0.001
Any IR	106,653	47.068	32,188	29.807	74,465	62.783	<0.001	4,031	7.237	1,321	5.238	2,710	8.89	<0.001
Sample size	226,593,618		107,987,092		118,606,526			55,703,085		25,218,543		30,484,542		

The data was collected from the VAERS and the CDC Covid-19 vaccinations data tracker as of August 30, 2023. The Incidence Rate(IR) per 100,000 was measured based on subjects with complete primary series vaccination and updated bivalent booster of COVID-19 vaccinations in the US. The sample size was from the CDC Data Tracker. *P* value was by chi-square, which tests the difference in AEs distribution according to age group.

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TABLE 2 Otorhinolaryngologic adverse effects of COVID-19 vaccination by age.

Adverse effects	Completed primary series									Updated bivalent booster								
	0–17 years		18–49 years		50–64 years		65+ years		*P* value	0–17 years		18–49 years		50–64 years		65+ years		*P* value
	n(%)	IR	n(%)	IR	n(%)	IR	n(%)	IR		n(%)	IR	n(%)	IR	n(%)	IR	n(%)	IR	
Hearing loss	155(3.79)	0.692	429(2.94)	0.437	885(4.53)	1.678	804(5.01)	1.576	<0.001	3(1.85)	0.098	17(6.32)	0.111	36(6.37)	0.264	79(4.83)	0.338	<0.001
Tinnitus (Ringing in the ears)	166(4.06)	0.741	724(4.96)	0.738	3,384(17.33)	6.417	2,056(12.8)	4.029	<0.001	9(5.56)	0.294	12(4.46)	0.078	81(14.34)	0.593	109(6.67)	0.466	<0.001
Ear infections (Otitis Media)	27(0.66)	0.121	49(0.34)	0.05	98(0.5)	0.186	76(0.47)	0.149	<0.001	5(3.09)	0.163	7(2.6)	0.046	21(3.72)	0.154	26(1.59)	0.111	<0.001
Meniere's disease	1(0.02)	0.004	2(0.01)	0.002	19(0.1)	0.036	20(0.12)	0.039	1	0	0	1(0.37)	0.007	0	0	2(0.12)	0.009	1
Vestibular neuronitis	2(0.05)	0.009	10(0.07)	0.01	24(0.12)	0.046	15(0.09)	0.029	<0.001	1(0.62)	0.033	1(0.37)	0.007	2(0.35)	0.015	6(0.37)	0.026	0.672
Dizziness or vertigo	3,291(80.5)	14.695	11,582(79.32)	11.799	11,978(61.33)	22.715	9,849(61.33)	19.3	<0.001	120(74.07)	3.915	159(59.11)	1.039	217(38.41)	1.589	537(32.86)	2.294	<0.001
Sinusitis	21(0.51)	0.094	76(0.52)	0.077	265(1.36)	0.503	284(1.77)	0.557	<0.001	3(1.85)	0.098	5(1.86)	0.033	32(5.66)	0.234	132(8.08)	0.564	<0.001
Rhinitis (Allergic and Non-allergic)	2(0.05)	0.009	13(0.09)	0.013	24(0.12)	0.046	26(0.16)	0.051	<0.001	0	0	2(0.74)	0.013	2(0.35)	0.015	3(0.18)	0.013	0.978
Epistaxis	127(3.11)	0.567	247(1.69)	0.252	333(1.71)	0.631	348(2.17)	0.682	<0.001	5(3.09)	0.163	4(1.49)	0.026	4(0.71)	0.029	18(1.1)	0.077	<0.001
Anosmia	53(1.3)	0.237	372(2.55)	0.379	753(3.86)	1.428	599(3.73)	1.174	<0.001	0	0	4(1.49)	0.026	39(6.9)	0.286	98(6)	0.419	<0.001
Nasal Polyps	0	0	2(0.01)	0.002	3(0.02)	0.006	4(0.02)	0.008	0.387	0	0	0	0	1(0.18)	0.007	1(0.06)	0.004	0.875
Snoring or difficulty breathing through the nose and sleep apnea	8(0.2)	0.036	36(0.25)	0.037	64(0.33)	0.121	131(0.82)	0.257	<0.001	1(0.62)	0.033	5(1.86)	0.033	21(3.72)	0.154	71(4.35)	0.303	<0.001
Allergies	147(3.6)	0.656	664(4.55)	0.676	963(4.93)	1.826	998(6.21)	1.956	<0.001	7(4.32)	0.228	34(12.64)	0.222	33(5.84)	0.242	67(4.1)	0.286	<0.001
Tonsillitis	3(0.07)	0.013	22(0.15)	0.022	11(0.06)	0.021	6(0.04)	0.012	0.607	0	0	2(0.74)	0.013	0	0	0	0	0.262
Laryngitis	1(0.02)	0.004	10(0.07)	0.01	36(0.18)	0.068	28(0.17)	0.055	<0.001	0	0	3(1.12)	0.02	8(1.42)	0.059	32(1.96)	0.137	<0.001
Vocal cord polyps and nodules	0	0	1(0.01)	0.001	10(0.05)	0.019	6(0.04)	0.012	0.001	0	0	0	0	0	0	0	0	
Laryngopharyngeal reflux (Acid Reflux)	3 (0.07)	0.013	26(0.18)	0.026	83(0.43)	0.157	39(0.24)	0.076	<0.001	0	0	1(0.37)	0.007	1(0.18)	0.007	9(0.55)	0.038	0.127
Epiglottitis	0	0	1(0.01)	0.001	2(0.01)	0.004	1(0.01)	0.002	0.745	0	0	0	0	0	0	0	0	
Pharyngitis	81 (1.98)	0.362	335(2.29)	0.341	594(3.04)	1.126	768(4.78)	1.505	<0.001	8(4.94)	0.261	12(4.46)	0.078	67 (11.86)	0.491	444(27.17)	1.897	<0.001
Any IR	4,088	18.253	14,601	14.875	19,529	37.035	16,058	31.467	<0.001	162	5.285	269	1.758	565	4.138	1,634	6.981	<0.001
Sample size	22,396,020		98,160,420		52,731,727		51,031,000			3,065,181		15,303,884		13,654,874		23,407,228		

The data was collected from the VAERS and the CDC Covid-19 vaccinations data tracker as of August 30, 2023. The Incidence Rate(IR) per 100,000 was measured based on subjects with complete primary series vaccination and updated bivalent booster of COVID-19 vaccinations in the US. The sample size was from the CDC Data Tracker. *P* value was by chi-square, which tests the difference in AEs distribution according to age group.

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TABLE 3 Otorhinolaryngologic adverse effects of COVID-19 vaccination by manufacturer.

Adverse effects	At least one dose							Updated Bivalent booster				
	PFIZER. BIONTECH		MODERNA		JANSSEN		*P* value	PFIZER. BIONTECH		MODERNA		*P* value
	n(%)	IR	n(%)	IR	n(%)	IR		n(%)	IR	n(%)	IR	
Hearing loss	3,391(4.62)	2.222	2,455(4.23)	2.543	464(3.43)	5.871	<0.001	113(4.76)	0.319	85(4.96)	0.423	0.047
Tinnitus (Ringing in the ears)	9,308(12.69)	6.100	7,049(12.14)	7.303	1,516(11.2)	19.182	<0.001	226(9.52)	0.637	168(9.8)	0.837	0.007
Ear infections (Otitis Media)	453(0.62)	0.297	345(0.59)	0.357	56(0.41)	0.709	<0.001	51(2.15)	0.144	37(2.16)	0.184	0.248
Meniere's disease	61(0.08)	0.040	50(0.09)	0.052	7(0.05)	0.089	1.000	2(0.08)	0.006	1(0.06)	0.005	0.920
Vestibular neuronitis	89(0.12)	0.058	66(0.11)	0.068	5(0.04)	0.063	0.619	6(0.25)	0.017	5(0.29)	0.025	0.520
Dizziness or vertigo	46,290(63.09)	30.336	36,646(63.14)	37.964	9,579(70.79)	121.202	<0.001	961(40.5)	2.709	668(38.95)	3.328	<0.001
Sinusitis	1,029(1.4)	0.674	941(1.62)	0.975	165(1.22)	2.088	<0.001	154(6.49)	0.434	117(6.82)	0.583	0.016
Rhinitis (Allergic and Non-allergic)	91(0.12)	0.060	83(0.14)	0.086	9(0.07)	0.114	0.020	4(0.17)	0.011	4(0.23)	0.020	0.414
Epistaxis	1,495(2.04)	0.980	1,072(1.85)	1.111	336(2.48)	4.251	<0.001	25(1.05)	0.070	20(1.17)	0.100	0.246
Anosmia	2,919(3.98)	1.913	2,032(3.5)	2.105	416(3.07)	5.264	<0.001	128(5.39)	0.361	101(5.89)	0.503	0.012
Nasal polyps	8(0.01)	0.005	6(0.01)	0.006	3(0.02)	0.038	0.002	1(0.04)	0.003	1(0.06)	0.005	0.683
Snoring or difficulty breathing through the nose and sleep apnea	568(0.77)	0.372	357(0.62)	0.370	58(0.43)	0.734	<0.001	121(5.1)	0.341	31(1.81)	0.154	<0.001
Allergies	4,134(5.63)	2.709	3,918(6.75)	4.059	439(3.24)	5.555	<0.001	126(5.31)	0.355	91(5.31)	0.453	0.075
Tonsillitis	50(0.07)	0.033	36(0.06)	0.037	8(0.06)	0.101	0.008	3(0.13)	0.008	1(0.06)	0.005	0.643
Laryngitis	135(0.18)	0.088	109(0.19)	0.113	15(0.11)	0.190	0.007	31(1.31)	0.087	24(1.4)	0.120	0.247
Vocal cord polyps and nodules	29(0.04)	0.019	13(0.02)	0.013	3(0.02)	0.038	0.225	(0)	0.000	(0)	0.000	
Laryngopharyngeal Reflux (Acid Reflux)	235(0.32)	0.154	193(0.33)	0.200	22(0.16)	0.278	0.002	13(0.55)	0.037	8(0.47)	0.040	0.852
Epiglottitis	6(0.01)	0.004	7(0.01)	0.007	2(0.01)	0.025	0.041	(0)	0.000	(0)	0.000	
Pharyngitis	3,076(4.19)	2.016	2,663(4.59)	2.759	429(3.17)	5.428	<0.001	408(17.19)	1.150	353(20.58)	1.759	<0.001
Any IR	73,367	48.081	58,041	60.129	13,532	171.218	<0.001	2,373	6.689	1,715	8.544	<0.001
Sample size	152,590,827		96,527,417		7,903,364			35,476,628		20,072,000		

The data was collected from the VAERS and the CDC Covid-19 vaccinations data tracker as of August 30, 2023. The Incidence Rate(IR) per 100,000 was measured based on subjects with complete primary series vaccination and updated bivalent booster of COVID-19 vaccinations in the US. The sample size was from the CDC Data Tracker. *P* value by Chi-square test. The CDC did not provide the number of the complete primary series, thus it was substituted with "At Least One Dose." The CDC did not provide the number of updated bivalent booster produced by Jassen because it was not used as one in the US.

study, utilizing an extensive sample size of 226,593,618 individuals, represents a significant step toward comprehensively characterizing the otolaryngological AEFIs associated with COVID-19 vaccinations. This large-scale analysis aims to move beyond isolated case reports and anecdotal evidence, providing a robust and detailed portrait of the otolaryngological AEFIs landscape in response to COVID-19 vaccinations.

One of the most salient findings from the study was the high incidence of dizziness/vertigo as an otolaryngological AEFIs post COVID-19 vaccination. This observation aligns with prior literature, notably the research conducted by Yan et al., which too highlighted a significant increase in episodes of dizziness/vertigo subsequent to COVID-19 vaccination (20). Drawing from the detailed assessment by Yan et al., it is interesting to note that the time to the onset of these symptoms post-vaccination was approximately 10 days, coinciding with the onset of IgG production. This suggests a potential immunological underpinning for the manifestation of these symptoms. Furthermore, their research emphasized the exacerbation of conditions such as Meniere's disease (MD) post-vaccination, potentially due to heightened immunological factors leading to aggravated endolymphatic hydrops (21). Other conditions such as Vertebrobasilar insufficiency (VBI) were also implicated, pointing to dysregulation of blood flow and factors such as altered plasma viscosity post-vaccination. Notably, while some vaccines, like the AstraZeneca (AZ) variant, demonstrated efficacy against SARS-COV-2, they were associated with a heightened risk of thrombotic events (22). Finally, it is essential to consider the backdrop against which these vaccinations are taking place. The ongoing stress and heightened anxiety levels during this pandemic might contribute to immunization anxiety-related reactions. Therefore, while this study

TABLE 4 Proportional reporting ratios in completed primary series.

Symptoms	Completed primary series			
	Specific AEs of COVID-19 vaccines	PRR	95% CIL	95% CIH
Hearing loss	4,319	1.554	1.487	1.625
Tinnitus (Ringing in the ears)	12,338	2.343	2.275	2.413
Ear infections (Otitis Media)	563	0.227	0.207	0.248
Meniere's disease	82	1.945	1.382	2.736
Vestibular neuronitis	98	1.217	0.924	1.603
Dizziness or vertigo	71,255	1.629	1.612	1.647
Sinusitis	1,333	0.832	0.777	0.891
Rhinitis (Allergic and Non-allergic)	126	0.056	0.047	0.067
Epistaxis	2,085	1.605	1.506	1.712
Anosmia	3,652	3.167	2.983	3.363
Nasal polyps	15	1.956	0.879	4.355
Snoring or difficulty breathing through the nose and sleep apnea	494	0.205	0.186	0.225
Allergies	5,983	0.251	0.244	0.258
Tonsillitis	73	0.491	0.375	0.642
Laryngitis	135	0.332	0.275	0.401
Vocal cord polyps and nodules	27	1.101	0.659	1.837
Laryngopharyngeal reflux (Acid Reflux)	337	2.632	2.187	3.168
Epiglottitis	8	0.348	0.159	0.759
Pharyngitis	3,730	0.573	0.551	0.596
Any IR	106,653			
Sample size	226,593,618			

Data are from the VAERS and CDC Covid-19 vaccinations data tracker through to August 30, 2023. PRR, proportional reporting ratio.

and others highlight significant otolaryngological AEFIs, it underscores the need for a comprehensive understanding and approach toward managing post-vaccination AEFIs.

A significant finding of the study was the identification of tinnitus as a notable AEFIs following COVID-19 vaccination. This aligns with the findings of other studies, such as the research conducted by Ahsanuddin et al. Their investigation, based on a comprehensive analysis of the FDA's VAERS database, also identified a significant occurrence of otolaryngologic symptoms post COVID-19 vaccination, with tinnitus being notably prevalent (13). Specifically, they highlighted the significant reporting rates of tinnitus (PRR: 3.97, ROR: 3.98) following the COVID-19 vaccination, emphasizing them as higher than the background reporting rates in the database. In this study, as a result of analyzing PRR in the same way as in previous studies, tinnitus was found to be statistically significantly higher. Looking deeper into the potential mechanisms behind these symptoms, Ahsanuddin et al. suggested that the effects of the virus on the vestibulocochlear nerve could be a plausible cause for symptoms like tinnitus, deafness, and vertigo (13). Another hypothesis postulated the involvement of the middle ear's epithelium, which, having a high expression of ACE2 receptors needed for the virus's entry, might undergo inflammation or direct damage (23, 24). As such, it is speculated that the immunological response against spike proteins in COVID-19 vaccines might interact with cranial nerves and the middle ear, producing symptoms reminiscent of a viral infection. Drawing parallels with this study's observations, the prominence of tinnitus as an AEFIs post COVID-19 vaccination cannot be understated. The findings resonate with previous research, such as the study by Dorney I et al., further emphasizing the importance of this particular AEFIs (25). While the precise mechanisms underpinning the development of tinnitus post-vaccination remain elusive, the accumulating evidence denotes a potential correlation between COVID-19 vaccines and the onset of tinnitus, necessitating more comprehensive clinical and mechanistic investigations.

The analysis of this study reveals a notable gender disparity in the frequency of otolaryngological AEFIs following COVID-19 vaccination, with a higher prevalence observed in females. This observation aligns with a cohort analysis conducted in Denmark and Iraq (26, 27), which also reported a higher frequency of AEFIs among females. This gender-based variation in response to vaccination, while not entirely understood, is becoming a salient feature in the growing body of research surrounding COVID-19 vaccines.

Systemic reactions, such as fever, have been more commonly reported among younger individuals following vaccination (28). However, contrasting findings from a study by Xiong et al. indicate that more severe outcomes, including serious AEFIs, permanent disabilities, hospitalizations, and death, were more frequently observed in older adults compared to younger adults aged between

18 and 64 years (29). Corroborating these findings, the analysis focusing on otolaryngological AEFIs similarly found a higher prevalence in older age groups. Specifically, within the cohort that received the completed primary series, there was a significant spike in AEFIs in the 50–64 age range. Additionally, data concerning the updated bivalent booster shot illustrated a more pronounced prevalence of AEFIs in individuals aged 65 and above. This accumulation of evidence suggests a distinct age-dependent variation in response to vaccination. This is further emphasized by studies showing that, compared to their younger counterparts, the older adult population seems to exhibit a diminished capacity to mount an effective immune response post-vaccination (30). For instance, Müller et al. demonstrated that older individuals had a reduced frequency of neutralizing antibodies following BNT162b2 vaccination relative to the younger demographic (31). Delving deeper into the causal factors underlying these age-related discrepancies necessitates further dedicated research.

The findings also shed light on differences across various vaccine manufacturers. Specifically, the rate of AEFIs following at least one dose of the Janssen vaccine was roughly twice as high as that observed with Pfizer and Moderna vaccines. Moderna, in turn, showed a slightly higher rate compared to Pfizer. This is consistent with previous reports suggesting that while local reactions may be more prevalent following mRNA vaccines (Pfizer and Moderna), systemic AEFIs, such as headache and fatigue, appear to be more prevalent following viral vector-based vaccines (e.g., Janssen) (32). These differences in AEFIs profiles among the vaccines are particularly noteworthy. They not only add depth to the understanding of the immune response triggered by different vaccine platforms but also highlight the need for personalized approaches to vaccination, taking into account factors such as age, gender, and individual health status.

In 2022, a study by Nguyen Dc et al. (33), involving 1,323 participants, demonstrated that the incidence of AEFIs following a booster vaccination was consistent with that of the first or second vaccination. However, this study has investigated that adverse reactions were more frequent after receiving the completed primary series (CPS) compared to the updated bivalent booster (UBB). Several factors might contribute to this observation. As individuals progress through the vaccination series, their adaptive immune response could become more refined and primed, potentially leading to fewer AEFIs after receiving the UBB compared to the CPS. Concurrently, there is the possibility of a reporting bias: individuals might initially be more vigilant in reporting AEFIs, viewing them as novel and anxiety-inducing. By the time they receive the booster shot, they might have grown accustomed to the vaccine and its potential side effects, resulting in decreased reporting. Despite these considerations, it remains crucial to acknowledge the limitations of the Vietnamese study due to its smaller sample size and a predominantly Asian participant demographic, which could introduce potential biases. Regardless, our findings hint at a degree of adaptability and tolerance developing in individuals as they progress through the vaccination series, serving as a reassuring indicator for public health campaigns aiming to boost vaccine uptake. Furthermore, it highlights the effectiveness of COVID-19 vaccination in containing SARS-CoV-2 spread and reducing the severity of COVID-19 disease, as well as the risk of developing long COVID (34).

This study, while extensive, has several inherent limitations that need to be acknowledged. The use of VAERS data, a passive and voluntary reporting system (35), likely leads to underreporting of AEFIs and may introduce reporting bias (36). Given the nature of this system, the quality and accuracy of the reported data may differ because one person can report multiple AEFIs. In addition, the study lacked a consistent denominator of administered doses, which restricted the capacity to accurately calculate incidence rates of AEFIs. Furthermore, this analysis predominantly focused on short-term post-vaccination effects, underscoring the need for longitudinal studies to assess potential long-term AEFIs among a more diverse and larger population. Finally, because the CDC only provides disaggregated information on gender, age, and manufacturer, only a univariate analysis could be conducted. Despite these limitations, these real-world, long-term descriptive studies are essential to further refine our understanding of the safety profile of COVID-19 vaccines. It is also imperative that future investigations corroborate reported AEFIs with additional clinical data and diagnostic tests to robustly establish causality.

5 Conclusion

The analysis contributes valuable insights into the landscape of otolaryngological AEFIs following COVID-19 vaccination, a relatively underexplored area in the current literature. It underscores the importance of vigilant post-vaccination surveillance and provides a foundation for further research aimed at elucidating the mechanisms behind these observations and informing safer and more effective vaccination strategies.

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.

Ethic statement

The studies involving humans were approved by the institutional review board of K University (KYU-2023-09-002). The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

JS: Conceptualization, Data curation, Methodology, Resources, Software, Validation, Writing – review & editing, Writing – original draft. SS: Conceptualization, Data curation, Formal analysis, Methodology, Resources, Validation, Visualization, Writing – review & editing, Writing – original draft. JL: Methodology, Writing – original draft. HR: Methodology, Writing – original draft. J-YK: Conceptualization, Funding acquisition, Supervision, Validation, Writing – original draft, Writing – review & editing.

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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

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1338862/full#supplementary-material

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Does the South African government have a duty to fund influenza vaccination of adults 65 years and older?

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In this paper, we draw on the thinking about solidarity, reciprocity and distributive justice grounded in Afro-communitarian ethics from the Global South to argue for institutions, particularly the South African (SA) government, have a *prima facie* duty to foster influenza vaccine uptake for adults 65 years and older. Although we focus specifically on the South African government to defend our position, we believe that our argument extends to all governments. Notably, these duties are that the SA government ought to make influenza vaccines freely available for the older adult in both the public and private health facilities, provided financial allocation and their extant relationships allow for this. Further, the SA government has a duty to improve influenza vaccine procurement and availability in the country, preferably through increasing manufacturing capabilities. This paper is intrinsically valuable to promote epistemic justice, thereby contributing toward the decolonization of the global healthcare system. Moreover, this project has social significance in contributing to mitigation efforts against future public health challenges associated with population aging in resource-limited developing African nations, wherein the impact of population transition will be felt most.

KEYWORDS

influenza vaccine, solidarity, reciprocity, Afro-communitarianism, decolonization

Introduction

This paper draws on the norms arising from the thinking about solidarity, distributive justice and personhood grounded in the African Ubuntu philosophy and African moral philosophy more broadly to argue that institutions, particularly the South African (SA) government, have *a prima facie* duty to fund seasonal influenza vaccination of the older adult aged 65 years and above in South Africa. This will likely contribute to vaccination uptake or foster influenza vaccine access by this population group. From the outset of this manuscript, it is essential to note that although our current focus is on influenza vaccine access by the older adult in South Africa specifically, our arguments can be contextually adjusted to ground the manuscript's thesis within other African countries. Subsequently, we believe that our argument extends to all governments. To this end, we draw on African norms that arise from values dominant in African regions.

This manuscript has become necessary since ethical reflections on *whether* governments have a duty to fund seasonal influenza vaccination for the older adult from the *unique underexplored African perspectives* are mostly missing. Existing ethical reflections on the

government's responsibility to fund the vaccination of older adults tend to adopt dominant theories from the Global North. One such position is the deontological argument that it is the government's responsibility to fund necessary healthcare in correspondence to citizens' right to healthcare (1). Furthermore, the older adult face specific age-related health challenges that other population groups may not experience (2). One of these age-specific health needs is prevention from influenza infection since 50–70% of influenza hospitalizations and roughly 90% of influenza-related deaths are adults aged 65 years and older (3). But vaccination programs (the most effective preventative public health measure against influenza) have been mostly aimed at infants and global vaccination coverage in the older adult is low. Miguel Kottow (4) posits that older people's physical and health-related vulnerabilities would imply that older adults should be afforded special rights to realize these specific health needs and achieve equality through simplifying accessibility to healthcare services, especially in developing countries.

Some scholars like David Ibom and Piyush Soni (5) deny that governments have this responsibility by drawing on the principle of utility grounded in consequentialism. According to them, it would benefit the greatest number of people if hospitals were operated as businesses so that governments could allocate those health funds to other sectors. This manuscript justifies that the government is responsible for maintaining these special rights of health prevention for the older adult by ensuring they have equitable access to age-specific preventative healthcare such as influenza vaccines.

Furthermore, this project has social significance in light of the United Nations', the Department of Economic and Social Affairs', Population Division's (6) estimate that the global population of those over 65 years will reach 1.5 billion by 2050. This population explosion will mostly occur in developing nations like South Africa. To effectively mitigate future public health challenges associated with population aging in resource-limited nations like South Africa, the government must prepare adequately for healthy aging through the development of comprehensive national policy in the promotion of a life-course approach (rather than only focusing on infants) to vaccination (2). This manuscript will be important in addressing the ethical considerations of influenza vaccine access for the older adult in South Africa and should contribute to more comprehensive policy formation.

In consideration of the older adult population group's vulnerabilities to influenza as well as the impact of the burden on the healthcare system, the South African government does currently provide influenza vaccines for the older adult at no cost through the National Immunization Program 2023. This is *only* available at the countries' public health facilities rather than in the private facilities (7). According to Statistics South (8), almost 68% of adults aged 60 and older accessed public healthcare facilities and over 31% accessed private healthcare facilities in 2021.

There are also limiting factors that undermine access to influenza vaccines, even at public health facilities. These are particularly challenging for the older adult such as prolonged waiting times, costs incurred by transport, and overburdened and understaffed health professionals (9). In fact, in 2019 (the most recently captured available data) only 67.4% of the older adult in South Africa that were surveyed were willing to consult a healthcare professional in a public health facility when ill and more concerning, 27.4% chose to self-medicate instead due to some of the barriers mentioned above to accessing public healthcare facilities (10). 31.2% of adults 60 years and older responded that they *usually* access private healthcare when ill (8). If influenza vaccines were made freely available to all older adult persons at private healthcare facilities (regardless of whether they can afford private health insurance), these challenges and barriers to accessing healthcare would significantly alleviate. Currently, at private facilities and pharmacies (such as Clicks, Dischem and Medirite) that are widely accessible by adults 65 years and above, the influenza vaccine comes at a cost, often between R109 and R250 (11). A South African study conducted in 2020 by Ijeoma Edoka and colleagues determined the cost-effectiveness of the influenza program in South Africa (which prioritizes certain vulnerable population groups) using the WHO Cost Effectiveness Tool for Seasonal Influenza Vaccination of vulnerable populations (people aged 65 years and above, pregnant women, people living with HIV/AIDS, those living with underlying medical conditions and children aged 6–59 months). The study found that the targeted vaccination program was in theory cost-effective for all the above groups except for children aged 6–59 months.

However, in South Africa, the National Immunization Program 2023 does not have the force of law and is akin to a guideline for influenza vaccine access for the older adult in South Africa exist (12). The implication is that there is a lack of willpower to enforce the guidelines. Equally, where some efforts have been made to enforce the same, it is difficult to accurately measure the success of the implementation and adherence of such guidelines since a system for adult vaccination records (other than that for COVID-19 and a paper register system for minors recording the Expanded Programme on Immunization) do not currently exist in South Africa causing barriers to efficient influenza vaccination surveillance (13), especially for specified risk-groups like older adults (14). The most recent report presenting data on vaccine coverage by age-group reported a vaccine coverage of 53% for adults 65 years and older. While this coverage rate may seem adequate, the accuracy and reliability of this data estimate may be greatly skewed due to the small sample size of 34 older adults (15). This estimate seems even more likely to be inaccurate when considering the reported statistic that only 5% of the number of doses required to immunize all vulnerable population groups in South Africa were utilized in the public sector in 2018 – just 4 years prior (16). This same study estimated the cost of vaccinating one person in 2018 was R43,61. Statistics South Africa also estimated that the South African population in (2022) included over 5.6 million older adult individuals aged 60 or older. Subsequently, we can provide an estimate that It would cost the government over R244 million to cover immunization for the entire older adult South African population (that is an additional R205 million spent on influenza immunization in the public sector compared to expenditure in 2018). Unfortunately, we could not access updated data on costs in 2023 nor were we able to find statistics on population number estimates of adults aged 65 years and above specifically. Furthermore, this estimate reflects the cost of providing free immunisastion in the public sector only and does not account for potential additional costs associated with providing it freely at a private national level as well. Our thesis that the SA government has a *prima facie* duty to make influenza vaccination available for adults

Abbreviations: SA, South Africa; OAG, Old Age Grants.

65 years and above also includes the responsibility of implementation. Additionally, we would provide clear guidelines on what concretely needs to happen to realize these duties in SA.

Research design and methodology

This is a mostly normative ethics paper, rather than an empirical one, that draws on moral norms arising from values dominant in the Global South to address the question, "Does the SA government have a *prima facie* duty to fund the influenza vaccination of adults 65 years and above at public and private health facilities?" This approach is essential and is reckoned by others to be equally valid for research articles because of their philosophical analytic method (17, 18). Other scholars like Luis Cordeiro-Rodrigues and Kevin Behrens have also used the philosophical method we adopt. Some core sections in articles that adopt include: Introduction, Research Design and Methodology, Discussion and Conclusion. As a philosophical analytic method, the manuscript builds on relevant articles that have been retrieved from databases like PubMed, PhilPapers, and Google Scholar, using key phrases like "solidarity and African moral philosophy," "vaccination, influenza and older adult," "older adult vaccination and South Africa," to name a few. For example, for our discussion on solidarity, we retrieved relevant articles from PhilPapers and Google Scholar by using key phrases like "solidarity and Afro-communitarianism," "formulations of solidarity in African moral philosophy," and "African philosophers and solidarity." We were not merely interested in reading about the common features in the formulations of solidarity in African moral philosophy. We also explored the differences in formulations, especially those that might have implications for our thesis.

Our theoretical approach is vital for several reasons. First, it is crucial for epistemic justice for policies and interventions in Africa to be shaped by African values so that the communities wherein they are implemented can fully identify with such guidelines. Policies and interventions that govern people should reflect their values and be cohesive with their beliefs for people to identify with them. Second, it would lend to the acceptability of these interventions in the communities and contribute to the success of the interventions if they are guided by values already ingrained in the communities. Finally, informing vaccine interventions in an African context with values that are dominant on the continent would contribute toward the decolonization of the health system in Africa, ending scientific or health colonialism and demonstrating the exact ways normative theories from the Global South are useful and relevant alternatives to the dominant normative theories elsewhere.

To realize the set object, we draw on the moral norms that arise from the thinking about solidarity, reciprocity and distributive justice that can be grounded *primarily* in African moral philosophy and Ubuntu philosophy. We use Afro-communitarianism to encompass African moral philosophy and Ubuntu philosophy. We conceptualize Afro-communitarianism in the same way it has been described by Cornelius Ewuoso and Susan Hall (19), as the moral philosophy informed by values that are dominant on the African continent. These values are not only found in the Global South. But the thinking about these values has not come to this continent from elsewhere.

In the first section, we will describe the thinking about solidarity, reciprocity, and distributive justice in the works of African philosophers, epistemologists and anthropologists and the key values that arise from these principles. For example, a value which arises from the thinking about solidarity is that acting in aid of others can be regarded the same as aiding oneself since they are an extension of oneself as a result of the existing relationship in the community with these individuals. This way of thinking gives grounds for valuing and caring for others the same way you would for yourself. In the second section, we draw from these outlined values described in the first section to justify that the SA government has *a prima facie* duty to fund seasonal influenza vaccination of the older adult aged 65 years and above at public and private health facilities in South Africa. In the third section, we address some objections to our thesis and outline what concretely needs to happen for the SA government to realize this duty.

Solidarity in Ubuntu philosophy and Afro-communitarianism

The term, Ubuntu, is a Nguni expression meaning humanness (20). To exhibit Ubuntu is to live a human way of life sincerely or display human excellence; to lack Ubuntu is to be deficient in human excellence (21). Thus, to exhibit Ubuntu, it is necessary to develop humanness wherein moral status, personhood and dignity are found and to lack Ubuntu is to no longer be considered a person. This begs the question, 'How should one develop humanness?'

A foundational maxim of Ubuntu philosophy, "A person is a person through other persons" (19), roughly infers that one develops humanness through forming positive communal relationships and valuing harmony with others (22). Augustine Shutte (23) states, "Our deepest [ethical imperative] is to become more fully human by entering more… deeply into community [or harmony] with others and forgoing selfishness." The thinking about solidarity grounded in Ubuntu requires that we conduct ourselves in a compassionate and considerate manner, that is, in a way that might benefit others. The intention behind this behavior in African thought is to care for the well-being of others (24). But to be able to show true solidarity requires acknowledging our interdependence. If we can do this, we will not feel obligated to just show compassion or try to benefit friends and family with whom we have close relations; we will equally try to benefit all other members of the community to whom we may not have personal ties but are aware that we are nevertheless connected to as a fellow functioning member within our society.

The knowledge that the well-being of others in our community is inextricably linked to our own well-being enables us to consider ourselves as a group and to act for the common good of our community and society. This way of thinking implies that we value other individuals the same as we value ourselves without needing to have personal direct ties to them because their value is found through their ability to contribute to society by their capacity to enter into relationships with others in society. Any act of aid for the greater good benefits both others around us and ourselves simultaneously. As such, there is no specific distinction between oneself and others around oneself because one regards themselves as a part of the greater community.

Contrastingly, other global conceptions of solidarity, such as that defined by Barbara Prainsack and Alena Buyx (25), which a Nuffield Council on Bioethics has used report, still lean toward a nuanced

individualistic perspective with a delineation of the individuals that comprise the basis of groups and they posit that these individuals should also be regarded on an individual level, not just on a group level. This conception of solidarity does distinguish between oneself and the larger group. This conception subtlety rejects the thinking of others as an extension of oneself and may present a barrier to valuing others in the community as equal to oneself. Barbara Prainsack and Alena Buyx (25) conception of solidarity can be useful to ground for both individual and collective interests, and so it tends to be more inclusive. However, it does not account for the location of individuals' place in communal relationships. A conception of solidarity wherein the individual and communal interest is not necessarily a dichotomy but could be considered compatible interests or where distinguishing between the two is actually irrelevant. This is also alluded to by Innocent Asouzu (26), an African philosopher who has produced numerous works in studying *Ibuanyidanda* (complementary reflection). He interestingly questions whether it is entirely necessary to categorize individualism as quintessentially Western because, in reality, both individual and communal interests inevitably exist simultaneously regardless of cultural association.

Notice that there are other ways the thinking about solidarity differs from the conception of the same in the Global North. For example, although this conception of solidarity from the Global North similarly prizes acting compassionately in aid of others, it sometimes evaluates actions in solidarity by their costs incurred. An action for the benefit of others incurring a cost implies that these beneficial deeds may become a burden or come at a disadvantage to oneself, further highlighting the individualistic perception that benefiting others does not necessarily entail concurrently benefiting oneself. Based on the preceding thinking about solidarity, solidary actions are primarily *individual-regarding*. By contrast, the African view of solidarity is other-regarding and often entails the moral duty to act for the well-being of others.

It is important to outline some conceptions of solidarity derived from common maxims and motifs in various African regions to underscore Global South's tautology of the principle of solidarity and how it can be understood in the African context and the norms deriving from it. One foundational maxim by John Mbiti (27), a Kenyan Christian philosopher often referred to as the 'father of modern African theology', is, "I am because we are; and since we are therefore I am." This maxim denotes the utmost importance of relationships with others in realizing one's moral duties and values and developing one's humanity or personhood. He also aptly highlights the necessity of interdependence, that one cannot exist as a human without being connected with others, and that others' states of being are intricately bound up with our own. West African traditional Igbo philosophers (of Nigeria) often use a set of allegorical statements to draw on the principle of complementarity or mutual dependence [(28), pg. 142–148]. "Ibu anyi danda" translates to 'no task is insurmountable for danda (a species of ants)' [(29), pg. 11]. *Danda* can move hauls much heavier than themselves when working in mutual dependence with one another (26).

From this allegory, other African philosophers derive values of togetherness and a sense of belonging (30). In a similar vein, consider the East African Luo proverb, "Alone a youth runs fast, with an elder, slow, but together they go far" which underpins the value of togetherness, that we can accomplish much more together than we could on our own in the communal project. In this proverb, the elders provide wisdom, knowledge and guidance while, among other things, the young can offer strength and put this guidance into action. There is a mutually complementary relationship that exists with this sense of togetherness, where all parties contribute toward the communal project in their capacity but their contributions are of equal value since it collaboratively bolters the common good of those in the community. This depicts a sort of *horizontal solidarity between community members* (31). Equally, to justify how we are implicated in each other's lives, some scholars use the motif of the Siamese Crocodile, with two heads but one stomach. This is a common motif in West Africa and it depicts how deeply connected and impacted lives are in Africa (32).

While the Global South conceptions of solidarity depicted above represent various nuanced understandings of solidarity from different African regions, it does not exhaust all possible conceptions of African solidarity. We acknowledge that within these conceptions of solidarity of the Global South remains a "missing link" of where the place of the individual can be located within the community (26). As such, the African principle of solidarity – like everything else in existence – exists in a state of incompleteness (33), wherein the space for many possibilities of enhancing and extending this principle arises. Possibly even to a conception of solidarity wherein a complementary relationship of mutual dependence between the individual and its interests and community interests can be found (26). Nonetheless, our analysis indicates that the moral imperative arising from solidarity in Afro-communitarianism often requires individuals to prize togetherness, fellowship, docility, and acting for the well-being of others.

Reciprocity and Afro-communitarianism

Reciprocity refers to the notion that one is morally obligated to help those in their community who need aid in whichever capacity one can since others are morally required to do the same (20). A common maxim used to express this idea is that *"the right hand washes the left hand and the left hand washes the right hand."* The moral norm that arises from this is that the relationship of mutual aid is moral, and ought to be promoted since this is who we are.

It is essential to state here that this act of mutual aid is not necessarily done *with the expectation of exchange*. Instead it is a mindset which Julius Nyerere (34) expresses aptly, "we took care of the community, and the community took care of us. We neither needed nor wished to exploit our fellow men." Again, the African thinking of interdependence, wherein others around us are merely an extension of oneself, encapsulates this motive to act in reciprocity.

The thinking about reciprocity in the Global South is typified by the common agricultural practice in Southern Africa known as *letsema*. This is the Sesotho practice wherein members of a community undertake to assist each other during each step in farming, including ploughing, sowing, weeding and harvesting (35). Directly translated, the Setswana word *letsema* means "a group of people coming together for a common purpose" (36). This practice encapsulates several norms implicit in the significance of reciprocity in communal living.

Letsema calls for mutual collaboration and cooperation underpinning collective responsibility among community members (37). Furthermore, it predicates compassion in contributing toward an agricultural project that will benefit others in the community. Reciprocity is highlighted by

those undertaking this practice in their recognition of the African maxims that "a single finger cannot remove fluff" and "two heads are better than one" (38). The value of collective efforts toward a communal project that brings about a common good (for those contributing as well as for others in community) is also aptly exemplified by the Setswana phrase "*kgetsi ya tsie e kgonwa ka go tshwaraganelwa*" which means "it takes collective effort to overcome a swarm of locusts" (36).

Reciprocity has also been derived from motifs from other regions in Africa. The previous section explains how the motif of the Siamese Crocodile explains the interconnectedness of lives. This Ghanian motif, *Funtumfunafu-Denkyemfunafu,* about the 'Siamese Crocodiles' originating from the Akan tribe is also a typology of reciprocity. The translated motif states, "Siamese crocodiles with a common stomach but struggle for food when eating" (39). This Adinkra symbol (Figure 1) depicts two individual crocodiles with separate heads and tails, but their torso is conjoined with one shared stomach (40). Although the food entering either crocodile's mouth will come to be in the same stomach, they wrestle and compete to relinquish the flavor of the food on their own tongues and harm their survival as a whole in doing so, as they then realize (41).

In realizing that the good that is acquired by individuals in the community comes to be a shared good of the community or a common good, competing for that good is no longer necessary (42). Furthermore, preventing one from acquiring goods out of competition only harms the community. This reflects back to the needlessness of exploiting fellow community members and that aiding others in the community will help oneself in the process.

This thinking about reciprocity is not unique to the Global South and can be found elsewhere in the Global North. For example, Care Ethics also conceptualizes reciprocity as mutual aid. However, the mutual freedom to enter a reciprocal exchange is necessary and requires a mutual agreement to this exchange. A response to reciprocal action by one party (which may be unequal) is then demanded by the other party to the agreement (43). This is not necessarily true in African thinking. For the reason that we are already in existing potential reciprocal relationships with everyone else with whom we are in the community. In other words, there is no specific agreement between parties to enter into a reciprocal relationship as such. Moreover, acts of goodwill to others in the community are done neither with the expectation of receiving anything in exchange nor to require an immediate reciprocal response of equal measure from others (34), as it tends to be the case with Care Ethics.

FIGURE 1
Akan symbol for *Funtumfunafu-Denkyemfunafu* - 'Siamese Crocodiles' illustrated by Ivana Bunuševac.

Distributive justice and African moral philosophy

Justice alone entails relating to others in a right manner wherein each person is given their due (44). Distributive justice in the scholarship on Ubuntu requires one in a state of authority to equitably distribute advantages and disadvantages accordingly to reach as close to a state of equality among disparity groups as possible (45).

Although distributive justice is not uniquely an African principle, there are unique features of this principle emanating from the literature in African philosophy that are worth highlighting. First, distributive justice is sometimes differentiated from commutative justice. Both distributive justice and commutative justice are considered as expressions of social justice in the literature on African (moral) philosophy. While distributive justice describes first-order duties of institutions and states to their citizens (to protect their civil liberties, distribute goods equitably and create a conducive environment for communal relationships), commutative justice describes the responsibilities of citizens to one another and the State. Notably, their responsibility to be solidary to one another and to the State (46).

Evidently, commutative justice also involves distribution of some sort, but this is a second-order duty that explores issues around equity and relations on the horizontal (among citizens or equal parties) and vertical (toward the State). For example, this conception of justice can enhance our thinking about citizens' duty to pay taxes or vote in elections. Contrastingly, distributive justice describes the State's responsibility to their citizens.

Second, although *social justice* and *distributive justice* are conceptually distinct, nonetheless, it is not uncommon to find that the discussion on distributive justice is sometimes framed as *social justice*. Specifically, matters of *social restorative justice* in Africa, such as land redistribution to rectify unjust colonial land distributions, have been reframed and understood as *distributive justice* in some publications (47). For example, Thaddeus Metz (48), one of Ubuntu's most prominent African philosophers, does not distinguish between social justice and distributive justice. He contends that Ubuntu philosophy bears many values reminiscent of social justice, such as respect for all, communal participation and societal inclusion. Ubuntu philosophy, he adds, is also representative of distributive justice wherein values of equity, through a culmination of collective responsibility and promoted interdependence, and respect for others, through caring about the wellbeing of others in the community (solidarity) as a motive to restore equality are located. In other words, the values found in Ubuntu are positioned as expressing core concerns about social *or* distributive justice.

Furthermore, in the scholarship of African authors who contend that a distinction ought to be made between distributive justice and social justice, it is not uncommon for one to read the following to be the core of distributive justice from that positionality; (i) it entails the responsibility of States and established organizations to honor the

rights of individuals, including their health rights, (ii) to create opportunities for individuals to enjoy a deep communal relationship, which may include funding their health care since illness can undermine their to enjoy communal relationships, and finally, to regulate interactions among individuals (46).

Although the main aim of this section is evaluative rather than descriptive, it is worth outlining that distributive justice in the African moral philosophy literature broadly. Ubuntu philosophy, in particular, requires governments and institutions to showcase humanity to their citizens by ensuring that they have a decent minimum to flourish, *viz.*, they can access the basic conditions necessary for participating in communal relationships or share a way of life with others (44).

In the subsequent section, we demonstrate how this will require governments to fund the vaccination of their older adult population, particularly in private healthcare facilities. Notably, suppose communal relationships (and/or the capacity for the same) are the basis of morality and moral status in the African Ubuntu philosophy. In that case, an essential way of fulfilling the duty of distributive justice is for governments and established institutions to remove conditions that undermine participation in communal relationships, especially when they can. Illness undermines participation in communal relationships. To understand how, notice that one needs to be a subject and object of a relationship to have full moral status in Afro-communitarianism. To be a subject is to be able to commune with others, exhibit caring or other-regarding behaviors toward others. Objects of communal relationships are those with whom one communes. Illnesses undermine one's capacity to be *subject* of this relationship since it reduces one to an *object* of others' care, love and compassion.

Notice that we have not claimed in this section that all sick people cannot exhibit caring relations toward others at all. Sicknesses and illnesses have a spectrum, and individuals may still be able to exhibit other-regarding behaviors to others, even in that state. Instead, we focus on the more intense forms of sickness, which are often lethal, like seasonal influenza in the older adult. We contend that these often undermine adults 65 years and above's capacity to enjoy deep communal relationships as *both* a subject and an object of these relationships. As we demonstrate, since governments have a responsibility to alleviate conditions that undermine citizens' capacity. In that case, they ought to fund the influenza vaccination of this population group. The preceding is, in fact, a moral response to the rights adults 65 years and above enjoy as a party in communal relationships with the government. In other words, communal relationships encumber. Thaddeus Metz aptly expresses this when he remarks that, "if one has been party to a communal relationship with others [such as the government]…. then one can have some strong moral reason to aid these intimates as opposed to strangers, even if the latter are worse off and if one did not promise to aid the former" [(49), pp. 44]. The basis of a State or government's duty of distributive justice to others is communal relationship. We provide further justification in the subsequent section.

Government's responsibility to fund influenza vaccination

In the previous section, we provided an overview of – and described the moral norms that can arise from – the principles of solidarity, reciprocity and distributive justice grounded in Afro-communitarianism broadly. Furthermore, we differentiated these conceptions from the thinking about the same in the Global North and compared various other conceptions of the same in the Global South. It is important to note that solidarity, reciprocity and distributive justice do not exhaust all the principles in the African (Ubuntu) philosophy. There are others like identifying with others. Nonetheless, these outlined principles are relevant to this section's evaluative goal. Equally, many other conceptions of solidarity, distributive justice and reciprocity globally are not represented in this paper but are no less critical in their applications in ethics broadly.

This section draws on the moral norms articulated in the previous section to justify why governments broadly, but the SA government in particular, have a *prima facie* responsibility to fund seasonal influenza vaccination of the older adult in private and public health care facilities. To enhance the public health importance of this manuscript, we also describe what efforts are required to ensure that such vaccines are *available* and *affordable*. Notice that we do not contend that accessibility issues *only concern* availability and affordability since such issues will also include concerns around *acceptability*. Nonetheless, we focus on availability and affordability in this manuscript and defer the discussion on acceptability for another manuscript.

To justify our position, notice that most older adult Africans are unemployed, and few receive a small pension fund or government grant, which is just enough to cover their living expenses. The situation is worse for older people in South Africa. A 2022 study shows less than 15% of adults aged 60 and older in South Africa are employed (50). Precisely, in South Africa in 2020, BankServAfrica (51) estimated under 19% of adults over 60 years old receive private pensions (some of which receive less than R6510 per month and, thus, fall under the qualifying threshold for social grants as well) and under 70% receive Old Age Grants (OAG). This is consistent with the abovementioned study that shows 69% of the older adult receive an OAG of only R1780 (50). BankServAfrica (51) also found that under 8% of adults over 60 were business owners or still employed in 2017. This leaves an estimate of over 6% of adults over 60 years old with no income, pension fund or government grant (including those with no income from partners or spouses) in South Africa (51). In the current climate in South Africa where unemployment has increased to about 32%, these individuals are vulnerable financially and physically, given their advanced years. Notably, many of them cannot work or procure income for themselves or easily attain free quality and adequate basic healthcare without aid. Physical and mental declines in this age group present further barriers to accessing healthcare services.

Moreover, 69% of older adults receiving only the OAG would fall far short of a "decent standard of living" according to SASPRI, the Studies in Poverty and Inequalities Institute, and the Labor Research Service (52). SASPRI contends that R7541 per person per month equates to a "decent standard of living" in South Africa in 2020. For argument's sake, say that 19% of adults receive private pensions of R6510, and all private pension owners also receive OAGs of R1780. In that case, about 50% of older adult citizens would receive only R1780 per month (not considering the number of older adult individuals that do not own their own housing and have to pay rent or individuals that live with other families). This means that over 56% of the older adult (including those with no income) would have a low standard of living and experience barriers to a good quality of life including accessibility to basic healthcare services.

Indicatively, low economic levels can significantly impact other quality-of-life factors such as household services and health. With 36.4% of the older adult living in households of three or more generations (50), overcrowding can become a devastating health factor during seasonal influenza outbreaks. A low economic status can also affect accessibility to quality healthcare services through barriers of transport costs and long waiting times at public facilities (9).

Although the manuscript focuses on adults 65 years and older, given that (i) this is the retirement age in South Africa, and (ii) adults 65 years and older tend to be more vulnerable than adults younger than 65 years. Nonetheless, it is worth stating that influenza vaccination for adults 60 years and older falls under basic healthcare and is a core requirement of what could foster the flourishing or well-being of this population group. This is because of the high risk of hospitalizations and mortalities influenza poses for this population group. Preventative healthcare, like vaccines for adults aged 65 years and older, should also be considered basic healthcare since it is often life-saving medical care. According to the American Medical Association (53), basic healthcare includes that which protects the most vulnerable population groups and, specifically, affords those that are historically disadvantaged (in this case, the older adult has been marginalized in preventative care, with curative and palliative care being the dominant alternative) with special care.

Suppose governments have a duty of distributive justice to their citizens to provide the essential minimum for their flourishing. Equally, suppose preventive healthcare, particularly seasonal influenza vaccination of adults aged 65 years and above, constitutes this population's basic health requirement. In that case, the government has a responsibility to fund this care for this population since, in fact, many individuals in this population group often struggle with a low standard of living. Accordingly, the government ought to make influenza vaccination accessible to adults in this group, even in private health care facilities. Notably, the older adult comprise one of the high-risk population groups (with lower immune systems).

For this reason, the requirement of distributive justice implies that governments should afford them a special minimal healthcare service to fulfill their specific health needs. This will be an appropriate moral response by subjects of communal relationships (the government) to the objects (adults aged 65 years and above) of these relationships since it is a crucial way of acting to improve the latter's life quality. Precisely, the moral imperative of distributive justice that can be grounded in communal relationships is that a party in this relationship ought to be willing to go out of their way to assist the object of this relationship to flourish, especially when the subject can. As a party in communal relationships, adults aged 65 years and above are also entitled (that is, they have a right) to be aided or supported by others since *communal relationships encumber.* Notably, "where there is some relationship, there are some obligations" [(44), pp. 4]. With certain rights held by this vulnerable population exist corresponding responsibilities by other parties (usually stronger parties or those in authority) to maintain, protect or create an environment for realizing these rights.

There is another justification – grounded in the thinking about reciprocity – for the claim that governments are responsible for maintaining and protecting these corresponding rights by ensuring influenza vaccines can be accessed by adults aged 65 years and above at no cost, including at private health facilities. Specifically, adults 65 years and above have contributed to society over the years. Equally, the older adult, including adults 65 years and above, are highly revered in many African communities. Both their age and life experience position them as conveyors of knowledge and moral education essential for youth formation. This is why the death of an older person is often considered a huge loss to the community (54). There are other ways adults aged 65 years and above have also contributed to the State, such as through tax contributions. These contributions entitle them to receive the government's support in realizing their basic (medical) needs. It is important to note that older adult individuals do not necessarily share their wisdom and educate younger generations merely because they expect a reciprocal act of care but because out of reciprocity, aiding others is a duty. What this means is that the older adult are aware that their acts of aide will be reciprocated in time – that they will be cared for like they have cared for others – but this is not necessarily what motivates the acts of aid/care. Rather, the older adult are aware that the wellbeing of others in the community are inextricably bound up with their own. Out of this knowledge springs the duty of care and aid which is carried by everyone in the community. Subsequently, one need not be afraid of being exploited through unreciprocated acts of aid and can rest in the fact that they will be adequately taken care of in their time of need. The act of care is out of compassion and responsibility for the wellbeing of others in the community and not necessarily because one expects a reciprocal act to repay this debt. However, it does provide a good motivation to avoid selfish acts. In the context of our argument, if governments do not provide freely available influenza vaccines for the older adult, it does not necessarily mean the older adult will stop sharing their wisdom and knowledge. But, rather this means that governments are not fulfilling the reciprocal duty of taking care of the older adult's medical needs which they now ought to do.

About medical health needs (such as vaccines), it is worth stating that the South African government sometimes subsidizes basic health services for vulnerable populations (often for those who are financially vulnerable like students and pensioners) to ensure any vulnerable person, no matter their background or circumstance would be able to afford and access the service to meet their health need. As previously noted, the government does this through public health facilities. However, this section contends that the government ought to make this opportunity available at private health facilities. Concretely, the section contends that the government has a responsibility to maintain and preserve the special rights of the older adult to life-saving preventative healthcare by ensuring that influenza vaccination is available *at no cost* for this older adult population at public and private health facilities.

One advantage here is that this position will have a secondary effect of promoting public health. Although there is a lack of data on vaccine effectiveness on the South African older adult population due to a lack of Randomized Control Trials, a study conducted in the United States found that the 2019–2020 influenza vaccine was associated with a 41% decrease in the risk for influenza-related hospitalizations for older adults (55). Notably, increasing influenza vaccine coverage for the older adult could significantly reduce the number of influenza-related hospitalization and greatly reduce the burden on the healthcare system and saving on limited resources in resource-constrained African nations.

Furthermore, suppose countries signed on to the WHO Global Influenza Strategy are serious about reaching the strategic goals of reducing the seasonal influenza burden, controlling the risk of zoonotic influenza and acting in preparation to alleviate the impact of influenza

pandemics. In that case, they ought to coordinate their behavior to be in line with meeting these goals by ensuring seasonal influenza vaccines are affordable most of all to the most vulnerable population groups, in this case, adults aged 65 years and older since this group has the highest influenza-related mortality and infection rates. They would need to coordinate their behavior and collaborate in the communal project of fostering influenza vaccine uptake in adults aged 65 years and older, expressly by making vaccination available to this population group. South Africa and all other WHO countries have a collective responsibility to achieve global health. For this to be realized, each country must act accordingly, forsaking selfish acts that might only benefit their own country in the short-run and bolstering compassionate, collaborative acts that would benefit all countries (health) in pursuit of this common goal. This is what it means to exhibit solidarity with the citizens and other countries. Notably, this derives from the interconnectedness of lives: the health of SA is deeply interlinked with the health of other countries and global health, in the same way that the health of citizens can have great implications for society. Suppose, as we have demonstrated in a previous paragraph, that the older adult perform essential roles in fostering the moral formation of the youths. In that case, the SA government ought to foster their basic health needs since health is required to perform this task. Also, suppose the older adult citizens are an extension of the government as valued community members. And if it is true, one should value others in the community the way one values himself. Then in that case, it is the government's prerogative to act within their power to preserve the valuable lives of older adult individuals in the community by ensuring that influenza vaccines are available. In doing so, the government would be identifying with older adult citizens by seeing themselves together with the older adult as part of a whole, by acknowledging the older adult as an integral part of the community as government leaders themselves are. Furthermore, the government would be exhibiting solidarity with the community by fulfilling the duty to ensure influenza vaccines are available and playing their part in fostering the uptake of influenza vaccines for the older adult.

By both exhibiting solidarity with vulnerable citizens (caring for their well-being in a considerate manner and acting to benefit citizens); equally by coordinating behavior to meet the WHO Global Influenza Strategy goals in identifying with other countries, thereby protecting these vulnerable populations from influenza infections and its complications, the SA government would be exhibiting solidarity or forming harmonious relationships with adults aged 65 years and older. By establishing and maintaining harmonious relationships in this way, the government would also develop personhood as they would become even more valuable in their ability and willingness to relate harmoniously with citizens.

Furthermore, suppose the global community wants the older adult to vaccinate against influenza to reduce mortality rates. In that case, influenza vaccination ought to be made available to them. It seems counter-intuitive or irrational to require the older adult to vaccinate against influenza but it fails to make vaccination easily accessible. Funding vaccination will be an important way of making it accessible since most individuals are pensioners, retired or unemployed. In this sense, the older adult are also vulnerable because they do not have the full financial ability to address their health needs, including the basic ones.

Finally, although the duty that this section defends is only a *prima facie* duty, implying that this duty must be weighed against other obligations that might be more important. Specifically, neither the moral imperatives that arise from the thinking about distributive justice nor solidarity/reciprocity imply that the duty this section defends is an absolute one. Contrary to consequentialist moral theories that require maximizing consequences, the African Ubuntu philosophy requires one to aid others or exhibit solidarity toward them while considering how one's extant obligations might be impacted. This is not to say that consequentialism is not effective as a moral theory in the normative application of public health dilemmas such as this. Rather, what we are emphasizing here is that while both normative theories can consider the impact of extant governmental obligations, consequentialism requires one to be impartial which is converse to the essence of solidarity. Subsequently, duties in consequentialism are borne out of the greatest potential positive/beneficial outcomes of fostering those duties, but Afro-communitarian duties are bound up in compassion for the needs of others. As such, there is a duty to meet the greater comparative (to other less vulnerable population groups) needs of minority and vulnerable groups through more urgent aid and greater attention to care, regardless of the public health consequences of not meeting their health needs. Afro-communitarian holds at its core, the value of distributive justice.

It is also worth emphasizing the academic importance of drawing on Afro-communitarianism. Particularly, the academic significance of our approach is that it contributes to epistemic justice so that future public health policy and policy reformation *in Africa* be informed by African values rather than by Western values which are sometimes in direct contradiction to their own (African) values as we have demonstrated above. Moreover, individuals are more likely to accept policies that align with their values.

Concretely, the SA government's primary function to protect life and property would imply that a government ought to fund influenza vaccination for the older adult unless doing so will significantly undermine this primary responsibility. For example, during a time of national crises (wars or pandemics to name a couple), say in this case the country would experience adverse public health outcomes if the health of injured soldiers in a war or frontline workers during a pandemic were not prioritized over health expenditure on vaccines for the older adult. In that case, the extant obligation to prioritize funding allocation to these more dire health needs would outweigh the duty to provide freely available influenza vaccines for the older adult during that time. It is impossible to be able to predict what these extant obligations might be. Moreover, governmental duties and priorities would vary greatly between different African nations. Subsequently, in our argument, we do not limit the potential governmental obligations to any such confined list but rather leave it open to maintain flexibility and adaptability between African countries. However, suppose a government could easily fund the health care needs of the older adult but fails to do. In that case, it disrespects the older adult, the object of communal relationships.

Institutions' responsibility to ensure availability of influenza vaccines

In the preceding section, we demonstrated how the principles of solidarity, reciprocity and personhood arising from African

philosophy provide grounds for the government's *prima facie* duty to ensure influenza vaccinations for older adult South Africans are free of cost in both public and private sectors to increase ease of accessibility. This section will describe what needs to happen to fulfill this duty.

In the context of influenza vaccine uptake strategies, we must address the dimension of availability in two-fold. First, referring to the availability of the vaccine in terms of supply meeting needs and second, the availability of vaccines to the older adult in locations in which the older adult most often access immunization services. In addition, it is equally important to consider the existing surveillance services' capacity to gather data to measure, monitor and evaluate the success and challenges of the proposed vaccine promotion strategy. Concerning the former, although a reported 14 out of 31 African countries have influenza vaccines available (14), the Global Alliance for Vaccines and Immunization (56) white paper report found a gap (between demand and supply) in the African vaccine market. To address this, there is a need for influenza vaccine manufacturing in African countries (57). Eight African countries have vaccine companies operating with just four of these facilities currently manufacturing vaccines at the time of this report and only one of which (located in Morocco) has been reported to handle influenza vaccines for importation, but is not involved in its manufacturing (58). There is a glaring need for the development of influenza vaccine manufacturing capacity in South Africa which would ultimately significantly relieve the burden of costs of vaccine import and could lessen the impact of transportation disruptions in the supply chain, thereby increasing availability in the long run. In addition to increasing vaccine manufacturing capacity in South Africa, research and development of influenza vaccines in South Africa, as well as addressing research-related ethical concerns such as funding and the ability to conduct randomized controlled trials with the older adult. For this, greater collaboration between the government and academia will be required.

Concerning the latter, it is the government's responsibility to ensure vaccines are made affordable for those with the most health need and the least able to afford it where they can access it.

It is important to consider where most communities in African countries access immunization and other health services to foster the uptake of influenza vaccination among different population groups broadly or tailor vaccine promotion strategies accordingly. A study has found that both children and adults access pharmacies for immunization services (59). In South Africa, a reported 7 out of 10 households choose to access public clinics or hospitals if a member needs medical care (60). One way to ensure vaccination accessibility in light of this manuscript's thesis is for government to address the barriers to the same that we mentioned in the previous section. Furthermore, the public healthcare system in South Africa consists of 422 hospitals and 3,841 clinics or health centers, which indicates how much easier access to health clinics/centers is for most communities than hospitals in terms of distance (60).

Mobile clinics may also be utilized. Mobile clinics are vehicles that have been refurbished to provide clinical services in remote locations such as rural areas and can provide vaccinations as well (61). In Kenya, these mobile clinics have a context-specific alternative to a motor vehicle – they use camel mobile clinics to travel to remote desert areas (62). SA government must adapt these clinics to the contextual reality of her people.

Keeping medical records of patients at each facility where individuals access vaccination (including records from mobile clinics) will enable an estimate of the required annual supply of influenza vaccines for each facility to cover adults 65 years and older. This can be done by assessing the number of older adult patients that have accessed each facility yearly and eliminating duplicates across facilities to ensure each access point has an adequate supply available for older adult citizens to vaccinate against influenza before influenza season each year. This strategy will eliminate waste and ensure the supply will meet the potential demand in a way that is easily accessible for the target group.

Additionally, this kind of geographical information would be useful in the formation of monitoring and evaluation of implementation strategies. This surveillance reporting must be upscaled so that both successes and challenges of strategies can be picked up and measured. It is also important to note that in some African countries, vaccination record systems for adults (other than for COVID-19) do not currently exist (13). Databases wherein health records of the annual number of influenza vaccines administered to adults aged 65 years and older at various service providers would be useful to measure the success of influenza uptake strategies that are implemented and in further age-specific influenza research studies as well.

Potential objections

This section explores some potential objections to the argument presented in this manuscript. Notably, a critic could contend that requiring the South African governments to provide influenza vaccines freely could spiral into forms of authoritarianism. The government may think that they have the responsibility to dictate their citizens' health habits or choices. The Chinese one-child policy is one example of how the position we endorse may encourage governments to make arbitrary health, including reproductive decisions for their citizens. Adults 65 years and above who exercise their freedom to refuse vaccination may be penalized or sanctioned. Freedom may be curtailed in the world where governments believe they have the prerogative to make health decisions for their citizens.

In response, notice that the position of this section is not that freedom *ought not* to be curtailed. While freedom of choice in health decisions is often important, the greater duty to foster overall public good or harmony (as we have seen with various forms of restrictive measures during COVID-19 outbreak) may require governments to limit an individual's right to freedom. Nonetheless, the counter-argument that this perspective could lead to an authoritarian government is a valid concern. However, we do not think this is necessarily warranted. This is for two reasons. First, authoritarianism will necessarily involve coercing individuals to act in certain ways. However, coercion entails acting in unfriendly ways toward another from the Afro-communitarian perspective (63). This is justified only if it is necessary to end similar unfriendliness. Exhibiting unfriendliness toward those who have not been unfriendly will be a failure to share a way of life with them or exhibit other-regarding behaviors toward them. Coercing individuals in certain ways when they have not been unfriendly will be a failure to exhibit solidarity toward them. This is what is entailed by authoritarianism. Specifically, this response demonstrates that suppose governments act in

authoritarian ways toward their citizens. In that case, this would not be a consequence of the philosophy this section draws on since – from this positionality – one ought to be friendly to those who have been friendly and unfriendly to those who have been unfriendly. Yet authoritarianism often entails acts of unfriendliness toward those who have been friendly.

Second, this concern is also unwarranted due to an evident disconnect. Particularly, defending a health intervention that requires the government to take the financial responsibility to increase accessibility by ensuring a vaccine is accessible to a population does not necessarily afford the government the authority to coerce the older adult to access these vaccination services involuntarily. Ensuring the vaccine is available to the older adult does not guarantee that these individuals will access it, but rather this action serves to alleviate an important barrier to accessibility for those who are voluntarily willing to accept the vaccine. This manuscript highlights that the government has this financial responsibility to ensure decent minimal healthcare is accessible since they have been given the authority to provide for such services, for example, with citizen's taxes. However, it is difficult to see how this responsibility implies that governments *ought to* limit all rights to freedom of choice in healthcare by individuals. As previously stated, limiting individuals' health decisions is permissible on the condition that this is necessary to end comparable unfriendliness. However, arbitrary health decisions would not be ethically justifiable because they would neither be considered a necessary measure in ensuring decent minimal healthcare for all nor would these actions garner harmonious relationships between the government and its citizens. In fact, directing arbitrary health decisions for citizens would harm relationships between the government and its citizens and could cause civil social tensions, as observed during the one-child policy in China (64).

Another critic may express doubts that my contribution will have the impact that it intends. For example, what needs to happen and at what level to realize the duty to fund the influenza vaccination of the older adult, particularly in South African private healthcare facilities? Suppose there are challenges or difficulties with accessing vaccination in public health facilities. In that case, what concrete changes need to occur to make influenza vaccination more accessible? It seems – to move from rhetoric to action – fine details concerning *how* the government can realize this duty (beyond merely claiming that they ought to fund) need to be outlined carefully and intelligently, and I have not done this to a significant degree.

To some extent, we have partly answered this question in a previous section. Nonetheless, we acknowledge the concern that this position can be construed as idealistic and rhetorical. However, we argue that concrete moral stances on how to increase accessibility ethically are important primary conversations to open in the discussion of increasing influenza vaccine uptake by the older adult in South Africa. The overall project of increasing influenza vaccine uptake is an ambitious, albeit not impossible, one to undertake. As such, in this manuscript, we mostly endeavor to provide a conceptual exploration of existing structures and barriers to accessibility by examining the availability and affordability dimensions of the influenza vaccine. In this regard, we acknowledge that the collaboration between the government, pharmaceutical companies and academia that we suggest in the previous section will be insufficient to foster uptake. Vaccines may be freely available and adults 65 years and above may still refuse to vaccinate. We will address this question in a future manuscript.

This manuscript provides a moral foundation for future conversations on how policy reformation should be grounded in African ethical considerations. However, this manuscript does not set out to outrightly propose how these policy changes ought to take place. Our proposal in this manuscript may be in a state of incompleteness, but it does not render our argument irrelevant or unnecessary by any means because it is, in fact, the very crucial first step of many in directing and informing future public health policy formation as many conceptual bioethical arguments are wont to do. Its very existence in incompleteness allows for a space where ethicists, policymakers, stakeholders and financial advisors can collaborate, transform and advance our contribution.

Notwithstanding, our manuscript brings to the forefront a significant equity problem in preventative health measures the older adult population faces in South Africa and calls for further discourse on where to go from here to address this problem. Specifically, while we argue that the government ought to fund influenza vaccines for the older adult in both private and public healthcare facilities to overcome accessibility barriers in the public domain and to increase the availability of vaccines to the target population, we do not pretend to have all the answers regarding the concrete implementation of this position. The intricacies of exactly how public and private funding ought to intersect or the amount of government interference in the private health sector to realize this objective must be worked out. Nonetheless, we believe that the direct cost of influenza vaccination of the older adult at private health facilities ought to be communicated directly to the government, who should defray this cost from the annual health project. The annual health budget may need to be expanded to accommodate this cost. Our argument also somewhat supports a mixed public-private funding landscape in South Africa that aligns with the vision of the National Health Insurance. Further research on financing structures for the availability of the influenza vaccine for the older adult at private facilities ought to be conducted.

Another critic may also point out that there are *far more important* ways for governments to support the older adult to meet their basic health needs beyond funding vaccination. For example, adults 65 years and above often suffer *more* from old-age-related diseases not limited to neurodegenerative and cardiovascular diseases. The focus on influenza vaccination seems to distract attention away from these health burdens.

This is quite an important and valid concern. While we acknowledge that non-communicable diseases are a great health burden on the older adult population and deserve attention and funding, we do not think there needs to be a dichotomy in choosing which health challenge deserves attention. We argue that this critique presents a false dilemma that the government cannot focus efforts on both communicable and non-communicable diseases and that this view, even if it may be true, does not necessitate avoiding discussion over preventative health methods for the older adult.

Even operating under the guise of the conditions of this premise that resources are so limited that focus should be given to either, we argue that this intervention is not a waste of resources and is in fact, using resources more sustainably. This argument is substantiated by numerous studies reporting the cost-effectiveness in targeting vulnerable populations for influenza vaccination, calculated by the number of influenza cases averted, hospitalizations and deaths averted and cost per quality-adjusted life year (65, 66). Encouraging vaccine uptake for the older adult will also be important in reducing anti-biotics and anti-virals prescribed as well as possibly decreasing

nosocomial infections without adding to the burden of life-long care costs, which plays a factor in the cost-effectiveness of the vaccine, a significant consideration in resource-constrained countries especially (67).

Although it is difficult to calculate the estimated cost burden averted, South Africa particularly lacks age-specific data collected by their three respiratory illness surveillance teams – Viral Watch influenza-like illness, influenza-like illness, and pneumonia surveillance (68). Furthermore, cost-effectiveness varies yearly according to several factors, such as the burden of HIV infection in the country, the type of influenza strain circulating, and the vaccine type (69). Nonetheless, we believe that preventative healthcare for adults 65 years and above will positively impact the collective ability to limit the impact that non-communicable diseases will have on them.

Finally, a critic may point out that even if a government provides free vaccines and the older adult reject the same, our argument will still not have the impact we hope it would have. The older adult also need to accept to be vaccinate for vaccination programs to be effective. Viruses are controlled when the majority of the population has either been exposed to the virus naturally, or through vaccinations. The smaller the percentage of the population that acquires immunity, the more hosts that the virus can infect. Thus, does the government also have an obligation to mandate vaccinations.

This is indeed an important question. Vaccine access tends to encompass three issues, (i) affordability, (ii) availability and (iii) acceptability. In this current manuscript, our primary focus is to address governments responsibility to make vaccines free to address the questions around affordability and viability. In a different manuscript, we draw on the key norms arising from incompleteness and conviviality in African scholarship to justify the moral responsibility of the older adult to vaccinate against influenza to address key questions around acceptability.

Conclusion

This primarily normative and theoretical paper has drawn on moral norms from the Global South, namely solidarity, reciprocity and personhood grounded in African philosophic thinking. In this argument, we addressed two main considerations surrounding the accessibility of influenza vaccines for adults 65 years and above in South Africa. Firstly, we claimed that African governments have a *prima facie* duty to make seasonal influenza vaccines free to the older adult. Secondly, we asserted that institutions (including the government) have an obligation to ensure influenza vaccines are available in respect to vaccine procurement and distribution at frequently accessed locations by the older adult. Finally, we responded to some potential counter-arguments on unintended consequences of the government holding power over arbitrary health decisions, that our argument lacks a concrete foundation to move from rhetoric to action and that other more important health concerns regarding the older adult ought to be advocated for instead of influenza vaccine uptake.

It is important to note that this paper forms part of a series and has only addressed the affordability and availability aspects of influenza vaccines for the older adult. We acknowledge that accessibility is also significantly contingent upon the acceptability of the vaccine. Subsequently, the next paper in this series seeks to address these ethical considerations of acceptability by focusing on factors such as cultural and traditional values, attitudes, beliefs and social norms held by the older adult population in South Africa. This is an important step in our project because only once we have comprehensively addressed all three dimensions of accessibility can we propose a more concrete framework with which to direct public health policy to drive a more actionable argument.

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.

Author contributions

RS: Conceptualization, Writing – original draft, Writing – review & editing. CE: Supervision, Writing – review & editing.

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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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How has research on the effectiveness and safety of COVID-19 vaccination been evaluated: a scope review with emphasis on CoronaVac

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Introduction: The control of the COVID-19 epidemic has been focused on the development of vaccines against SARS-CoV-2. All developed vaccines have reported safety and efficacy results in preventing infection and its consequences, although the quality of evidence varies depending on the vaccine considered. Different methodological designs have been used for their evaluation, which can influence our understanding of the effects of these interventions. CoronaVac is an inactivated vaccine, and it has been assessed in various studies, including clinical trials and observational studies. Given these differences, our objective was to explore the published information to answer the question: how has the efficacy/effectiveness and safety of CoronaVac been evaluated in different studies? This is to identify potential gaps and challenges to be addressed in understanding its effect.

Methods: A scoping review was carried out following the methodology proposed by the Joanna Briggs Institute, which included studies carried out in humans as of 2020, corresponding to systematic reviews, clinical trials, analytical or descriptive observational studies, in which the effectiveness and/or safety of vaccines for COVID19 were evaluated or described. There were no age restrictions for the study participants.

Results: The efficacy/effectiveness and safety of this vaccine was assessed through 113 studies. Nineteen corresponded to experimental studies, 7 of Phase II, 5 of Phase IV, and 4 were clinical trials with random assignment. Although some clinical trials with random assignment have been carried out, these have limitations in terms of feasibility, follow-up times, and with this, the possibility of evaluating safety outcomes that occur with low frequencies. Not all studies

have used homogeneous methods of analysis. Both the prevention of infection, and the prevention of outcomes such as hospitalization or death, have been valued through similar outcomes, but some through multivariate analysis of dependencies, and others through analysis that try to infer causally through different control methods of confounding.

Conclusion: Published information on the evaluation of the efficacy/effectiveness and safety of the CoronaVac is abundant. However, there are differences in terms of vaccine application schedules, population definition, outcomes evaluated, follow-up times, and safety assessment, as well as non-standardization in the reporting of results, which may hinder the generalizability of the findings. It is important to generate meetings and consensus strategies for the methods and reporting of this type of studies, which will allow to reduce the heterogeneity in their presentation and a better understanding of the effect of these vaccines.

KEYWORDS

COVID-19, SARS-CoV-2, vaccines, CoronaVac, review

1 Introduction

Starting from the first reports coming from China and from countries in Europe and Asia, about the infection produced by SARS-CoV-2, its high contagion, and lethality of up to 14% in older adults, and the subsequent declaration of a COVID-19 pandemic, and together with the measures established by the healthcare authorities to manage the disease, efforts began to develop effective and safe vaccines that would contribute to speeding up the control of this health condition, through the reduction of infections, complications, and deaths associated with this disease (1).

For this reason, pandemic control efforts have focused on developing vaccines against SARS-CoV-2 that are capable of acting against infection, disease, or transmission, and thus contribute to disease control (2). In this context, different research groups have developed vaccines using different platforms, including mRNA, viral vectors, and inactivated viruses (3).

Unlike most drugs, whose benefits are limited to the individual taking them, vaccines have the potential to produce far-reaching effects on general public health and well-being, cognitive development, and, ultimately, economic productivity (4). However, the global advances in vaccination coverage achieved during the first years of the 21st century have been threatened by the emergence of anti-vaccination groups that have questioned vaccine efficacy to create public distrust of vaccines and immunization programs. This requires an adequate and conscious evaluation of both the efficacy/effectiveness and the different aspects that can affect the safety of the people who receive them (5).

In general, vaccines that have gained approval for human use have been effective in preventing COVID-19, particularly in preventing severe disease and death. However, reports on their implementation are mainly based on follow-up studies of the adult population (6). Additionally, if the vaccination prevents symptoms from developing and asymptomatic infections are less likely to be discovered than symptomatic ones, it is feasible that the effectiveness against any infection has been overstated. A competitive tendency toward underestimate arises when estimates are based on tests with inadequate specificity, particularly when testing are conducted more frequently than has been estimated for various COVID-19 vaccinations (7).

All vaccines seem to be safe and efficacious against all variations of interest in preventing hospitalization, death, and severe COVID-19; however, the quality of the data differs significantly between the vaccines under consideration (8).

Different methodological designs have been used to evaluate the effectiveness and safety of vaccines for COVID-19. Most clinical trials were carried out before the appearance of variants of concern, and the duration, subgroups evaluated, and analysis methods were not homogeneous between vaccines, creating uncertainty about some effects and comparisons (9).

CoronaVac is an inactivated whole-virus vaccine against COVID-19 adjuvanted with aluminum hydroxide created from African green monkey kidney cells (Vero cells) inoculated with SARS-CoV-2 (strain CN02). The Chinese company Sinovac Biotech developed the vaccine, and on June 1, 2021, the World Health Organization (WHO) approved the vaccine for emergency use (10). Using two 3 μg doses of CoronaVac, the overall efficacy for avoiding symptomatic COVID-19 (before the emergence of concerning variations) has been assessed at 67.7% (95%CI: 35.9 to 83.7%) (10). Compared to COVID-19 prevention, its impact in preventing hospital stays, ICU admissions, and fatalities has been much stronger. Three-dose regimens have also been shown to raise seroconversion levels of neutralizing antibodies, even against variants like Omicron. Few serious vaccine-related adverse reactions have been reported (10).

However, given the differences that may exist in the methods used to assess the efficacy, effectiveness, and safety of vaccines against COVID-19, our objective was to explore the published research on COVID-19 vaccines, focusing on CoronaVac, in order to answer the question: How has the efficacy/effectiveness and safety of CoronaVac been assessed in different designs and study phases of the vaccines used to control COVID-19?

2 Methods

A scoping review was carried out under a protocol registered in the Open Science Framework (OSF; osf.io/aeut4), and following the methodology proposed by the Joanna Briggs Institute (11), which included studies carried out in humans as of 2020, corresponding to systematic reviews, clinical trials, and analytical or descriptive observational studies in which the effectiveness and/or safety of vaccines for COVID19 were evaluated or described. There were no age restrictions on the study participants.

Abstracts from congresses were not evaluated because they had not been subjected to systematic peer evaluation at the time, nor were studies published in languages other than English or Spanish.

2.1 Search methods for study identification

To identify potentially relevant articles for review, the following databases were searched, starting from 2020: MEDLINE, EMBASE, LILACS, Scopus, and Cochrane.

The following valid strategy was used for MEDLINE through PubMed and then adapted to other databases:

(((SARS-CoV-2[MeSH Terms]) OR (COVID-19[MeSH Terms])) OR (Coronavirus[MeSH Terms])) AND ((COVID-19 Vaccines[MeSH Terms]) OR (Coronavirus vaccines[Title/Abstract])).

The full search strategy is presented in the Supplementary material.

2.2 Study selection

The initial screening of the studies was independently performed by two reviewers in pairs (PA-AG and PR-SR). The RIS files of each database were uploaded to Rayyan software (12). Disagreements were resolved by a third author (JA).

Both reviewers assessed all titles and abstracts and excluded those considered irrelevant for the review, those not meeting the inclusion criteria, or because they were duplicates. Subsequently, 15 reviewers independently (JA, PA, DA, AC, AG, LL, LM, DO, GQ, SR, CR, PR, MS, CT, MA) evaluated the full text of the studies to verify the eligibility criteria. A cross-review was carried out for studies evaluating CoronaVac by four reviewers (PA, AG, PR, and SR).

2.3 Variable

Of the definitively selected studies, the following variables were extracted in a paired form: (i) type of study, (ii) population studied, (iii) intervention (vaccine) evaluated, (iv) control, (v) follow-up time, (vi) efficacy and/or effectiveness outcomes, and (vii) safety outcomes.

2.4 Data synthesis

For each outcome, a description of the results was made following the description in the document and/or Supplementary material of the article.

3 Results

3.1 Study selection

The search identified 42,813 titles for the initial evaluation, of which 40,372 were excluded after a review of the title, abstract, and possible duplication. A total of 2,441 full texts were reviewed to verify the eligibility criteria, of which 1,685 were included in the synthesis (Figure 1; Supplementary material).

3.2 Synthesis of the results

One hundred vaccines were evaluated through randomized clinical trials (RCT). The other studies corresponded to observational studies, 705 (43.9%) analytical studies, and mainly cohort studies (467; 29.1%). Three hundred and seventy-seven patients (23.5%) were series or case reports.

One hundred twenty-six studies (7.8%) did not specify the vaccine evaluated. Other studies have evaluated one or more specific vaccines. Seven hundred thirty-two studies did not include a vaccine or a control group. Two hundred and thirty-eight evaluated several types of vaccines, and 160 compared a vaccine against a placebo. The number of patients or vaccine doses evaluated in each study went from one (case report) to 306,473,169 doses of applied vaccines (13).

Regarding the population assessed, 44.4% of the studies evaluated the effects of vaccines on adults. 3.4% in adults and adolescents, 2% in adolescents, 1.2% in immunosuppressed individuals, 1.2% in children, 0.9% in pregnant women, and 0.25% in people living with HIV. The overall monitoring time ranged from hours to 6 months; this difference occurred between studies that evaluated immunological outcomes, which could occur within hours or days, and those that evaluated clinical outcomes.

A total of 15.1% of the studies evaluated the effectiveness or efficacy of vaccines by evaluating their effects on preventing infection, hospitalization, or death from infection. 59.1% of the studies corresponded to the description of safety events. The events were described heterogeneously. In some studies, they are only recorded as "mild adverse events" or "mild systemic events." Few studies reported specific events such as myocarditis, and hepatic or allergic alterations. Of the studies, 25.8% described immunological outcomes, 368 studies through the measurement of antibodies, and 64 through the effects mediated by cellular immunity.

3.2.1 CoronaVac

The efficacy, effectiveness, and safety of this vaccine have been assessed in 113 studies. Nineteen corresponded to experimental studies, seven of Phase II, five of Phase IV, and four were clinical trials with random assignment, carried out in adults in Chile, Indonesia, and Turkey (14–17), comparing the effect of the vaccine versus placebo. The other studies were observational studies, most of which were case reports, case series, or descriptions of cohorts. Of these, 45.1% were conducted in Asia, 23% in Latin America, and 22.1% in Europe, mainly in Turkey (of 27/29 European studies).

As for the population, 87.6% of the studies were conducted in adults, while the representation of studies in pregnant women, children, immunosuppressed people, or people living with HIV ranged between 0.9 and 3.5% of the studies.

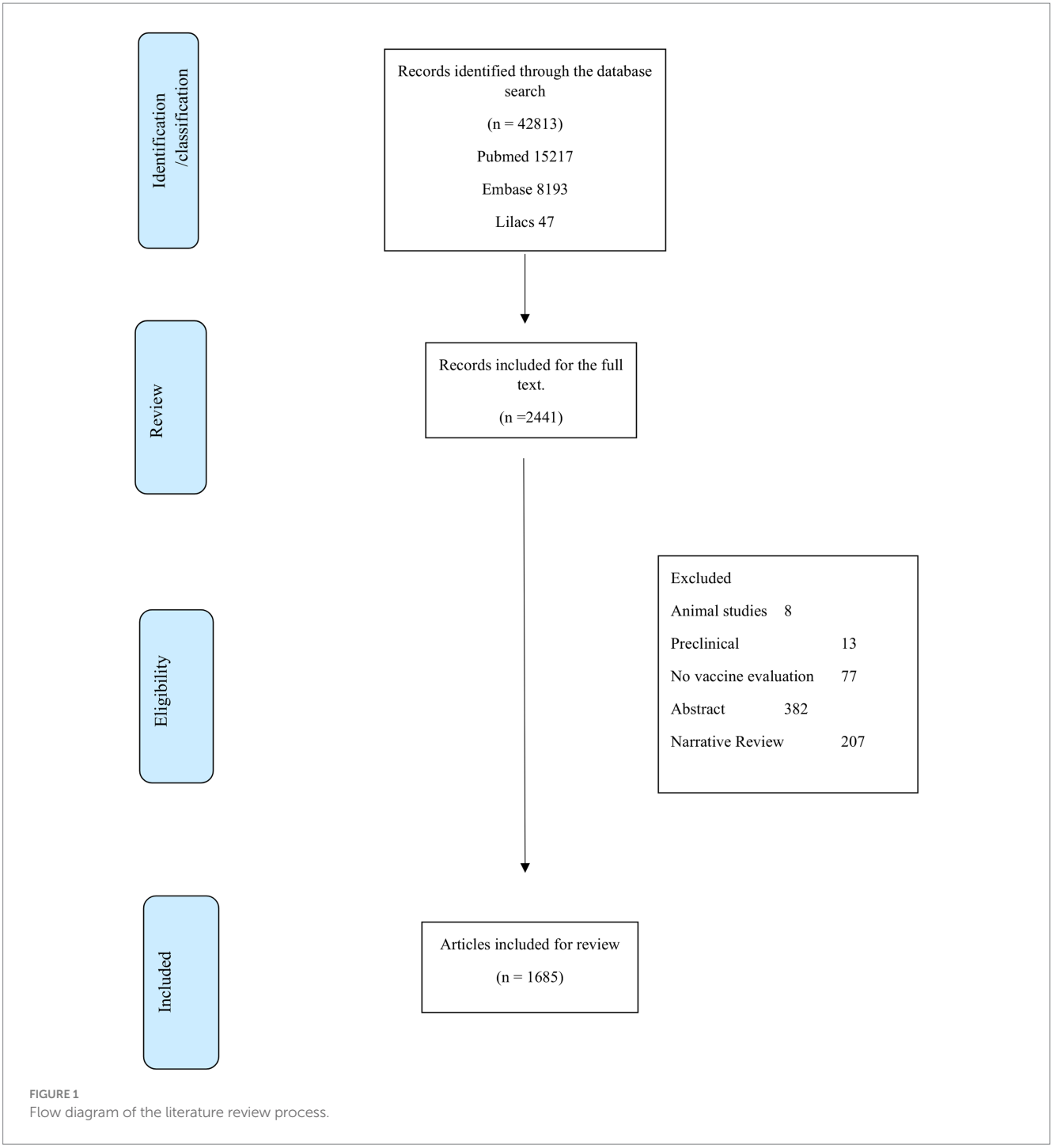

FIGURE 1
Flow diagram of the literature review process.

Sixty studies (53.1%) evaluated the effect of CoronaVac in a control group. The others were case reports or descriptions of cohorts without comparison. Of these, 42 (70%) described events in patients who received CoronaVac and another vaccine, without performing an effectiveness or efficacy analysis. Other studies evaluated the efficacy and effectiveness by measuring the effect of preventing hospitalization, death, or COVID. Of the total, 34 studies evaluated CoronaVac (30.1%) and described some immune outcomes.

Although the objective of the review was not to assess the effectiveness of the vaccine, but rather how it has been evaluated, the results of some of the identified studies are shown below in order to present relevant information about the methods used and possible differences between them, which lead to discussing the effect that this can have on the analysis and use of CoronaVac and other vaccines. More details on the results of the identified studies can be found in the Supplementary material section.

3.2.2 Efficacy/effectiveness of CoronaVac

3.2.2.1 Prevention of COVID-19

Cheng et al. (18) evaluated the effectiveness of BNT162B2 and CoronaVac in patients with chronic kidney disease in Hong Kong.

28,374 people were not vaccinated, 27,129 received two doses of BNT162b2, and 47,640 received two doses of CoronaVac in this retrospective cohort analysis. Following inverse probability of treatment weighting with 1% extreme values, a cohort that was well-balanced and had a standardized mean difference of less than 0.1 was generated.

The effectiveness of CoronaVac on Turkish healthcare professionals was assessed by Can et al. (19). 4,067 medical personnel worked at a University Hospital in Istanbul, where this retrospective cohort study was carried out. In the fully vaccinated group, the follow-up period was defined as beginning 14 days following the second dose. If PCR test findings were positive or the trial came to an end, healthcare personnel were excluded. Healthcare personnel who were not vaccinated were prohibited from participating in any COVID-19 vaccination. The vaccine's unadjusted and adjusted effectiveness were calculated using the incidence rate ratio and Cox regression. 29% of the healthcare staff had not received any vaccinations, whereas 71% had received all recommended doses.

Jara et al. (20) conducted an evaluation of a prospective, observational, national-level cohort of individuals (≥ 16 years) associated with the Fondo Nacional de Salud insurance program in Chile. They used individual-level data to assess the efficacy of booster vaccines, namely BNT162B2 (Pfizer-Biontech), AZD1222 (Oxford-AstraZeneca), and CoronaVac (Syovac Biotech), in individuals who had completed a primary immunization schedule with CoronaVac, in comparison to those who had not received any vaccinations. The hazard ratios were estimated using inverse probability-weighted and stratified survival regression models that took into account the time-varying vaccination status and adjusted for pertinent clinical, socioeconomic, and demographic confounders. An estimate was made of the change in risk associated with the primary immunization series and booster shot from being unvaccinated to vaccinated. 11,174,257 persons in total fulfilled the trial's eligibility conditions; of these, 4,127,546 finished the two doses of the CoronaVac primary immunization regimen and got a booster dose during the study period. 2,019,260 (48.9%) individuals received a BNT162b2 booster, 186,946 (4.5%) received a homologous booster with CoronaVac, and 1,921,340 (46–5%) participants received an AZD1222 booster. The weighted stratified Cox model was utilized to compute the modified vaccination efficacy in preventing COVID-19.

Utilizing hospitalization, vaccination, and National COVID-19 notification data, Cerqueira-Silva et al. (21) conducted a case–control study in Brazil to evaluate the efficacy of four vaccines (CoronaVac [synovac], ChAdOx1 nCoV-19 [AstraZeneca], Ad26.COV2.S [Janssen], and BNT162b2 [Pfizer-Bionntech]) in individuals with laboratory-confirmed prior SARS-COV-2 infection. The probabilities of test positivity and the likelihood of hospitalization or death from COVID-19 were compared based on vaccination status and the amount of time that had passed from the first or second dose of vaccinations using multivariable conditional logistic regression.

The same authors conducted a similar study in Brazil (22), using linked national Brazilian databases to conduct a negative-test design study with nearly 14 million participants (~ 16 million tests) to estimate the effectiveness of the CoronaVac vaccine over time and the BNT162B2 booster vaccination against severe COVID-19 outcomes (hospitalization or death) and severe acute respiratory syndrome, as confirmed by RT-PCR (SARS-COV-2).

To evaluate the effectiveness of homologous and heterologous boosters against COVID-19 in the context of OMICRON, Ranzani et al. (23) conducted a nationwide case–control study (with negative PCR results) to assess homologous and heterologous (BNT162B2) booster doses in adults who received two doses of CoronaVac in Brazil in the OMICRON context.

A case–control research was carried out in Thailand by Sritipsukho et al. (24) to assess the efficacy of various vaccination regimens in preventing COVID-19 during the time when the delta variant was the predominant causing virus (≥ 95%). By correcting for individual demographic and clinical factors, the efficacy of vaccines was assessed.

3.2.2.2 Prevention of hospitalization and death

Cheng et al. (18) found that both vaccines reduced hospitalization and death related to COVID-19, which was the opposite of the outcome of preventing COVID-19 infection. The vaccination efficacy for BNT162b2 users was 64% (95% CI: 57–69%) for hospitalization associated to COVID-19 and 86% (95% CI: 80–90%) for COVID-19-related death. Regarding hospitalization and death associated to COVID-19, the vaccine efficacy for CoronaVac was 44% (95% CI: 37–49%) and 70% (95% CI: 64–75%), respectively.

In the Jara et al. (20) study, the adjusted effectiveness of the vaccine against hospitalization due to COVID-19, ICU admission, and death was 86.3% (83.7–88.5), 92.2% (88.7–94.6), and 86.7% (80.5–91.0) for a CoronaVac homolog booster; 96.1% (95.3–96.9), 96, 2% (94.6–97.3), and 96.8% (93.9–98.3) for a BNT162b2 booster; and 97.7% (97.3–98.0), 98.9% (98.5–99.2), and 98.1% (97.3–98.6) for an AZD1222 booster, respectively.

In Brazil (21), the effectiveness against hospitalization or death 14 or more days after the completion of the vaccination schedule was 81.3% (75.3–85.8) for CoronaVac, 89.9% (83.5–93.8) for ChAdOx1 nCoV-19, and 57.7% (−2.6–82.5) for Ad26.COV2.S, and 89.7% (54.3–97.7) for BNT162b2.

3.2.2.3 Immunological outcomes

Bueno et al. (14), conducting a randomized placebo-controlled clinical trial in Chile, assessed the effectiveness of CoronaVac by assigning participants to either a placebo or two doses of CoronaVac spaced 2 weeks apart. Enrollments totaled 434, with 397 individuals in the 18–59 age range and 37 in the 60+ age range. 81 subjects had hemoral assessments. 2 and 4 weeks after the second dosage, respectively, the seroconversion rates for specific anti-S1-receptor binding domain (RBD) immunoglobulin G (IgG) were 82.22 and 84.44% in the 18–59 years age group and 62, 69 and 70.37% in the ≥60 years age group. A notable rise in the amount of neutralizing antibodies in circulation was noted two and 4 weeks following the second dosage. 47 participants had their cells evaluated. After stimulation with Mega Pools of SARS-CoV-2 peptides, a notable increase in T cell responses was seen, as evidenced by the release of interferon-γ (IFN-γ).

According to Zeng et al. (25) the following were the findings of two single-center, double-blind, randomized, placebo-controlled phase II clinical trials: adults from Jiangsu, China, aged 18 to 59 years were first assigned (1:1) into two vaccination schedule cohorts: one for the days 0 and 14 of vaccination (cohort 1), and another for the days 0 and 28 of vaccination (cohort 2). Each cohort was then randomly assigned (2:2:1) to either a placebo group or a 3 μg or 6 μg dose of

CoronaVac. A third dose was given to half of the participants in each cohort 6 months after the second dose, and an additional dose was given to the other half of the individuals 28 days following the second dose, as a result of a protocol revision. In a separate phase II experiment carried out in Hebei, China, individuals who met the eligibility criteria of 60 years or above were randomized to receive three injections of 1.5, 3, or 6 μg of vaccine or a placebo. The first two doses of the vaccine were given 28 days apart, while the second and third doses were given 6 months apart. For the per-protocol population (those who finished their allotted third dose), the primary research outcomes were geometric mean titers (GMTs), geometric mean increments (GMIs), and seropositivity of neutralizing antibodies to SARS-CoV-2. Out of the 600 participants, who were between the ages of 18 and59, 540 (90%) were qualified for a third dose. Of these, 269 (50%) received the third primary dose (cohorts 1a-14d-2 m and 2a-28d-2 m) 2 months after the second dose, and 271 (50%) received a booster dose 8 months later (cohorts 1b-14d-8 m and 2b-28d-8 m). For the 1b-14d-8 m cohort ($n = 53$; GMT 3.9 [95% CI 3.1–5.0]) and 2b-28d-8 m cohort ($n = 49$; GMT 6.8 [95% CI 5.2–8.8]), neutralizing antibody titers elicited by the first two treatments in the 3 μg group declined after 6 months to close or below the seropositive cut-off point (GMT of 8). The GMTs measured 14 days later increased to 137.9 (95% CI: 99.9–190.4) for the 1b-14d-8 m cohort and to 143.1 (110.8–184.7) 28 days later for the 2b-28d-8 m cohort when a booster dose was administered 8 months following a second dose. After the principal third dosage, GMTs increased somewhat in cohorts 1a-14d-2 m (n = 54) and 2a-28d-2 m ($n = 53$). In cohort 1a, GMTs increased from 21.8 (95% CI: 17.3–27.6) on day 28 after the second dose to 45.8 (35.7–58.9) on day 28 after the third dose. Six months following the third dose, GMTs had dropped to almost the positive threshold: in the 1a-14d-2 m group, they were 9.2 (95% CI 7.1–12.0), while in the 2a-28d-2 m cohort, they were 10.0 (7.3–13.7). Similarly, 6 months following the initial two-dose series, neutralizing antibody titers dropped to almost or below the seropositive threshold among people 60 years of age or older who received booster doses (303 [87%] of 350 participants were eligible for a third dosage). Eight months following the second treatment, which markedly raised neutralizing antibody concentrations, a third dose was administered: After the second dose on day 28, GMTs climbed to 42.9 (95% CI: 31.0–59.4), and after the third dose on day 28 ($n = 29$), GMTs increased to 158.5 (96.6–259.2).

Chantasrisawad et al. (26) assessed healthy children aged 5 to 11 who were given two intramuscular doses of either Covilo or CoronaVac and 10 μg of BNT162b2. Neutralizing antibodies against the Omicron version were assessed using a pseudovirus neutralization test (pVNT, ID50) and a surrogate viral neutralization test (sVNT, % inhibition) 14–21 days following the booster. The antibody responses were contrasted with those of a concurrent cohort of kids who got two BNT162b2 doses separated by 3 weeks. A total of 59 children, consisting of 20 CoronaVac recipients and 39 Covilo recipients, were registered between April and May 2022, with a mean age (SD) of 8.5 years (1.7). The primary series' median interval was 49 days, with an interquartile range of 33–51. Following the booster, the geometric means (MG) of pVNT and sVNT were 499 (95%CI: 399–624) and 72.2% inhibition (95%CI: 67.2–77.6), respectively. From zero to 72 %, the percentage of kids with sVNT against Omicron strain ≥68% inhibition rose. In comparison to the parallel cohort, the geometric mean ratios (GMR) of sVNT and pVNT were 4.3 and 12.2, respectively. In comparison to children who received a booster dosage between 4 and 6 weeks, the GMR of sVNT and pVNT among those who received it at a time interval of more than 6 weeks was 1.2 (95% CI: 1.1–1.3) and 1.8 (95% CI 1.2–2.7).

In Turkey, (27) et al. assessed the variables influencing the antibody response in 235 adults over 65 years of age following two doses of the inactivated SARS-CoV-2 vaccination (CoronaVac). Four weeks following the first and second vaccination doses, the mean levels of anti-SARS-CoV-2 IgG antibodies were 37.70 ± 57.08 IU/mL and 194.61 ± 174.88 IU/mL, respectively. Additionally, 4 weeks following the first vaccination dose, 134 out of 235 participants (57.02%) had an antibody level of less than 25.6 IU/mL (negative); 4 weeks following the second vaccination dose, this percentage was 11.48% ($n = 27$). Eight participants (29.6%) had no comorbidities, while 19 (70.4%) with an antibody level less than 25.6 IU/mL 4 weeks after the first dose of the vaccination had at least one comorbid condition, including diabetes mellitus ($F = 2.352$, $p = 0.006$). Individuals with comorbidities and those 65 years of age or older showed lower antibody response rates.

Demirbakan et al. (28) examined the presence of immunoglobulin G antibodies in the receptor-binding region of the S1 subunit of the SARS-CoV-2 spike protein in 1072 healthcare workers following immunization in a descriptive observational research. 28 days, 21 days, and 3 months following the first, second, and second dosages, respectively, were the times at which blood samples were taken. Anti-spike antibodies were found in 834/1072 (77.8%) subjects 4 weeks following the initial vaccination dose. Between 18 and 34 years of age, seropositivity was observed to be greater in both men and women (84.6%) compared to 70.6% ($p < 0.001$) in the former group. In 1008 of 1,012 (99.6%) cases, anti-spike antibodies were found 21 days after the second dose, and in 803 of 836 (96.1%) cases, anti-spike antibodies were found 3 months later.

3.2.2.4 Safety

According to Bueno et al. (14) in their placebo-controlled clinical trial, pain at the injection site was the primary adverse reaction in 434 volunteers, and it occurred more frequently in the vaccine arm than in the placebo arm. The majority of the negative effects that were seen were modest and limited. No significant negative events were noted.

The frequency of adverse reactions was reported by Zeng et al. (25) without providing any additional effect measurements. In every immunization group, all adverse responses that were reported within 28 days after the third dose were classified as either grade 1 or 2. In the 1a-14d-2 m cohort, 150 participants reported three serious adverse events (2%); in the 1b-14d-8 m cohort, 150 participants reported four (3%); in the 2a-28d-2 m and 2b-28d-8 m cohorts, 150 participants reported one (1%); overall 349 people reported 24 (7%) serious adverse events.

Cheng et al. (18) observed an incidence rate of any adverse events of special interest following the first vaccination dose of 34.28 (95% CI: 29.81–39.23) and 38.39 (95% CI: 34.81–42.23) per 10,000 doses of BNT162b2 and CoronaVac, respectively, in their retrospective cohort of patients with chronic kidney disease. BNT162b2 (incidence rate ratio [95% CI]: first dose: 0.86 [0.69–1.08]; second dose: 0.96 [0.76–1.22]; third dose: 0.60 [0.33–1.10]) and CoronaVac (incidence rate ratio [95% CI]: first dose: 0.76 [0.64–0.91]; second dose: 0.86 [0.71–1.05]; third dose: 0.74 [0.36–1.54]) did not show an increased risk of

overall adverse event of special interest when compared to the baseline period.

4 Discussion

The COVID-19 pandemic has affected the world's population with a high morbidity and mortality rate. Recent reports have described persistent symptoms that extend beyond the initial period of the disease. It has been observed that adverse consequences, in addition to respiratory effects, are produced at different levels: cardiovascular, neurological, or immunological; cutaneous, gastrointestinal, or kidney manifestations, as well as in mental health, both as a result of acute infection and by the so-called post-COVID-19 syndrome (29). In this context, developing effective and safe vaccines was the determining control measure for pandemic management since, in addition to reducing the transmission of infections and allowing the control of the disease, vaccines had a determining role in reducing severe and fatal complications associated with infection (30). In addition to the above, the time in which the vaccine candidates were available, where it took less than a year for developers to complete the design, manufacturing, efficacy and safety testing and evaluation and approval for use, is an immeasurable scientific and public health learning, as well as an example of cooperation between healthcare authorities, the scientific community and private sector (31).

This review presents an analysis of the methods, populations, and scope of the studies that have evaluated the efficacy/effectiveness and safety of the vaccines available for COVID-19, emphasizing CoronaVac. Differences were found in terms of the proportion of populations evaluated, follow-up times, and times of the studies regarding the appearance of variants of concern.

Although some clinical trials with random assignment have been carried out to assess efficiency and safety outcomes with CoronaVac, these have limitations in terms of feasibility, follow-up times, and with this, the possibility of evaluating safety outcomes that occur with low frequencies (32). In this sense, it is important to carry out observational data analysis. However, not all studies have used homogeneous methods of analysis. Both the prevention of infection, and the prevention of outcomes such as hospitalization or death, have been valued through similar outcomes, but some through multivariate analysis of dependencies, and others through analysis that try to infer causally through different control methods of confounding. Studies have compared the evaluation of the same outcome through different methods, including multivariable logistic regression, propensity matching, propensity adjustment, and propensity-base weighting. However, researchers described that the estimates are very sensitive to the explicit or implicit weighting system in an adjustment technique, so it must be clear for which population a global treatment estimate is most appropriate (33).

It is important to recognize that there are common challenges in the collection, notification, and use of epidemiological data, such as the exhaustiveness and representativeness of the results and their comparability in time, among others. Therefore, it is necessary to identify the strongest analytical designs (among them the interrupted temporal series and comparative longitudinal studies), accompanied by sensitivity analysis of the results and being explicit, starting from the design, in the type of biases and problems that can be found in the data analysis that is available (34).

Concerning the evaluation of the immune response to the different types of vaccines, it has been oriented both to the antibody-mediated response and that mediated by cellular immunity. Among the antibody-mediated response, the reference standard has been established with the specific neutralizing antibody response against spike proteins of the virus, and a proxy to this response assessing neutralizing capacity has been measured in other studies by immunoglobulin G (IgG) antibody levels against the SARS-CoV-2 receptor binding domain (RBD) (35).

In the different studies, the decrease in the response levels to specific neutralizing antibodies was assumed to indicate the vaccine protection level when the levels of specific neutralizing antibodies fell between 4 and 6 months. The statistical methods used for their measurement are not homogeneous among all studies which has been used to recommend the application of boosters with vaccines produced in homologous or heterologous platforms of those received in established vaccination schemes (36, 37).

To assess the duration of vaccine protection in the real world, it is also important to consider the difficulties in assessing the cellular memory immune response. The measurement of the CD4+ and CD8+ T lymphocytes response expressed in the production of different activation markers is heterogeneous, depending on antigenic stimuli such as peptides from circulating virus variants, cells from infected individuals, or peptides from different vaccines, in addition to diversity in the host response, which does not allow to have precise indicators to define optimal vaccination schedules (38, 39).

In this context, inactivated whole virus vaccines, such as CoronaVac, by preserving epitopes of the virus, could respond in a broader spectrum to the different variants of circulating viruses or to new mutations, which could lead to the optimization of global vaccination schedules (10).

The main strength of our study lies in its systematic development, which reduces the possibility of biases in study selection. The use of different databases, including Latin American ones, allows for a broader search, although it is acknowledged that due to the magnitude of research on this topic, there may still be unreported or unfound studies, behaving as gray literature. The review results enabled us to achieve our objective, which was to describe how the efficacy/effectiveness of COVID-19 vaccines has been evaluated, with emphasis on CoronaVac. This allowed for the identification of some differences in these methods and some persisting gaps in defining more homogeneous methods for evaluation, regardless of whether these studies had high or low certainty in their evidence, which should be revisited if the objective is to evaluate the effectiveness and/or safety in the population of these interventions. However, the findings presented could be assessed and discussed with broader groups of experts in the field, which would help generate more accurate recommendations regarding their significance and potential implications.

In addition to the mentioned limitations, it is important to acknowledge that this type of review, having less precise question definitions compared to systematic reviews of effectiveness and safety (with their PICO structure), may result in some gaps in the application of search terms that could affect the results. Additionally, the vast amount of information, as was the case in our review, can create difficulties in synthesis and analysis, so it is crucial, as mentioned, to continue the discussion in groups with increasingly greater expertise in the subject (40). Lastly, while it is tempting to provide quantitative

results regarding the synthesis conducted, the most important aspect is to address the original question regarding the gaps in the evaluation of these vaccines.

5 Conclusion

Published information on the evaluation of the efficacy/effectiveness and safety of the different vaccines against COVID-19 is abundant. However, there are differences in terms of vaccine application schedules, population definition, outcomes evaluated, follow-up times, and safety assessment, as well as non-standardization in the reporting of results, which may hinder the generalizability of the findings. It is important to define the relevance of the analysis methods in advance, considering these differences and the heterogeneity that can be produced in the analysis and meta-analysis of this information. It is important to generate meetings and consensus strategies for the methods and reporting of this type of studies, which will allow to reduce the heterogeneity in their presentation and a better understanding of the effect of these 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.

Author contributions

JA-Á: Conceptualization, Methodology, Writing – original draft, Writing – review & editing, Investigation. PA-V: Writing – original draft, Writing – review & editing, Investigation. DA-L: Writing – original draft, Writing – review & editing, Investigation. AC-E: Writing – original draft, Writing – review & editing, Investigation. AG-H: Writing – original draft, Writing – review & editing, Investigation. LL-C: Writing – original draft, Writing – review & editing, Investigation. IM: Writing – original draft, Writing – review & editing, Investigation. DO-L: Writing – original draft, Writing – review & editing, Investigation. GQ: Writing – original draft, Writing – review & editing, Investigation. SR-B: Writing – original draft, Writing – review & editing, Investigation. CR-B: Funding acquisition, Writing – original draft, Writing – review & editing, Investigation. PR: Writing – original draft, Writing – review & editing, Investigation. MS-O: Writing – original draft, Writing – review & editing, Investigation. CT-A: Writing – original draft, Writing – review & editing, Investigation. MA-M: Funding acquisition, Project administration, Writing – original draft, Writing – review & editing, Investigation, Project Administration.

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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.2024.1321327/full#supplementary-material

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Coverage and determinants of second-dose measles vaccination among under-five children in East Africa countries: a systematic review and meta-analysis

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Background: One of the biggest breakthroughs of contemporary medicine is measles vaccination. It is essential for the total elimination of measles. Understanding the magnitude and determinants of effective second-dose measles vaccination coverage is a critical task. Accordingly, we set out to check the best available evidence of the pooled second-dose measles vaccination coverage among under-five children in East Africa.

Method: We searched electronic databases such as PubMed, Google Scholar, Cochrane, and others. Two reviewers separately carried out the search of the Joanna Briggs Institute, selection of studies, critical appraisal, and data extraction. A third party was involved in resolving the disagreement among the reviewers. Seven studies included in this study, four from Ethiopia, two from Kenya, and one from Tanzania were cross-sectional and published in English language, with publication dates before 29 November 2023. Articles lacking full-text, the intended outcome, and that are not qualitative studies were excluded from the analysis. The Microsoft Excel checklist was used to extract the data and then exported to STATA 11. In addition, I^2, Funnel plots, and Egger's test were employed to measure heterogeneity and detect publication bias, respectively. A random effect model was used.

Result: The meta-analysis includes a total sample size of 4,962 children from seven articles. The pooled prevalence of second-dose measles vaccination among under-five children in East Africa was found to be 32.22% [95% CI; (18.82, 45.63)], and the significant factors were as follows: birth order (1.72; OR = 95% CI: 1.32, 2.23), information about measles-containing second-dose vaccine (MCV 2) (7.39; OR = 95% CI: 5.21, 10.50), mother's marital status (1.47; OR = 95% CI: 1.05, 2.07), complete immunization for other vaccines (2.17; OR = 95% CI: 1.49, 3.17), and distance of vaccination site (3.31; OR = 95% CI: 2.42, 4.53).

Conclusion: The current study found that pooled prevalence of second-dose measles vaccination coverage among under-five children was still very low. It was also observed that birth order, distance of the vaccination site, complete immunization for other vaccines, mother's marital status, and information about MCV were factors associated with second-dose measles vaccination. These factors imply that there is a need for countries and their partners to act urgently to secure political commitment, expand primary health service and health education, and increase vaccination coverage.

KEYWORDS

children, coverage, East Africa, immunization measles, second dose, vaccination

Introduction

Measles is a highly contagious virus that can result in serious illness, lifelong problems, and fatalities (1). The first dose of the measles-containing vaccine should be given to infants as early as 9 months of age in nations where the disease is still spreading, and the second dose should be given as late as 15–18 months (2). The World Health Organization (WHO) recommends that two doses of the measles-containing vaccine (MCV) be included in all national immunization regimens. An estimated 169 million children worldwide are believed to have missed out on receiving the first dose of the measles vaccine between 2010 and 2017 and an additional 19.2 million in 2018 (3, 4). Furthermore, measles led to a loss of 140,000 lives worldwide in 2018, according to estimates from the United States Centers for Disease Control and Prevention and WHO (4). Countries in all the six WHO regions have adopted measles elimination goals (5). The elimination of measles is confirmed by the absence of endemic measles transmission in a region or other defined geographical area for a minimum of 1 year within the framework of an efficient surveillance system. Between 2000 and 2015, there was a 70% decline in the global number of recorded cases of measles, from 853,479 to 254,928, and a 75% fall in the incidence of measles cases per million people, from 146 to 36. These patterns show progress toward both regional and global measles elimination targets as well as milestones for measles control (3, 6). Moreover, WHO, UNICEF, and other partners created the Global Measles and Rubella Strategic Plan 2012–2020 (7). This strategy plan's primary goal was to provide the measles-containing second-dose vaccine (MCV2) to every child (8). However, none of the 2020 milestones or elimination goals (less than one case per 100,000 population per year) were met (9). Some nations still experience repeated outbreaks of measles despite the UNICEF and WHO's comprehensive measles reduction strategy, as well as the cooperation of international organizations for reducing mortality due to measles (3). The vaccination of at least 95% of the population with two doses of the measles vaccine effectively prevents the incidence and transmission of the disease within that community, ensuring herd immunity and the protection of all individuals, including those who are not vaccinated (10). MCV2 coverage in the WHO European Region was just 90% (11). Although MCV2 has recently been introduced in Africa, most nations still have minimal coverage. Of the 26 nations that implemented MCV2, only eight achieved a coverage rate of above 80% in 2015 (5). In seven nations, the coverage ranged from 60 to 80%, while in eight countries, it was <60% (5). Nonetheless, a great number of people die due to the highly contagious measles every year (12). An estimated 207,500 measles deaths were reported worldwide in 2019, with 147,900 (more than 70%) of those deaths occurring in African nations (12). Over the past 10 years, there has been a decrease in the death rate due to measles in Africa (13); however, the disease remains an issue in the region (14, 15). Although some studies have reported the determinants of second-dose measles vaccination coverage in East Africa, none of them have systematically reviewed the second-dose measles vaccination coverage, which varies and is not uniform throughout the nation. Public health stakeholders must choose the optimal vaccination schedules based on their nation's epidemiology, the features of its health system, and the best available data regarding the second-dose measles vaccination coverage at measles elimination in order to control the disease. The reported determinants include antenatal care (ANC), mother's education, place of delivery, birth order, receiving pentavalent 3, age of the child, information about MCV2, distance of the vaccination site, knowledge about immunization, attitude, maternal age, complete immunization, postnatal check, waiting time, residence near the health facilities, family size, household wealth status, maternal occupation, and mother's marital status (16–18). Thus, the current study aims at identifying relevant studies and summarizing major determinants of second-dose measles vaccination coverage in East Africa. The results of this review will add to existing knowledge about the problem and guide policymakers to improve second-dose measles vaccination coverage in East Africa.

Abbreviations: ANC, antenatal care; MCV, measles-containing vaccine; MeSH, Medical Subject Headings; JBI, Joanna Briggs Institute; PRISMA, Preferred Reporting Items for Systematic Review and Meta-Analysis statement; UNICEF, United Nations Children's Fund; WHA, World Health Assembly; WHO, World Health Organization.

Method and materials

Searching strategy and data source

All published studies conducted in East Africa reporting the second-dose measles vaccination coverage from September 2016 to 2022 were included. Only cross-sectional, human,

and English language research were included in the search parameters. The Preferred Reporting Items for Systematic Review and Meta-Analysis statement (PRISMA) guidelines were followed in reporting the review's findings (19). To get the relevant articles, PubMed, Cochrane, Google Scholar, and other electronic databases were accessed. Furthermore, articles were searched by looking through the reference lists of previously recognized articles as well as the gray literature that was available in the repository of the local university. The article search was conducted independently and systematically by the authors. Furthermore, a manual cross-referencing search of the gray literature was conducted to locate additional noteworthy articles. The core search terms and phrases were "Child," "Children," "Coverage," "Second Dose Measles," "Vaccination," "magnitude of Second Dose Measles coverage," "associated factors," "Immunization Coverage," and "East Africa." We used various Boolean operators to construct search algorithms for the Medical Subject Headings (MeSH terms) below. Particularly, to fit advanced PubMed database, the following search strategy was applied: (((((((((Epidemiologic) OR (Child)) OR (Children)) AND (Coverage, Second Dose Measles)) OR (Second Dose Measles coverage)) OR (Coverage, Vaccination)) OR (Vaccination coverage)) OR (Immunization Coverage)) OR (Coverage, Immunization)) AND (East Africa).

Inclusion and exclusion criteria

Those studies included in this systematic review and meta-analysis were the studies with the prevalence and/or at least one associated factor of second-dose measles vaccination coverage, studies conducted in East Africa, studies published in English language, and studies published before 29 November 2023. Unpublished studies, book reviews, and case reports, publications with only an abstract, studies that did not identify the intended outcome, qualitative studies, and studies conducted outside East Africa were excluded.

Types of exposure

To evaluate the effects on second-dose measles vaccine coverage, factors influencing such coverage were taken into account as exposure variables in this systematic review and meta-analysis.

Outcome of interest

The second-dose measles vaccination coverage was calculated by dividing the number of children who received a second dose of the measles vaccination by the total number of children involved in the research and then multiplying the result by 100. Mothers' verbal reports and/or immunization cards were used in studies that were included in this systematic review and meta-analysis to ascertain whether or not a child received the vaccine. The identified predictors were antenatal care (ANC) (<4, and ≥ 4), mother's education (formal education and non-formal education), place of delivery (health facility vs. home), birth order (first vs. two and above), received pentavalent 3 (yes vs. no), information about MCV2 (yes vs. no), distance to the vaccination site ($\leq$ min and >30 min), knowledge about immunization (yes vs. no), attitude (good vs. poor), complete immunization (yes vs. no), postnatal check (yes vs. no), waiting time (<1 and ≥ 1 h), residence (urban vs. rural), family size (≤ 5 and >5), household wealth status (rich vs. poor), maternal occupation (employed vs. unemployed), and marital status (married vs. unmarried).

Study selection

The authors TGA and ATG conducted an initial search across several databases in order to eliminate duplicate studies. The retrieved studies were exported to the reference manager program, Endnote version 9. The titles and abstracts of the research were checked and evaluated by the same two authors (TGA and ATG), who then independently evaluated the full texts. Disagreements were resolved by consensus.

Methods of data extraction and quality assessment

All studies that were accepted based on the full-text screening were retained for data extraction.

A data extraction form was developed, which the authors TGA and BT then used for extracting data from each of the included studies. To retrieve the data, a standardized data extraction form for Microsoft Excel was used. Significant information was acquired from the included studies, including the first author's name, the year of publication, the study location, the nations under investigation, the study design, associated variables, sample size, the number of outcomes, the prevalence (magnitude), the risk estimate (odds ratio), and 95% confidence interval (CI). A quality appraisal checklist from the Joanna Briggs Institute (JBI) was used to assess the quality of the included studies. Cross-sectional studies were evaluated using the following eight criteria: inclusion criteria, study subject and setting description, valid and reliable exposure measurement, objective and standard criteria applied, confounder identification, confounder handling strategies, outcome measurement, and appropriate statistical analysis. When a study achieved a quality assessment indicator score of 75–100%, it was considered high quality, a score of 50–74% indicated moderate quality, and a score of 0–49% represented low quality. These indicators resulted in six studies rated as high quality and one as moderate quality (Table 1).

Data processing and analysis

Pooled analysis was conducted using weighted inverse variance random-effects model (20). For the meta-analysis, STATA version 11 statistical software was employed. The funnel plot and Egger's regression test were used to more objectively assess publication bias (21). The studies' heterogeneity was measured using the I-squared statistic; An I-squared statistic of 25, 50, and 75%, respectively, indicated low, moderate, and high heterogeneity (22, 23). Sensitivity analysis was used to see how one study affected

TABLE 1 Characteristics and quality status of the studies included to assess the pooled magnitude of second-dose measles vaccination coverage in East Africa.

ID	First author	Year of publication	Country	Study design	Study population	Sample size	Number of outcome	Prevalence	Quality status
1	Joseph Obiero Ogutu, et al.	2020	Kenya	Cross-sectional	Children aged 19–59 months	417	213	51.08	Low risk
2	Atalay Goshu Muluneh, et al.	2019	Ethiopia	Cross-sectional	Children aged <36 months	965	120	12.44	Low risk
3	Aynalem Demewoz, et al.	2020	Ethiopia	Cross-sectional	Children aged 24–35 months	837	403	48.15	Low risk
4	Fredrick Mike Makokha, et al.	2016	Kenya	Cross-sectional	Children aged 24–35 months	571	102	17.86	Low risk
5	Richard Magodi	2017	Tanzania	Cross-sectional	Children aged <5 years	1,000	442	44.20	Low risk
6	Addisu Waleligne Tadesse, et al.	2022	Ethiopia	Cross-sectional	Under-five children	372	158	42.47	Low risk
7	Achamyeleh Birhanu Teshale, et al.	2019	Ethiopia	Cross-sectional	Children aged 24–35 months	800	79	9.88	Low risk

the estimate as a whole. To determine the relationship between determinant factors and outcome variables in the included articles, the odds ratio was employed.

Results

Searching results

The search strategy retrieved 15 articles from Cochrane library, 19 from Pub Med, and 6,360 from Google Scholar. After retrieval, 3,011 articles were removed as they were duplicates, 3,239 due to outcomes mixed with other non-relevant indicators, and 126 due to study area. A total of 18 articles were selected for full-text review. Out of them, 11 articles that failed to provide the outcome of interest were removed from the analysis following full-text reviews. Finally, this systematic review and meta-analysis comprised seven articles to determine the coverage of second-dose measles vaccination and associated factors in East Africa (Figure 1).

Characteristics of the included studies

Four studies were found in Ethiopia (17, 18, 24, 25), two in Kenya (16, 26), and one in Tanzania (27). All the seven studies employed a cross-sectional study design. Regarding the year of publication, four studies were published before 2020 and three studies were published between 2020 and 2022 (Table 1).

Magnitude of second-dose measles vaccination coverage in East Africa

The pooled prevalence of second-dose measles vaccine coverage in East Africa was estimated by a meta-analysis encompassing seven studies with a total of 4,962 participants. Consequently, the overall pooled prevalence of second-dose measles vaccination coverage in East Africa was 32.22% [95% CI; (18.82, 45.63); $I^2 = 99.3\%$ (Figure 2)].

Subgroup analysis

Based a country-based subgroup analysis, Tanzania had the highest prevalence of second-dose measles vaccination coverage of 44.20% (95% CI: 41.12, 47.28), followed by Kenya at 34.42% (95% CI: 1.86, 66.97) (Figure 3).

Publication bias

The Egger's regression test and a funnel plot were used to assess publication bias. Subjectively, a funnel plot with an uneven distribution (Figure 4) suggests the existence of publishing bias. In addition, the objective *p*-value of 0.019 from the Egger's regression test indicated the existence of publication bias.

Sensitivity analysis

To determine the weight of each study on the aggregated effect size of magnitude of second-dose measles vaccine coverage, we performed a sensitivity analysis. The Der Simonian-Laird random-effects model sensitivity analysis revealed that no single study had an impact on the overall magnitude of second-dose measles vaccination coverage in East Africa (Figure 5).

The association between birth order and second-dose measles vaccination coverage

Among the included seven studies, four studies reported the association between birth order and second-dose measles vaccination coverage. The pooled odds ratio from these studies was

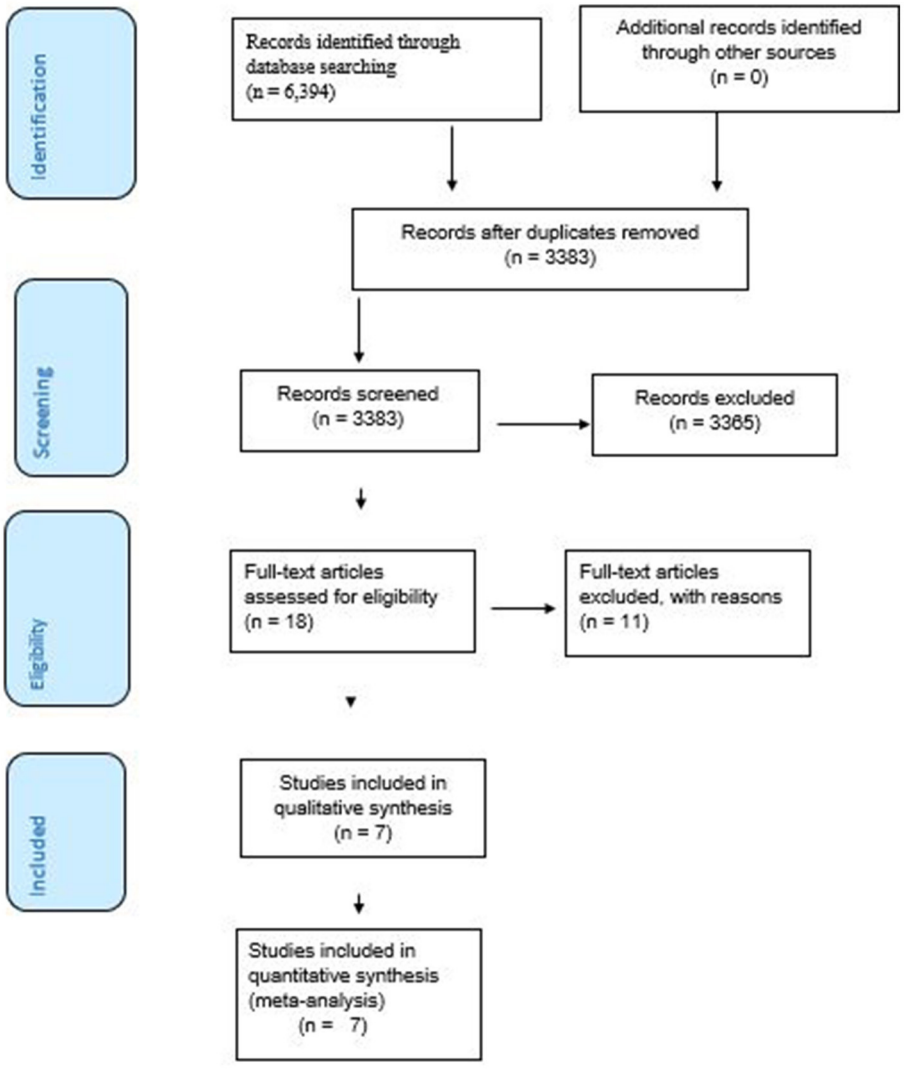

FIGURE 1
A PRISMA flow diagram of articles screening and process of selection.

1.72 (95% CI: 1.32, 2.23), which revealed that under-five children with birth orders larger than one were 1.72 times more likely than their counterparts to receive the second dose of the measles vaccination (Figure 6).

The association between information about MCV2 and second-dose measles vaccination coverage

Three of the seven included studies revealed an association between coverage of the second dose of the measles vaccination and information of MCV2. The pooled odds ratio was 7.39 (95% CI: 5.21, 10.50), indicating that mothers who were aware of the second dose of the measles vaccine were 7.39 times more likely to vaccinate their children than those who were unaware of the second-dose measles vaccination (Figure 7).

The association between marital status and second-dose measles vaccination coverage

Four of the seven included studies revealed an association between the coverage of second-dose measles vaccination and mother's marital status. The pooled odds ratio was 1.47 (95% CI: 1.05, 2.07), indicating that children from married women are 1.47 times more likely to receive the second dose of the measles vaccination than children from unmarried women (Figure 8).

The association between complete immunization for other vaccines and second-dose measles vaccination coverage

Two of the seven included studies revealed an association between the coverage of second-dose measles vaccination and complete immunization for other vaccines. The pooled odds ratio

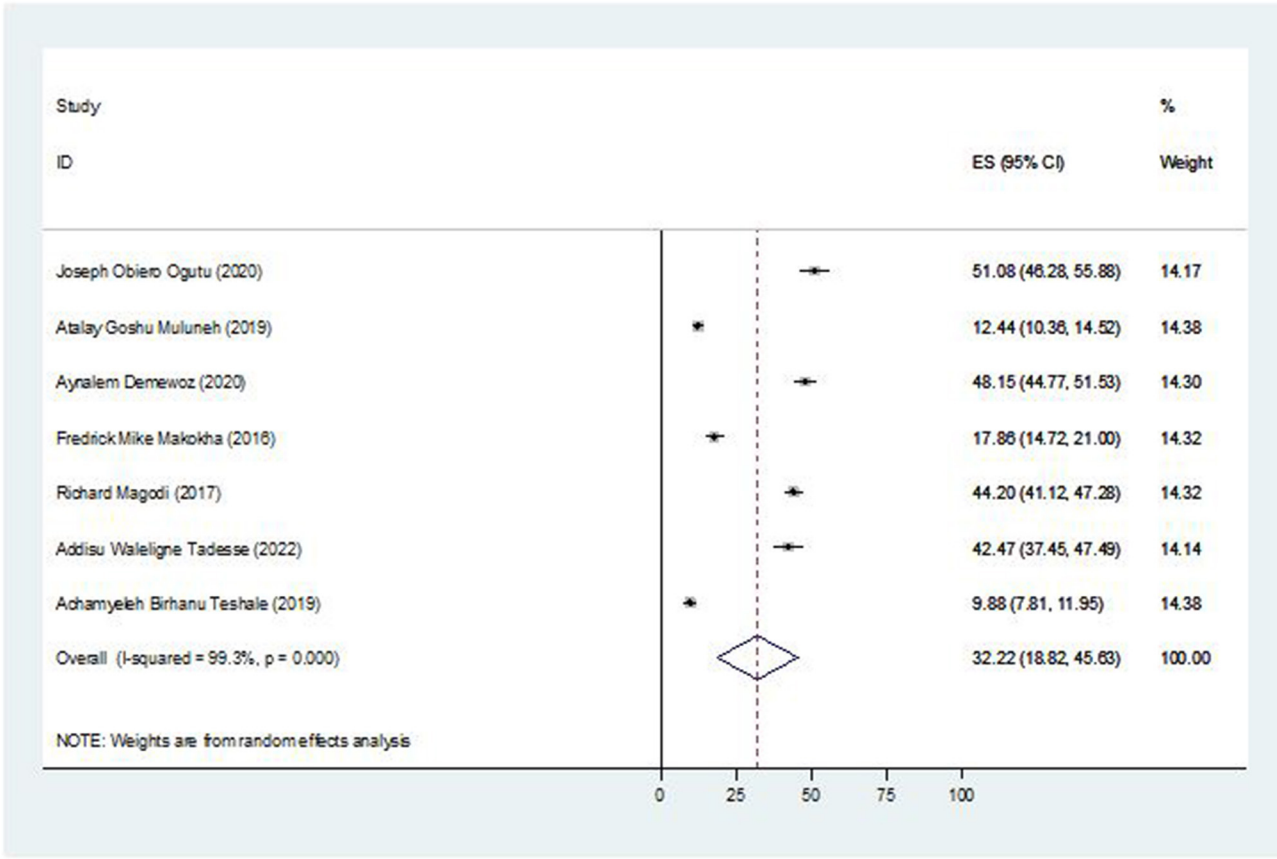

FIGURE 2
Forest plot of the pooled prevalence of second-dose measles vaccination coverage in East Africa, 2023.

was 2.17 (95% CI: 1.49, 3.17), indicating that children who had received all other recommended vaccinations were 2.17 times more likely to receive the second dose of the measles vaccine than children who had not received all other recommended vaccinations (Figure 9).

The association between distance of vaccination site and second-dose measles vaccination coverage

Of the seven studies that were considered, two of them showed an association between the coverage of the second dose of the measles vaccination and the distance from the immunization site. The pooled odds ratio was 3.31 (95% CI: 2.42, 4.53), showing that mothers who live closest to the immunization site are 3.31 times more likely to bring their child for the second dose of the measles vaccination than mothers who have to travel a long distance to receive the vaccination (Figure 10).

Discussion

To the best of our knowledge, the current meta-analysis is the first of its kind for exploring the second-dose measles vaccination coverage among under-five children in East Africa. Despite employing different strategies and approaches, countries are still having difficulty reaching their vaccine coverage targets, particularly for the second dose of the measles vaccination. This systematic review and meta-analysis study assessed the pooled prevalence of second-dose measles vaccine coverage among under-five children in East Africa. Additionally, birth order, distance of vaccination site, complete immunization for other vaccines, marital status, and information about MCV2 were found to be significantly associated with second-dose measles vaccination coverage in East Africa. Among the limitations of this study is the fact that we only examined cross-sectional research, which can potentially introduce bias into the analysis.

The overall pooled prevalence of second-dose measles vaccination coverage in East Africa was 32.22% [95% CI; (18.82, 45.63)]. The pooled prevalence of this study is consistent within the Africa WHO region 2018 report (25%) (3). However, it is lower than different regions of the WHO in its 2019 report such as Eastern Mediterranean (82.4%), European (91.6%), and Western Pacific (80.7%) (28). Similarly it is lower than the United States (91.5%) (29), South-East Asia Region (80%) (30), and measles vaccination coverage trend in Myanmar from 2014 to 2018; the MCV2 coverage in 2018 was 87% (31). A difference in the vaccine's introduction period and the respondents' sociocultural traits, such as difficulty accessing immunization services, lack of comparably

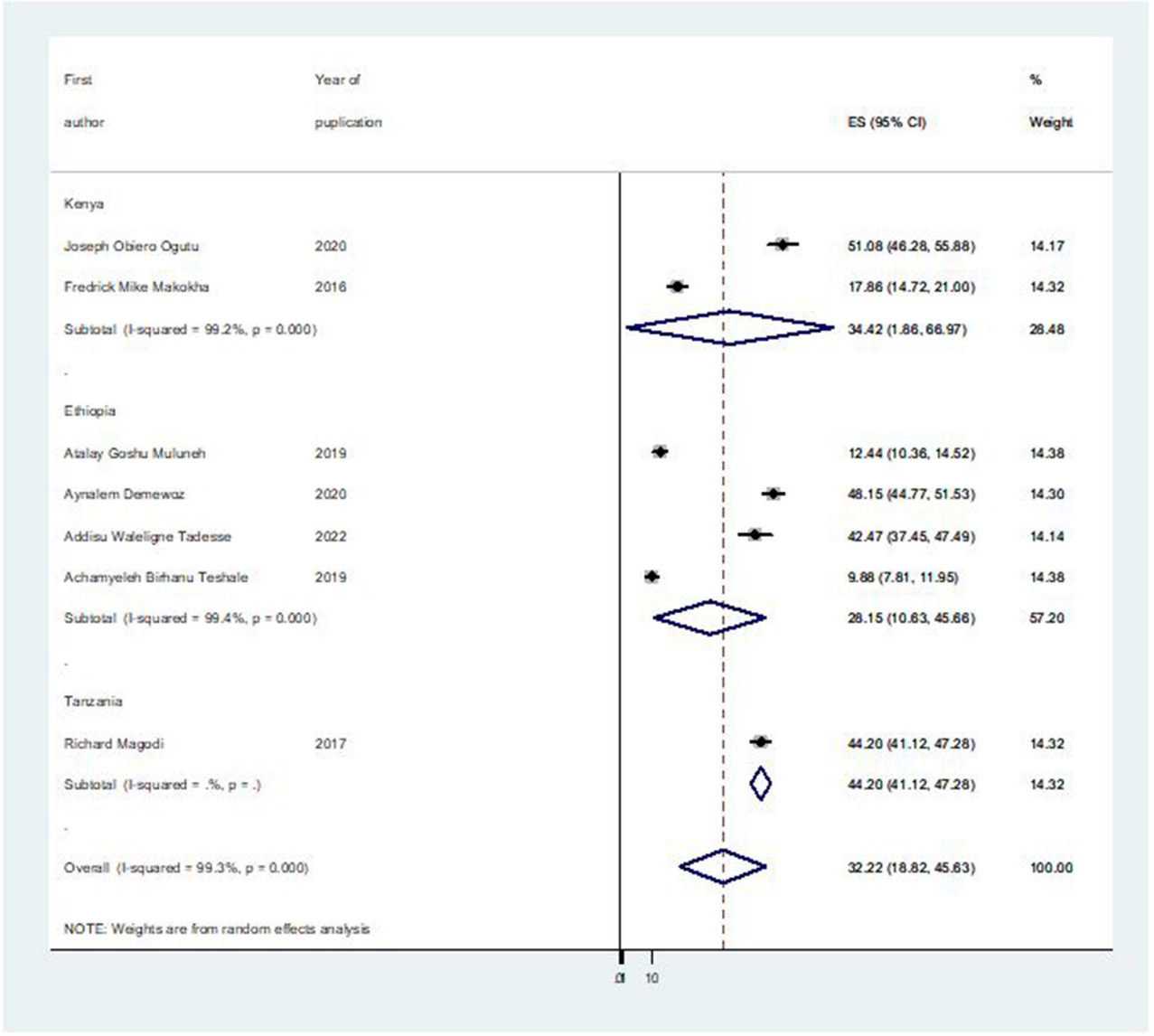

FIGURE 3
Forest plot of the subgroup prevalence of second-dose measles vaccination coverage in East Africa, 2023.

better infrastructure, low socioeconomic position, low literacy rate, and lack of information availability, could be the cause of the low coverage of the second dose of the measles vaccination (32). The other explanation might be that women make different decisions and have poor attitudes and perceptions about vaccinations, which negatively affect the rate of vaccination coverage (33). In order to meet the regional and global targets for the eradication of measles, it will be critical to retain political commitment and assure significant, ongoing investments in addition to increasing the second dose of the measles-containing vaccine.

This study found between-country differences in the second-dose measles vaccination coverage among under-five children in East Africa. The lowest prevalence was observed from Ethiopia (28.15%; 95% CI: 10.63, 45.66) while the highest was in Tanzania (44.20%; 95% CI: 41.12, 47.28). It is very lower than the World Health Assembly (WHA) target to increase routine coverage with the second dose of a measles-containing vaccine, and it is far below (>95%) the second dose of measles coverage than the WHO-recommended coverage for global measles elimination (13). Additionally, there are issues that require extra attention, especially in East Africa where routine vaccinations are taken into account while developing programs. Specific strategies and approaches are required to guarantee access to and appropriate use of immunization services, particularly for the second dose of measles vaccination.

This study found birth order to be a significant determinant of second-dose measles vaccination coverage among under-five children. In this regard, we found that, compared to the first birth order child, children with a higher birth order had a higher likelihood of receiving MCV2. However, it is inconsistent with the

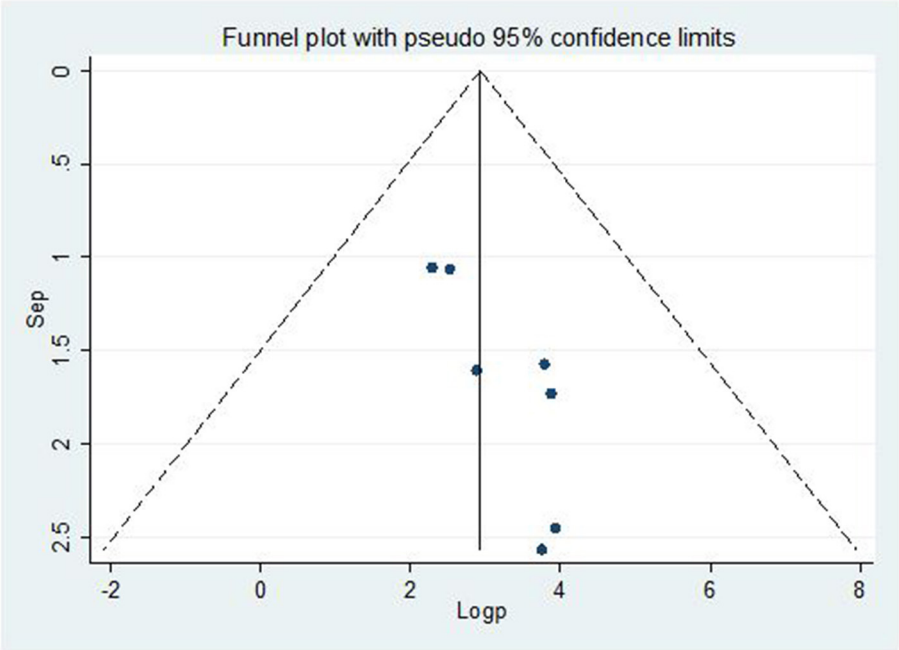

FIGURE 4
Funnel plot for publication bias, Log prop, or log of proportion (LNP) represented in the *x*-axis and standard error of log proportion in the *y*-axis.

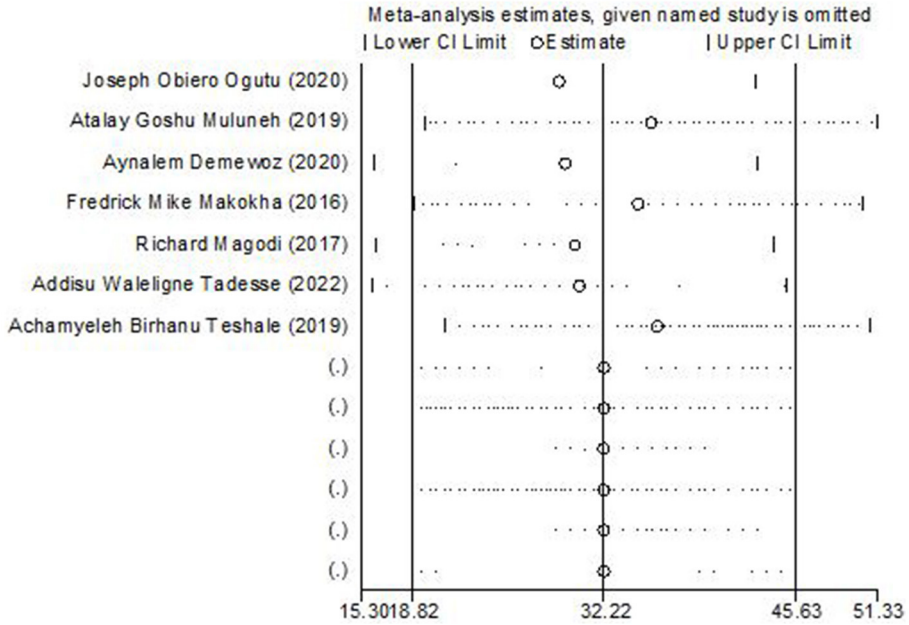

FIGURE 5
Sensitivity analysis of the included studies.

finding of a study conducted in China on second-dose measles vaccination (34). Additionally, it contradicts the findings of the study done in East Africa on other types of vaccinations (35), which might be the case because mothers with higher birth orders have firsthand experience of the advantages of immunizations from previous pregnancies and deliveries. Furthermore, compared to their peers, children who had all of the other basic immunizations had a higher chance of receiving MCV2. This finding is due to the possibility that mothers had additional services and health information during their children's earlier vaccinations.

This study also found that mothers who live closest to the immunization site are 3.31 times more likely to bring their child

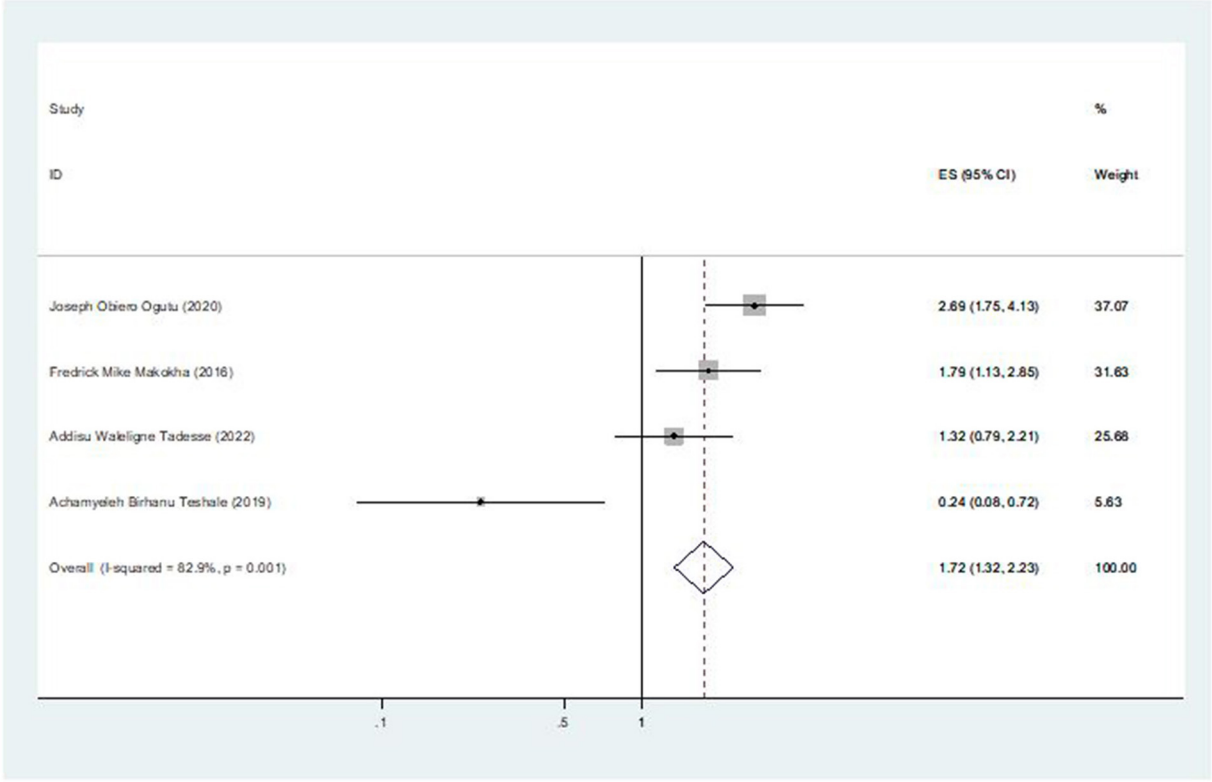

FIGURE 6
The pooled effect of birth order on second-dose measles vaccination coverage in East Africa.

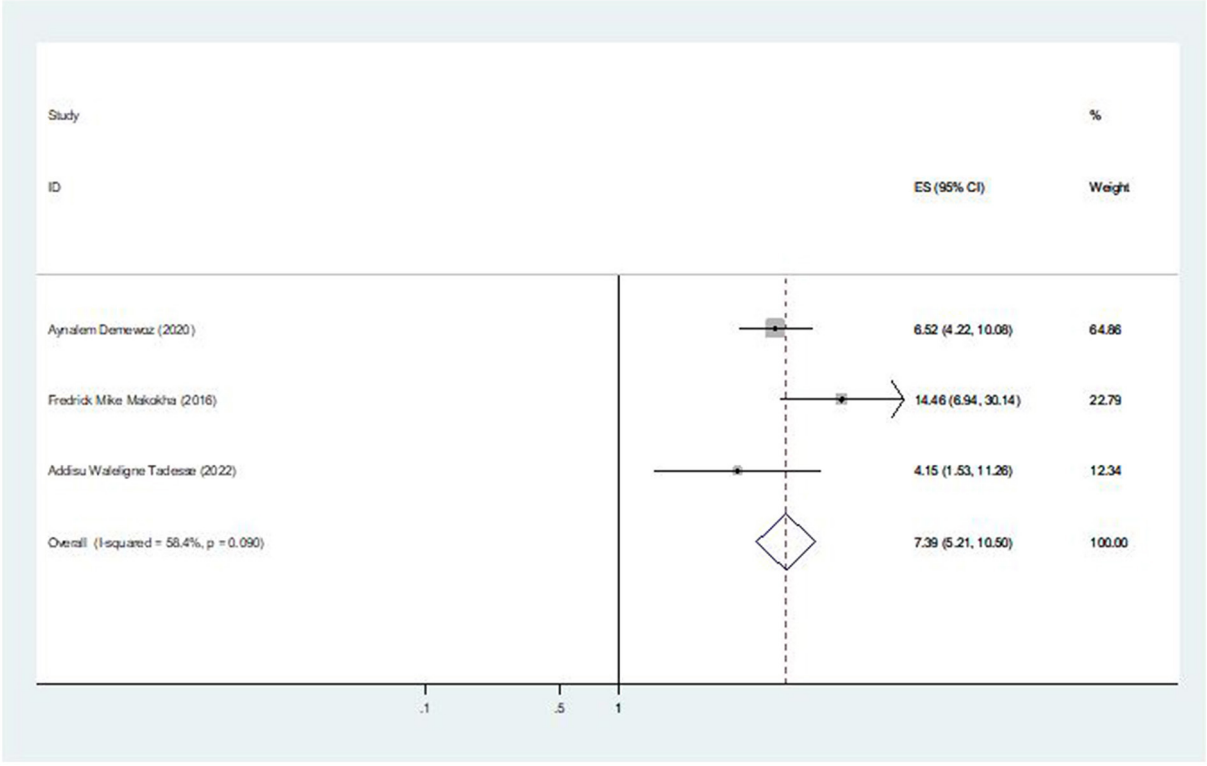

FIGURE 7
The pooled effect of information about MCV2 on second-dose measles vaccination coverage in East Africa.

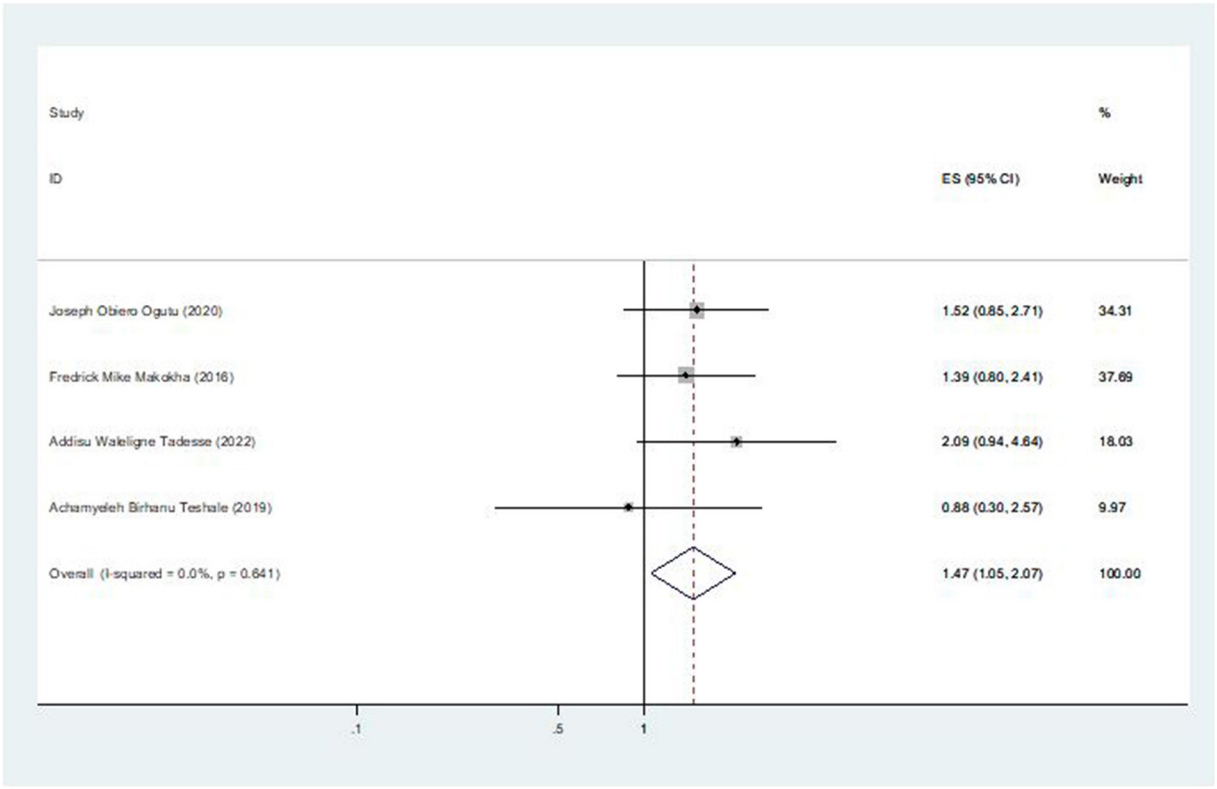

FIGURE 8
The pooled effect of marital status on second-dose measles vaccination coverage in East Africa.

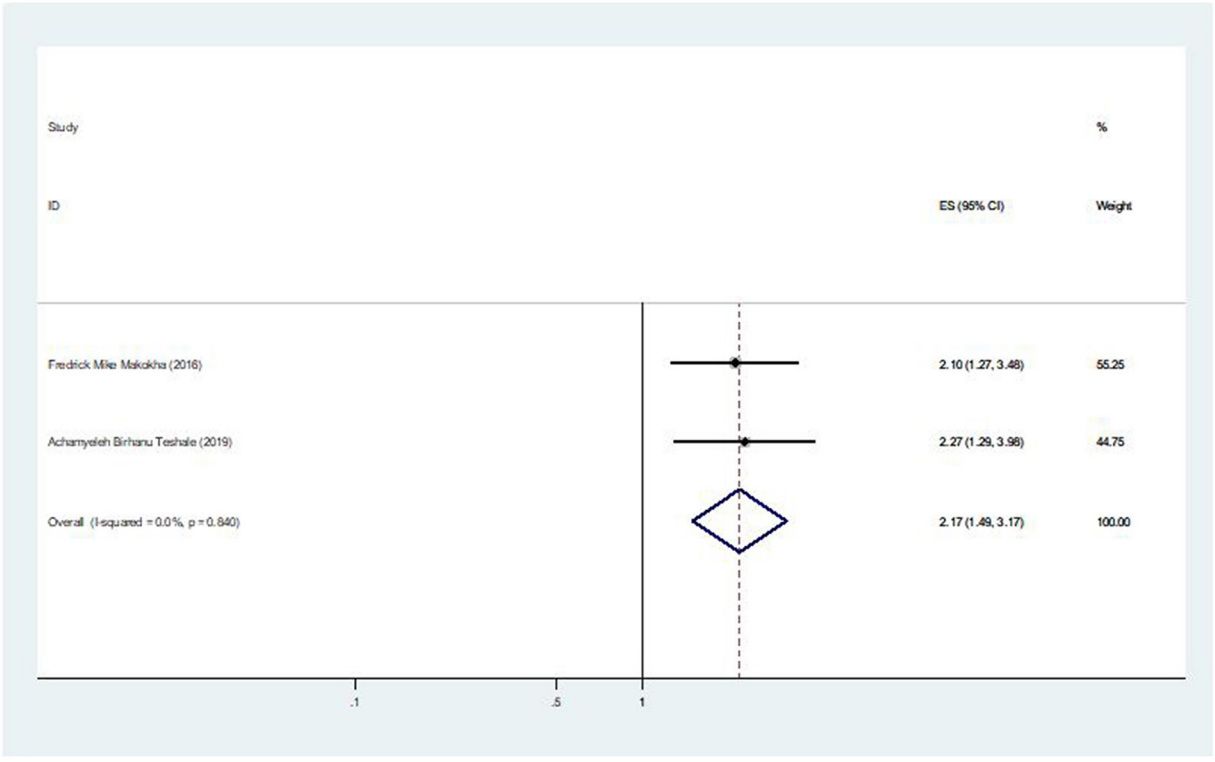

FIGURE 9
The pooled effect of complete immunization for other vaccines on second-dose measles vaccination coverage in East Africa.

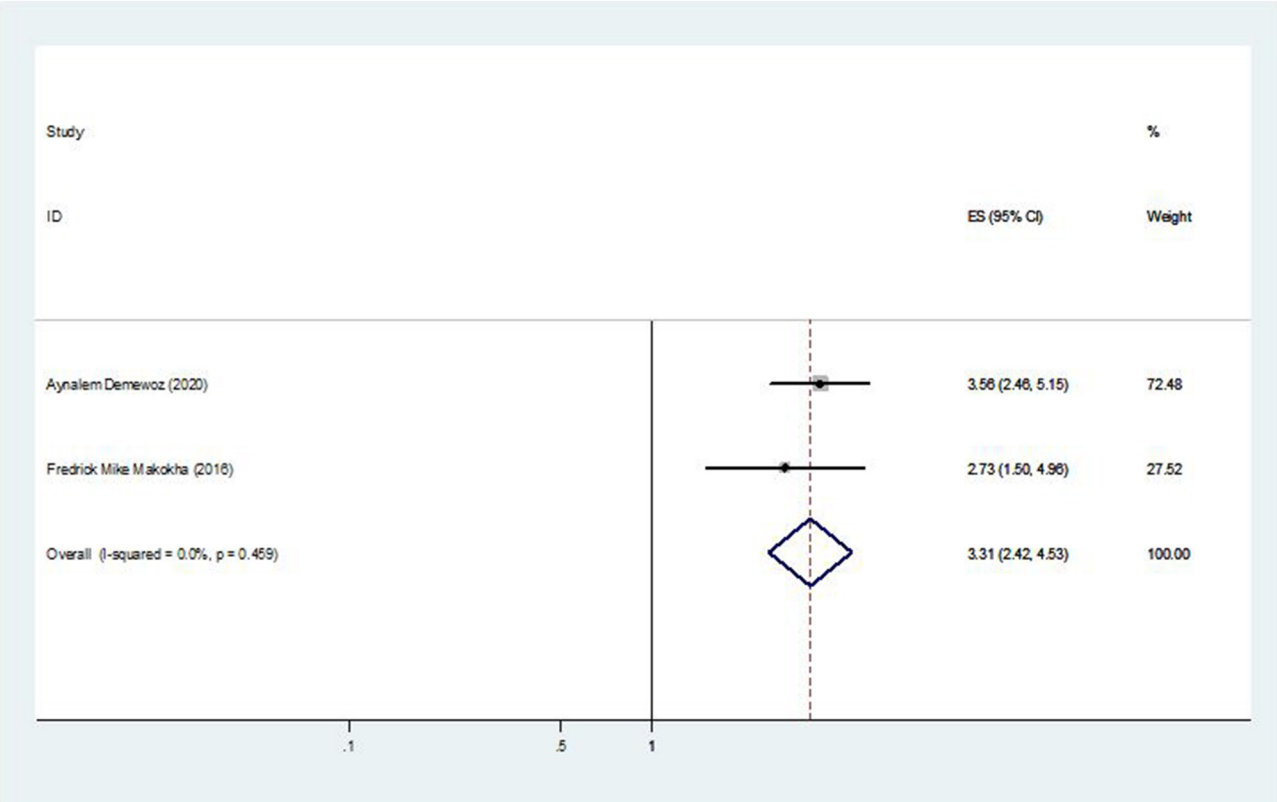

FIGURE 10
The pooled effect of distance of vaccination site on second-dose measles vaccination coverage in East Africa.

for the second dose of the measles vaccination than mothers who have to travel long distance to receive the vaccination. This finding was consistent with the finding of the study conducted in Shenzhen in East China (36). However, it contradicts the findings of a study conducted in the province of Aceh Jaya, Indonesia (37). The possible reason might be due to mothers who travel very far to bring their children to the vaccination site, their present schedule commitment, and workload from home duties. In addition, it might be due to the fact that majority of people would not travel more than 5 m for basic curative and preventive care. An important factor influencing the usage of healthcare services was distance (38).

Additionally, it was found that, among under-five children, receiving the second dose of the measles vaccination was significantly influenced by them receiving all other recommended vaccinations. In this regard, children who received all other recommended vaccinations were 2.17 times more likely to receive for the second dose of the measles vaccination than children who had not received all other recommended vaccinations. This finding is due to the possibility that mothers had additional services and health information during their children's earlier vaccinations (39). Moreover, mothers may know the routine schedule and the appropriate age for the second-dose vaccination of measles.

The present study also found a significant association between marital status and second-dose measles vaccination coverage. Mothers who are married were 1.47 times more likely to take their child for the second-dose measles vaccination than mothers who are unmarried. Partner involvement has been shown to improve health-seeking behavior and seeking health services (40). One explanation might be that married women receive unfettered emotional and financial support; their spouse might even remind them to get the child vaccinated. Thus, unmarried women can have a disproportionately greater psychological influence, which can affect vaccination uptake.

Moreover, this systematic review and meta-analysis observed that mothers who were aware of the second dose of the measles vaccine were 7.39 times more likely to vaccinate their child than those who were unaware of the second-dose measles vaccination. This finding is consistent with studies from Nepal and India that showed that lack of knowledge of the immunization schedule was the cause of incomplete or partial vaccination (41, 42). This lack of knowledge could be because women who were aware of the vaccination schedule were probably also aware of the benefits of vaccination and the minimum age at which immunizations must be completed. Mothers' intention to vaccinate their children may also be influenced by their increased knowledge of the second dose of the measles vaccine.

Strengths and limitations

The strengths of this review included a rigorous, standardized methodological approach, broad inclusion criteria, and the

involvement of multidisciplinary expertise. Despite prudently extensive search and planned reviews, more than two reviewers minimized all possible risk of bias. The current study is not without limitations. Some of the limitations comprise the fact that we have reviewed only cross-sectional studies that are prone to confounding the number of studies that were not equally distributed among countries. Regarding the intended result, bias may exist, particularly for women without immunization records, and the number of studies included in the current study was very few and may affect the overall result.

Conclusion

The current study found that the pooled prevalence of second-dose measles vaccine coverage among under-five children was much lower than WHO's target for second-dose measles vaccination coverage and far lower than the prevalence of second-dose measles vaccination coverage across the world. These findings also showed that second-dose measles vaccination among under-five children is affected by birth order, distance of vaccination site, complete immunization for other vaccines, marital status, and information about MCV 2. These factors imply that there is a need for countries and their partners to act urgently to secure political commitment, expand primary health service and health education, and increase vaccination coverage to improve second-dose measles vaccination coverage among under-five children.

Data availability statement

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

Author contributions

TA: Conceptualization, Data curation, Formal analysis, Methodology, Software, Validation, Writing – original draft, Writing – review & editing. TT: Formal analysis, Methodology, Software, Writing – review & editing. BW: Conceptualization, Data curation, Formal analysis, Methodology, Writing – review & editing. EM: Conceptualization, Data curation, Formal analysis, Writing – review & editing. MA: Conceptualization, Formal analysis, Methodology, Writing – review & editing. AZ: Data curation, Formal analysis, Software, Writing – review & editing. MW: Formal analysis, Software, Writing – review & editing. AK: Conceptualization, Methodology, Validation, Writing – review & editing. BT: Conceptualization, Methodology, Software, Writing – review & editing. AG: Conceptualization, Formal analysis, Methodology, Validation, Writing – original draft, Writing – review & editing.

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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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From classical approaches to new developments in genetic engineering of live attenuated vaccine against cutaneous leishmaniasis: potential and immunization

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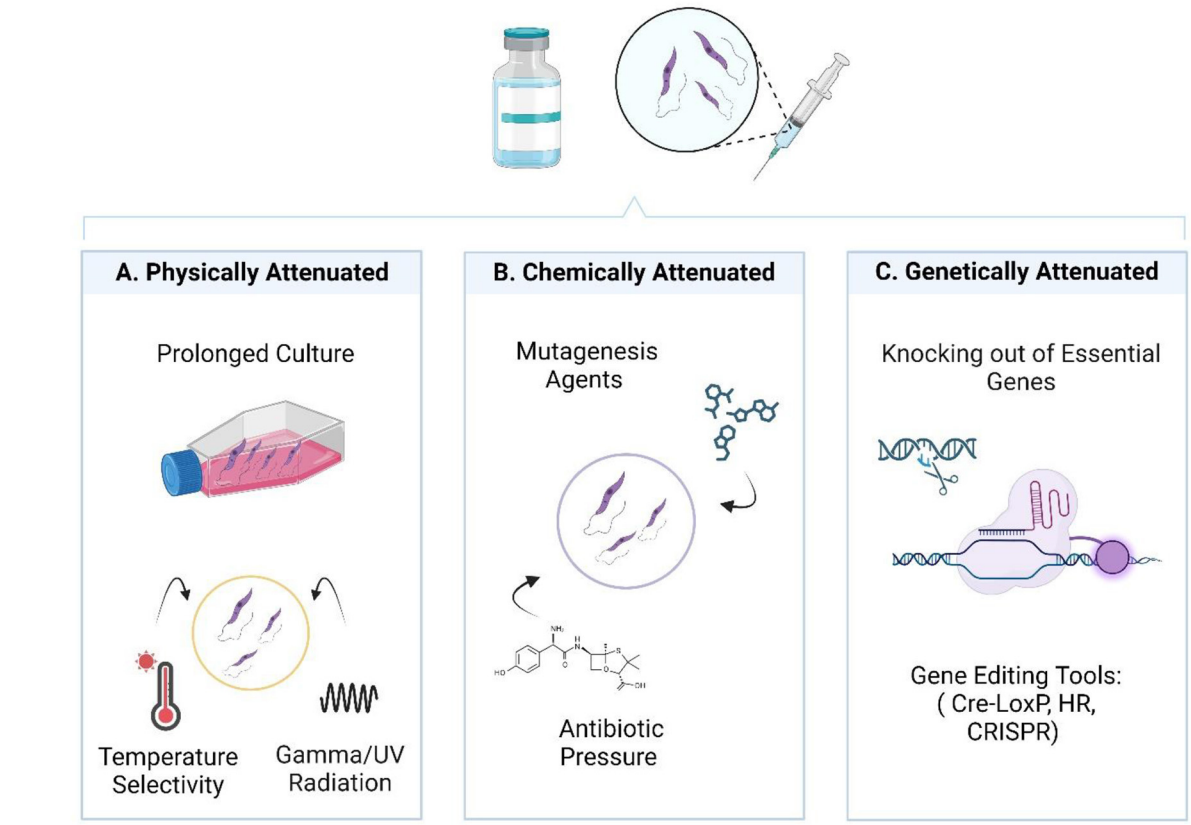
Despite the development of a vaccine against cutaneous leishmaniasis in preclinical and clinical studies, we still do not have a safe and effective vaccine for human use. Given this situation, the search for a new prophylactic alternative to control leishmaniasis should be a global priority. A first-generation vaccine strategy—leishmanization, in which live *Leishmania major* parasites are inoculated into the skin to protect against reinfection, is taking advantage of this situation. Live attenuated *Leishmania* vaccine candidates are promising alternatives due to their robust protective immune responses. Importantly, they do not cause disease and could provide long-term protection following challenges with a virulent strain. In addition to physical and chemical methods, genetic tools, including the Cre-*loxP* system, have enabled the selection of safer null mutant live attenuated *Leishmania* parasites obtained by gene disruption. This was followed by the discovery and introduction of CRISPR/Cas-based gene editing tools, which can be easily and precisely used to modify genes. Here, we briefly review the immunopathology of *L. major* parasites and then present the classical methods and their limitations for the production of live attenuated vaccines. We then discuss the potential of current genetic engineering tools to generate live attenuated vaccine strains by targeting key genes involved in *L. major* pathogenesis and then discuss their discovery and implications for immune responses to control leishmaniasis.

KEYWORDS

attenuated vaccines, CRISPR, cutaneous leishmaniasis, drug resistance, leishmanization, immunization

Introduction

Leishmaniasis is a vector-borne infection caused by *Leishmania*—an obligate intracellular protozoan parasite. The two morphologically distinct forms of this are the promastigote, which is passed on by female Phlebotomine sandflies, and the amastigote, which occurs in mammalian hosts. The several clinical forms of the disease can be grouped into three main clinical forms: visceral (VL), mucocutaneous (MCL), and cutaneous



GRAPHICAL ABSTRACT

leishmaniasis (CL) (1). CL is a painless and chronic ulcer at the site of sandfly bites and is the most common clinical syndrome in many affected regions, especially in the Middle East, where it has been reported in two main forms: zoonotic CL (ZCL) caused by *Leishmania major* and anthroponotic CL (ACL) caused by *Leishmania tropica* and mixed infection with them, which is high there (2, 3). In 2022, WHO reported that 85% of the global CL incidence occurred in eight countries, Afghanistan, Iran, Iraq, Syria, Algeria, Brazil, Colombia, and Peru (4). New outbreaks in the Middle East in recent years have been linked to wars in Syria, Yemen, Turkey, and Iraq. Refugee migration from endemic to non-endemic areas and vice versa, poor hygiene, malnutrition, weak immune systems, poor housing, lack of resources, environmental conditions, climate change, poor urbanization management, use of agricultural lands for residential purposes, and changes in vector populations link to a substantial rise in CL prevalence, which are present circumstances in most of the Middle East (3, 5, 6) (Figure 1). Although the first line of treatment of leishmaniasis with pentavalent antimonials is affordable and generally available in many endemic countries in the Middle East, economic sanctions, war, and counterfeit drug markets make access to the standard treatment difficult. In addition, the efficacy of this type of treatment is variable due to drug resistance and induction of organ toxicity (2, 3).

Fortunately, the development of immunity to the parasite in infected individuals following rehabilitation has highlighted the role of vaccination in disease management (5). In addition, the partial understanding of the immunopathogenesis of leishmaniasis has motivated immunologists and researchers in the leishmaniasis field to investigate and develop the different types of vaccines required. In the early 20th century, controlled inoculation of live virulent *L. major* promastigotes was used to immunize people in hyperendemic regions, preventing parasite infection in up to 80% of people. However, leishmanization as effectively powerful to control CL had several disadvantages that led to its abandonment (except in Uzbekistan, where this method is still used), including permanent skin lesions, safety concerns about HIV transmission, limitations in immunosuppressed people, and issues with Good Manufacturing Practice (GMP) standards (7, 8). Given these challenges, vaccine development shifted to inactivated vaccines. Due to the simplicity and cost-effectiveness of the production process, inactivated vaccines have been developed in various formulations. They are considered safe human vaccines and have been used as an alternative medication for drug-resistant type CL (9). Inactivation of the parasite while preserving the antigenic structures has been achieved by physical methods such as heat, chemicals, sonication, or UV radiation. This category has been studied in many clinical trials, but none of them have been

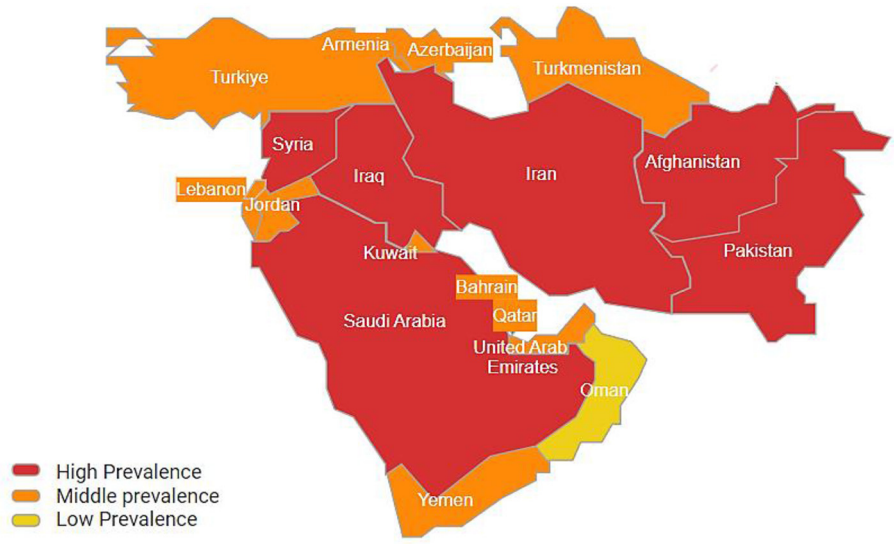


FIGURE 1
Leishmaniasis prevalence in different Middle East countries.

approved by the World Health Organization (WHO) due to the lack of remarkable efficacy and the need for multiple vaccine doses (7, 8).

In addition to extended vaccines based on whole organism components, purified immunogenic fragments of the parasite have been developed as vaccine candidates, reducing the possibility of adverse reactions. Leishmune® –a commercial canine vaccine consisting of fucose–mannose ligand (FML) from *Leishmania donovani* adjuvanted with QuilA saponin shows moderate clinical signs and lesions in vaccinated/infected dogs (8, 10). Remarkable advances in molecular biology have led to a new generation emergence of subunit or synthetic leishmaniasis vaccines based on membrane or soluble parasite proteins, replacing the previous native form vaccines. Cost-effectiveness and a straightforward manufacturing process allow their large-scale production. There is no live pathogen and no risk of infection in immunosuppressed individuals. With all these advantages, there are also some disadvantages, including an attempt to escape immune system deactivation and increased immunogenicity. Variations in the final conformation and structure of peptides occur due to heterologous expression systems, which could almost be related to post-translational modifications. Also, the epitopes could be selected to induce the desired immune response, and a particular antigenic arrangement could be chosen to induce a milder immune response (8, 11).

The *Leish*-111f vaccine is a tandem combination of three highly conserved *Leishmania* antigens, thiol-specific antioxidant (TSA), *L. major* stress-inducible protein 1 (LmSTI1), and *Leishmania* elongation initiation factor (LeIF), resulting in a 111 kDa polyprotein. In addition, studies indicated that *Leish*-111f formulated in IL-12 induces antibody response and IFN-γ production as well as soluble *Leishmania* antigen (SLA), but MPL-SE is considered a suitable alternative due to problems related to the manufacturing process and uncertainty of safety (12). *Leish*-111f is the first leishmaniasis vaccine to demonstrate immunogenicity in human clinical trials (12). In human clinical trials, *Leish*-111f is the first leishmaniasis vaccine that has demonstrated immunogenicity. A total of 77 healthy Indian subjects, with or without previous exposure to *Leishmania*, were administered three doses of *Leish*-F1+MPL-SE and followed for 168 days. Results showed safe and mild reactions associated with an increase in Th1-type cytokines (13). Purified peptides from different hosts administered with CpG adjuvant in BALB/c mice and eukaryotically expressed vaccine resulted in greater immune protection than the prokaryotic vaccine due to critical modifications that occur during protein construction in *L. tarentolae*, such as glycosylation, which involves the attachment of carbohydrate molecules to the N- or C-terminus of proteins, responsible for efficient peptide folding and interaction. Moreover, many studies have shown that glycosylation improves the immunogenicity and duration of conjugated vaccines compared to non-glycosylated vaccines (14, 15). Recently, significant advances in gene editing tools and *Leishmania* genome manipulation and generation of mutant weakened parasites have been explored as a desirable means of disease management. In this paper, we have reviewed the development of genetically live attenuated *Leishmania* vaccines.

Leishmania immunology

Following the entry of *Leishmania* promastigotes into the host's dermal layer via the sandfly bite, the parasites reside in phagocytic

cells such as tissue macrophages and dendritic cells or neutrophils. *Leishmania* GP63 directly uses complement C3 cleavage to prevent complement-mediated lysis, allowing C3bi to interact with the phagocytic cell receptor CR3 for facilitating attachment and uptake. Activated dendritic cells migrate from sites of antigen acquisition to draining lymph nodes and present *Leishmania* antigens to naive T cells, accompanied by the production of cytokines leading to CD4+ and CD8+ activation. The future fate of the parasite depends on the polarization and the final phenotype of the macrophages. The differentiation of macrophages into pro-inflammatory (M1) or anti-inflammatory (M2) phenotypes, known as macrophage polarization, plays a critical role in the immune response to leishmaniasis. Resistance to *Leishmania* infection is associated with the M1 phenotype, whereas the M2 phenotype dominates in susceptible environments. The balance between M1 and M2 macrophage polarization can be regulated by cytokines produced by CD4+ Th1 and Th2 lymphocyte subpopulations. The M1 macrophage polarization is mainly due to LPS, IFN, TNF, and GM-CSF, which also activates the complement system and recruits the immune cells. The polarization of macrophages into the M2 subset by the *Leishmania* parasites under secretion of Th2 cytokines and reduction of dendritic cells results in a decrease in antigen presentation and an immunosuppressive environment that supports their survival (16–18). Toll-like receptors (TLRs) play a key role in enhancing the immune response in the context of cutaneous vaccination by identifying pathogens. Some TLR ligands, such as prokaryotic CpG oligodeoxynucleotide (ODN) motifs, are considered effective adjuvants identified by TLR9. CpG ODNs induce the production of pro-inflammatory cytokines, including IL-12 and IFN-γ, which promote the development of a Th1 immune response (19). In a case-control study, gene expression measurement of IL-12 P40, IFN-γ, IL-1β, IL-4, and IL-10 from peripheral blood mononuclear cells (PBMC) of patients with anthroponotic cutaneous leishmaniasis (ACL) who responded and those who did not respond to meglumine antimoniate treatment showed a significant increase in Th1 cytokines (IL-12 P40, IFN-γ, and IL-1β) in the responsive group and Th2 cytokines (IL-4 and IL-10) in the non-responsive group (20). It has also been reported that the CD4+ T-cell response weakens in people with symptomatic visceral leishmaniasis but could return along with central memory T-cells that induce immunity after medication (21).

Strategies to produce attenuated vaccines

Attenuated vaccines could be produced by limiting the pathogenicity of the parasite through some techniques (Table 1). Weakened pathogens as whole-organism vaccines could present a set of antigens to the immune system, limiting the effect of antigenic polymorphism and genetic variation (22). It could also simulate actual infection and potentially activate the Th1 immune response. But sometimes, depending on the attenuation method, important immunogenic epitopes cannot be generated. This is a major drawback that limits the use of attenuated vaccines in immunosuppressive conditions such as HIV infection, organ transplantation, chemotherapy, or pregnancy. Strategies used to attenuate parasites based on defined and undefined genetic alterations include chemical, physical, and genetic attenuation (Table 1).

Physical methods include techniques such as prolonged subculture, use of radiation (gamma rays or UV), and temperature sensitivity. Treatment with mutagenic agents or promastigote culture under antibiotic pressure is considered chemical attenuation. The gentamicin-attenuated *L. major* vaccine is now in clinical trials and has shown promising results in mice and humans.

On the other hand, it also defined modifications that lead to the knocking out of genes responsible for pathogenicity. Today, this approach could be a suitable alternative that reduces the potential for reversibility (23–25). In addition, unlike the old method of leishmanization, mutant parasites altered using precise gene manipulation tools led to the appearance of an improved leishmanization in terms of non-pathogenicity and protection against all divergent *Leishmania* species (26).

Genetically attenuated parasites

Good candidate gene for attenuated vaccines

Live attenuated *Leishmania* vaccines as non-pathogenic parasites that provide the immune system with whole antigens that are almost identical to the wild type stimulate immunologic memory cells and are considered potent vaccine candidates (35). Disruption of the activity of *Leishmania* genes could be achieved by knocking out one or two alleles. Parasites with one mutated allele, although showing a different phenotype from wild-type parasites, are considered dangerous vaccines due to the possibility of reversion. Knocking out two alleles results in loss of function (homozygous inactivation), thus maintaining survival in the host and culture environment and eliminating the risk of reactivation and pathogenesis, which could enhance immunity (25). The identification of *Leishmania* growth factors and virulence biomarkers, which play an important role in the immunomodulatory mechanisms and host interactions, was considered essential. The expansion of genetically live attenuated *Leishmania* vaccines could be improved through the attenuation of these biomarkers. Furthermore, the complete representation of the genetically live attenuated parasites prepares the analysis of the characteristics such as virulence and growth potential or the strength of immunogenicity (36).

There is strong evidence for the efficacy of genetically attenuated vaccines against malaria and leishmaniasis. Currently, mutant forms of Plasmodium falciparum have been produced that are reproducible parasites with the ability to be attenuated at the appropriate time of liver stage development, so-called early liver stage-arresting, replication-deficient (EARD) genetically attenuated parasites (GAP). These attenuated parasites were able to infect hepatocytes and transform into trophozoites (37). Next-generation GAPs, in addition to critical gene deletions, have acquired a specific gene sequence (gain of function) or additional function that results in the ability of the parasite to self-destruct at a desired time (38). Genetic knockout of the sporozoite liver-stage asparagine-rich protein (SLARP or SAP1) disrupts parasite growth

TABLE 1 Different live attenuated leishmaniasis vaccines according to attenuation approach.

Attenuation method	Species	Animal model	Result	References
Physical approaches				
Prolonged *in vitro* culture	• *Leishmania major* • *Leishmania tropica*	C57BL/6, BALB/c.H-2^b, BALB/c.H-2^k, BALB/c	BALB/c, BALB/c.H-2^b, and BALB/c.H-2^k have been protected partially against CL	(27)
Prolonged *in vitro* culture	*Leishmania chagasi*	BALB/c	Without immunization	(28)
Prolonged *in vitro* culture	*Leishmania amazonensis*	C57BL/6	Decrease in parasite burden and increase in IFN-γ amounts	(29)
Temperature selectivity and treatment with mutagenesis agent	*Leishmania braziliensis*	BALB/c	Complete protection against infection and reduced in lesion size	(30)
Gamma irradiation	*L. major*	CBA, BALB/c	High protection after subcutaneous challenge with *L. major*	(31)
Chemical approaches				
Chemical mutagenesis (N-methyl-N-nitro-N-nitrosoguanidine)	*L. major*	BALB/c	Reduced lesion size	(32)
Gentamicin pressure	• *L. major* • *Leishmania mexicana* • *Leishmania infantum* • *Leishmania donovani*	BALB/C	Induced protection and no skin lesion	(33)
Gentamicin pressure	*L. infantum*	Dogs	No clinical manifestation and parasite in internal organs, higher IFN-γ	(34)

in the primary liver stage before nuclear division. There is a broad consensus that the existence of the parasite in the hepatocyte, with its dynamic metabolism and restricted cell division, is necessary for long-term protection and immunity (39). The first in-human clinical trial and evaluation of the non-replicating, live, genetically attenuated *Plasmodium falciparum* sporozoite vaccine (PfSPZ-GA1), a double knockout parasite lacking the *b9* and *slarp* genes important for liver development (Pf$\Delta b9\Delta slarp$), demonstrated safety, immunogenicity, and efficacy in malaria-naive Dutch volunteers (40).

In the case of genetically attenuated *Leishmania*, there is no limit to the selection of different target genes, provided that the disruption results in parasites that can infect cells and induce strong immunity without clinical observations. Various protein gene deletions such as metabolic enzymes, signaling pathway proteins, cell surface, and cytoskeleton-related proteins could be considered as suitable interventions (26) (Table 2). Namely, mutated *L. major* parasites with deletion of gene encoding the p27 protein (41), DHFR-TS (42, 43), GP63 (44), LPG (45), *Centrin1*, and many other genes have shown a significant reduction in parasite burden and symptoms as well as high immunity to challenge (46). Characterization of some live attenuated *L. donovani* vaccine candidates with deletion of the *Centrin1* and p27 genes has shown that the expression pattern of immunomodulatory proteins, such as HSP70 and tryparedoxin tubulins, DEAD-box RNA helicases, and host-protective proteins, including cytochrome c, calreticulin, and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) are regulated in these parasites (47). Thus, these proteins could be studied as biomarkers for their role in attenuating the reproductive effect.

L. major mutant strains generated using advanced gene editing techniques, in which the targeted modification of the *Centrin* gene is accompanied by the insertion of an antibiotic resistance marker into the genome, are superior for development in Phase I human clinical trials. *L. major Centrin* gene-deleted parasites (*L.mCen*–/–) have also been shown to be safe and protective in immunodeficient mouse models. In addition, *LmCen*–/– parasites demonstrated immunity to sandfly challenge (48).

Cre-*loxP* system

The Cre-*loxP* system has been used as a genetic engineering tool to enhance recombination between two *loxP* sequences for *in vivo/vitro* studies. The Cre recombinase gene is located near an inducible promoter to perform controllable or stage-specific gene deletion during the recombination process, which is advantageous for the phenotypic analysis of different genes. Genome editing by excision action of the Cre recombinase enzyme on the sequences flanked by the locus of crossover of the bacteriophage P1 (*loxP*) sites has been used in mammalian systems, given the absence of a regulated induction system, not long ago had not been administered to *Leishmania*. The advent of diCre technology overcame some of the system's drawbacks, such as sensitivity to leakage and promoter type. In this system, the Cre protein is cleaved into two functional inactive domains and lined to FKBP12 (FK506 binding protein) and FRB (binding domain of the FKBP12-rapamycin-associated protein). The addition of rapamycin or its analogs leads to fusion and activation of the separate domains, resulting in a recombination process between *loxP* sequences.

TABLE 2 Genetically engineered live attenuated Leishmania.

Gene editing tool/gene	Function	*Leishmania* strain	Animal/cell model	Consequence	References
Homologous recombination					
Dihydrofolate reductase-thymidylate synthase (DHFR-TS)	DNA and pyrimidine synthesis	*Leishmania major*	BALB/c, Rhesus monkey	Low parasite burden and infection *in vivo* Potent immune response	(42) (43)
P27 protein	An element of cytochrome c oxidase complex associated with oxidative phosphorylation	*L. major*	Dogs	Indicating prolonged protection against virulent *Leishmania infantum* and no presence of lesion, reduced DTH reaction	(41)
Cysteine protease a and b (cpa/b)	An essential role in parasite pathogenesis	*Leishmania mexicana*	• BALB/c, C57BL/6, CBA/Ca • Hamster	Showed resistance, reduced parasite burden, and small lesions	(49) (50) (51)
B galactofuranosyl transferase (LPG 1)	Surface lipophosphoglycan synthesis	*L. major*	BALB/c	Showing a minimal delay in lesion induction	(45)
Sterol 24-c-methyltransferase (SMT)	Ergosterol synthesis	*L. major*	BALB/c, C57BL/6	Delayed in lesion induction and lower parasite load	(52)
Mannose-1-phosphate guanylyltransferase (GDP-MP)	Mannose donor in the glycosylation process	*L. mexicana*	BALB/c	Permanent immunity, complement susceptibility, decrease in parasite burden	(53)
2,4-dienoyl-coA reductase (DECR)	Essential for fatty acid β-oxidation	*L. major*	BALB/c	Reduced parasite burden	(54)
Alkyl-dihydroxy-acetonephosphate synthase (ADS1)	Ether lipid synthesis	*L. major*	BALB/c	Reduced parasite load, complement susceptibility	(55)
Fructose 1,6 bisphosphatase (FBP)	Essential role in gluconeogenesis	*L. major*	BALB/c	Induced protection against challenge, induced Th1 response, reduced parasite burden	(56)
Nucleobase transport (NT4)	Purine base uptake	*L. major*	BALB/c BMDM	Suppressing intracellular amastigotes	(57)
ATP-binding cassette protein subfamily G 1/2 (ABCG 1,2)	Membrane-bounded transporters responsible for drug resistance	*L. major*	BALB/c	• Low infection and parasite load • Homologous recombination	(58)
Mitochondrial carrier protein (MIT 1)	Iron transporter in mitochondria	*Leishmania amazonensis*	C57BL/6	No lesions, low parasite burden	(59)
Glucose transporter (GT) 1,2,3	Transport of glucose	*L. mexicana*	BALB/c	Low infection and parasite burden, without lesions	(60)
Kharon (KH)	Essential for flagellar transit of GT1, cytokinesis process and amastigote survival inside the cells	*L. mexicana*	BALB/c	Low parasite load, high IFN-γ, IgG, IL-17	(61)
Leishmanolysin (GP63)	Membranous metalloproteinase as an antigen involved in pathogenicity	*L. major*	BALB/c	Small lesions, complement, susceptibility.	(44)
KIN 29 DEATH kinesin	The motor protein inside the cell	*L. mexicana*	BALB/c	No appearance of lesion or disease	(62)
Bardet-bidle syndrome 1 protein-like (BBS 1)	Trafficking process related to primary cilium, in human	*L. major*	BALB/c	Low infection and parasite load, small lesions	(63)
Target of rapamycin kinase3 (TOR 3)	Regulation of cell proliferation and growth	*L. major*	BALB/c	Low parasite load and small lesions	(64)
PIWI-like protein 1 (PWI)	A mitochondrial argonate-like protein involved in the apoptosis process	*L. major*	BALB/c	Low parasite load and pathogenicity	(65)
Signal peptidase type 1 (SPase I)	Elimination of signal peptide portion of secretory proteins	*L. major*	BALB/c	Low parasite load, no lesion	(66)

(Continued)

TABLE 2 (Continued)

Gene editing tool/gene	Function	*Leishmania* strain	Animal/cell model	Consequence	References
CRISPR-Cas system					
Centrin1 (*Cen 1*)	A cytoskeletal calcium-dependent protein involved in proliferation and centrosome duplication	• *L. mexicana* • *L. major*	BALB/c, C57BL/6 BMDM and BMDC	Increase in NO level, IFN-γ, IL-2, TNF-α and Th1 response. Decrease in anti-inflammatory cytokines and parasite load	(67) (48)
Eukaryotic translation initiation factor 4E-1 (eIF4E1)	Translation initiation factor	*L. mexicana*	RAW264.7 Macrophage	Low infection rate	(68)
Flagellum attachment zone protein 7 (FAZ 7)	Attachment of flagellum to the cell body involved in cytokinesis	*L. mexicana*	BALB/c	Low rate of growth and pathogenicity	(69)
Protein BTN1	Involved in vacuolar transport of Arg, also in Batten disease	*L. mexicana*	BALB/c	Parasite load and lesion size have no difference in WT and CRISPR groups	(70)
diCre *loxP*					
Cdc2-related kinase 3 (*CRK3*)	Involved in *leishmania* proliferation, a functional homolog of CDK1	*L. mexicana*	BALB/c	Lower parasite burden and smaller lesion of the footpad	(71)

This technique is an effective way to reduce the side effects of overexpression of active, potentially cytotoxic Cre recombinase. The diCre approach is unlikely to apply to some important genes that are organized in multi-copy arrays. Also, diCre will not avoid compensatory genetic reorganization in long-term null mutant studies (72, 73). For example, the inducible diCre system was used to knock out the *CRK3* gene in *Leishmania*, demonstrating the requirement for *CRK3* function in the regulation of mitosis and clearly showing growth failure in the cells 48 h after targeted deletion of *CRK3* (71).

CRISPR

Clustered regulatory interspaced short palindromic repeats—the CRISPR/Cas system is a defense mechanism in bacterial microorganisms against foreign genetic material. CRISPR-Cas interference occurs when an infection occurs, and viruses or foreign plasmids enter the bacterial cell. After infection, unknown genetic sequences integrate into the bacterial CRISPR locus as spacer arrays, conferring immunity to subsequent infections associated with these viruses. RNA polymerase then transcribes pre-CRISPR RNAs (pre-crRNAs) from the spacer sequence of the CRISPR region, which eventually bind to Cas nucleases and form hydrogen bonds specifically with the DNA sequence target. This is accompanied by a transcription of the trans-activating crRNA (tracrRNA) from the CRISPR locus, leading to the maturation of the pre-crRNA by the enzyme RNase III and crRNA-directed DNA cleavage. The tracrRNA: crRNA complex is packaged with CRISPR-associated nuclease (Cas) to form a ribonucleoprotein (RNP) complex. This active complex releases Cas nuclease to create a double-strand break (DSB) in the DNA at the target sequence correlative to the crRNA sequence (72, 73). The Cas9 endonuclease, the class 2 type II CRISPR system, is the most widely used and precise genome editing tool. The first Cas9 endonuclease used in mammalian systems for gene editing belongs to *Streptococcus pyogenes*. The Cas9 enzyme has two endonuclease domains, RuvC and HNH, which cleaves the DNA strand non-complementary to the spacer sequence and the complementary strand, respectively (74, 75). Adhesion of the Cas-RNA complex to the target DNA spacer sequence (~20 nucleotides) near the protospacer adjacent motif (PAM 5′-NGG) induces the two Cas9 domains to cooperate, resulting in blunt double-strand breaks in DNA (76). Most of the DSBs could be repaired by DNA repair systems, including microhomology-mediated end joining (MMEJ) or homology direct repair (HDR) (77).

CRISPR technology has several advantages, such as its availability and simplicity for consumers, high efficiency, and suitability for genetic screening, which have allowed the application of this technique in all major fields (78). However, despite the efforts that have been made, there are some major concerns and limitations for the adoption of CRISPR/Cas9. The high incidence of off-target genome editing, probably more than 50%, has been observed and is mostly related to DNA modifications in non-specific regions or by misguidance of single guide RNA (sgRNA). An efficient approach to reduce off-target effects is to use Cas variants such as Cas9 nickase, which produces single-stranded breaks, whereas a double sgRNA targets both DNA strands at the target site and produces the DSB. Another limitation of CRISPR/Cas9 is the need for a PAM sequence adjacent to the target region.

CRISPR could cause DNA damage and apoptosis as a result of DSBs rather than the targeted gene editing (75). CRISPR has great superiority in indel efficiency in various cells compared to some gene-editing nucleases, but insufficient indels and high HDR could be increased depending on the variation of the target region (78). Designing an efficient gRNA for post-transcriptional modification of mRNA is a challenge for CRISPR technology. In 2014, Gao et al. designed an artificial gene RGR (ribozyme-gRNA-ribozyme) that promotes guide RNA production feasible (79). In addition, targeted delivery of CRISPR/Cas9 effectors is critical. Delivery methods vary depending on the cell type

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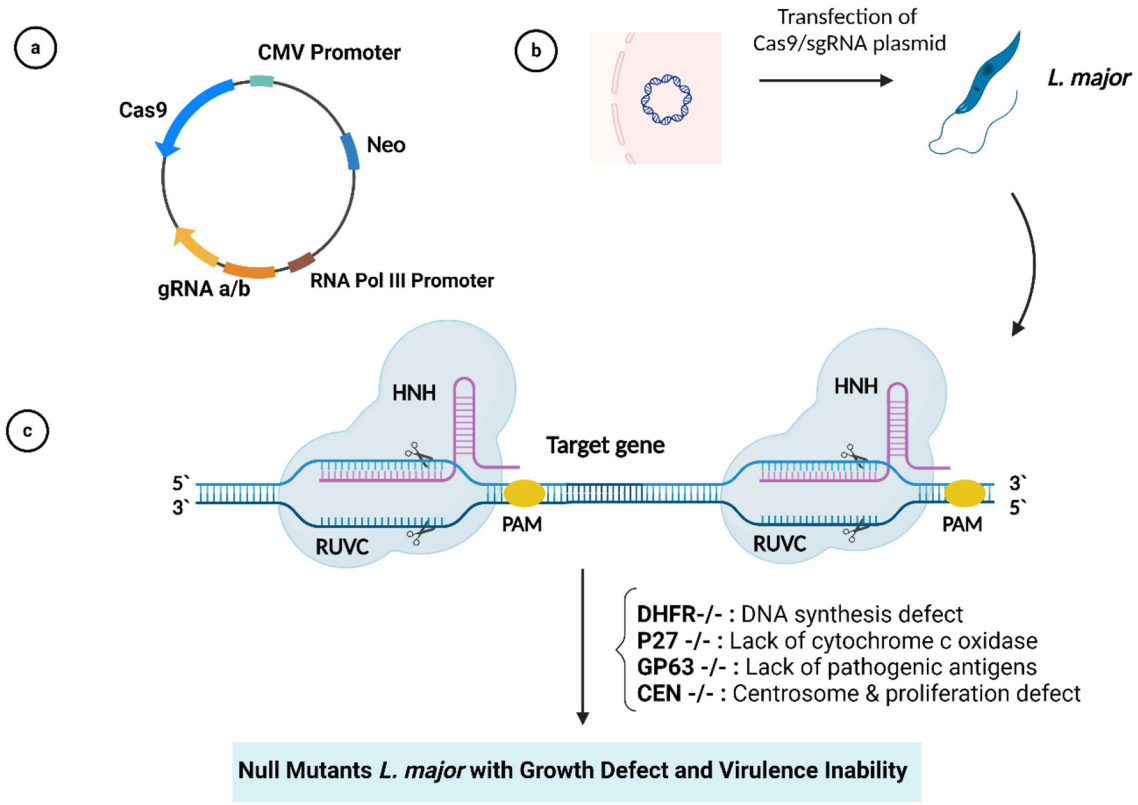

FIGURE 2
(A) Plasmid with Cas9/gRNA sequences. **(B)** Plasmid transfection into *Leishmania major*. **(C)** CRISPR/Cas9-mediated target gene deletion.

and include physical methods and viral methods (adenovirus or lentivirus vectors).

To date, major improvements in gene editing tools such as CRISPR technology have enabled the creation of genetically modified parasites with reduced virulence, persistent survival, and growth rate (35). Recent studies have shown that *Leishmania* strains, as polyploid organisms, have more than one set of chromosomes, and that genome evolution and repair mutations lead to the breakdown of the gene editing process. *Leishmania* could adapt to unstable situations through evolutionary mechanisms; furthermore, this parasite makes use of heterogeneous genome and regulatory procedures at different levels such as genomic, transcriptomic, and translational steps, which contribute to the ultimate survival and reversion of the pathogen so that genetic manipulation of crucial genes of trypanosomatids is considered more challenging than it seems (26, 80). Before the CRISPR-Cas9 era, gene deletion in *Leishmania* was more challenging due to low recombination capacity and the presence of an extra chromosome. Since the initial approval of CRISPR/Cas9 technology in *Trypanosoma cruzi*, *Leishmania,* and *Trypanosoma brucei*, gene replacement in trypanosomatids has become convenient and time-saving. It has also contributed to the study of basic biological mechanisms and functions in parasites (81).

Second-generation leishmanization was presented by introducing an attenuated *L. major* strain mutated in the *Centrin1* gene (a cytoskeletal protein involved in mitosis) (*LmCen*−/−) using the CRISPR/Cas system (Figure 2). This attenuated parasite was found to be free of antibiotic resistance markers and there were no detectable off-target mutations, allowing it to be developed into a Phase 1 clinical trial. Animal models immunized with this attenuated vaccine showed a strong immune response but no visible lesions after the challenge with the infected sandfly, while non-immunized mice showed visible lesions and higher parasite loads. *LmCen*−/− is considered safe and effective compared to conventional leishmanization. It does not induce leishmaniasis in immunocompromised animals but does induce host immunity against sandfly infection (48). Of note, to fully exploit the editing potential of CRISPR/Cas9, they must be successfully delivered into target cells or tissues using appropriate viral and non-viral vectors, as reviewed in Goyal et al. (82) and Ayari-Riabi et al. (83).

Overall, new live vaccine platforms are also being explored but are still in the early stages of development for use against infectious pathogens. However, similar to classical whole-organism vaccine platforms, these novel vaccines also require the cultivation of the pathogen. Moreover, one of the disadvantages of this platform is that it must be delivered directly into cells, which requires a special injection device or a carrier molecule and carries the risk of low transfection rates and limited immunogenicity. However, next-generation live vaccines can be constructed using only the genetic sequence of the pathogen, significantly increasing the speed of development and manufacturing processes.

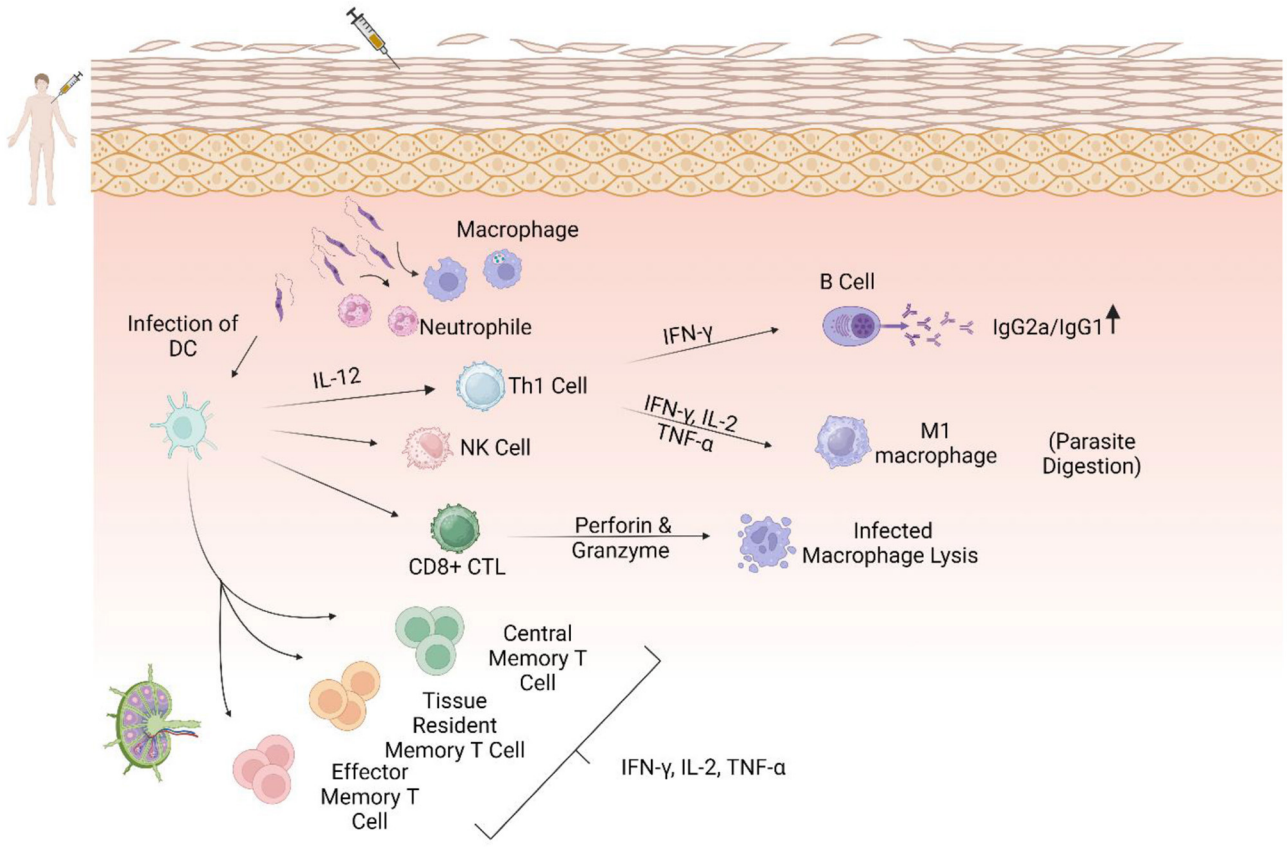

FIGURE 3
The central role of the Th1 response in immunization against leishmaniasis. Dendritic cells as antigen-presenting cells (APCs) after some interactions, including TLR4-L. LPG and phagocytic process, migrate to the lymphatic drains, activate CD4+ and CD8+ T cells, and secrete IL-12, which could promote a Th1 immune response. Th1 cells secrete pro-inflammatory cytokines such as IL-2, IFN-γ, and TNF-α, which activate M1 macrophages and increase NO and ROS production, leading to parasite clearance. In addition, CD8+ cells become cytotoxic T cells that produce perforin and granzymes that lyse infected macrophages. Increasing the ratio of IgG2a/IgG1 could lead to a protective immune response.

Immunization of genetically live attenuated vaccines

The development of genetically modified live attenuated *L. major Centrin*-deleted parasites as a second method of leishmanization could induce protection via the action of IFN-γ-secreting Ly6+CD4+ T effector cells and multifunctional T cells that secrete cytokines such as IFN-γ, which is necessary for their production and survival. The *LmCen−/−* vaccine could also generate CD4+ skin tissue-resident memory (TRM) T cells that proliferate at the site of infection and secrete more IFN-γ and granzyme B in immunized animal models (46, 48). Central memory T cells (TCM) and skin TRM have been characterized as *Leishmania*-independent memory T cells (Figure 3). TRM cells are particularly suitable for protection, probably due to their localization and recruitment following vaccination or *Leishmania* infection. Following the parasite challenge, TRM cells immediately begin to reduce parasite loads, and it has been suggested that development strategies involving these cells will be helpful in pursuit of a leishmaniasis vaccine (84).

In addition, Greta Volpedo et al. reported that immunization with *Centrin*-deficient *L. mexicana* also results in higher levels of IL-12 and generation of central memory T cells (CD4+CD44+CD62L+) and significantly higher Th1 immune responses in the skin and lymph nodes of BALB/c mice compared to non-immunized mice. Overall, the ratio of IFN-γ/IL-10 to IFN-γ/IL-4 represents the physiological balance between Th1 and Th2 responses that determines disease outcome and can make the difference between resistance and susceptibility. However, when compared to the New World *Leishmania* strains that cause cutaneous disease, *L. major* exhibits different immunological characteristics and pathologies. Analysis of metabolic responses in immune cells following immunization with *LmexCen−/−* revealed increased aspartate metabolism and pentose phosphate pathway (PPP), which induce M1 polarization in macrophages, and PPP also promotes nitric oxide production. In addition, increased taurine/hypotaurine metabolism at the site of infection and linoleic acid in lymph nodes could motivate macrophage and T-cell activation against the parasite. In addition, arachidonic acid (AA)—an endocannabinoid metabolite with significant anti-inflammatory properties—showed an escalation in the course

of infection *in vivo*. In general, the discovery of metabolic and immunological interactions following *Leishmania* vaccination could improve the development of innovative strategies in vaccine formulation (67). Given the endemicity of CL, a vaccine that prevents severe disease could have a significant impact on public opinion. However, a live attenuated vaccine that could also block parasite infection and thus prevent both cutaneous manifestations would have a much greater impact by reducing community transmission and potentially establishing herd immunity. Advances in molecular parasitology, creating deleterious gene mutations, altering replication fidelity, optimizing codons, and exerting control through genetic engineering tools, particularly the CRISPR/Cas9 system, which offers new ways to control *L. major* infection and replication, are renewing interest in a new generation of live attenuated vaccines, although potentially safer and more broadly applicable live vaccines require further testing before further advancing to human trials.

Conclusion

The spectrum of leishmaniasis varies due to host genetics and situation, parasite strain, and climate change. However, enough studies have shown that different forms of leishmaniasis can be prevented by vaccination. Unfortunately, there is currently no vaccine approved for human immunization on the global market. The development of an effective vaccine depends on its profitability for key stakeholders, vaccine developers, and manufacturers. Vaccine production requires a high level of trust in the public interest. Of course, government support attention to public health problems and international reflection are considered effective. Great advances have been made in the field of biological technologies to expand the range of vaccines. Recombinant multi-peptide adjuvanted vaccines such as *Leish*-F1 + MPL-SE and adenovirus-based DNA vaccines such as ChAd63-KH are now available. The priority of live attenuated *Leishmania* vaccines is considered to be a strong technique for the control of leishmaniasis, which has gained great attention due to the improvement of genetic engineering technologies such as the CRISPR/Cas system. The evaluation of gene candidates in terms of efficacy and immune response against the wild parasite has shown that *Centrin1* is the most encouraging and is recognized as a good option for genetically live attenuated *Leishmania* vaccines. As we know, all the *in vivo* studies have been performed in animal models, which represent the early stages of the development of genetically attenuated vaccines and have not yet reached human clinical trials. In general, confirmation of logical guidelines related to live attenuated *Leishmania* development could administer a fine direction to major studies before handling human clinical trials and seriously reorganize the timeline of vaccine candidates.

Author contributions

ZR: Investigation, Visualization, Writing – original draft. HD-M: Conceptualization, Investigation, Project administration, Supervision, Validation, Visualization, Writing – review & editing. ME: Conceptualization, Investigation, Writing – review & editing. HK: Funding acquisition, Project administration, Resources, Supervision, Writing – review & editing.

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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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Towards contextualized complex systems approaches to scaling-up hepatitis B birth-dose vaccination in the African region: a qualitative systematic review

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Background: Despite the longstanding implementation of universal hepatitis B infant vaccination programs, the World Health Organization African region (WHO AFRO) maintains the highest prevalence (2.5%) of chronic hepatitis B virus (HBV) infection among children ≤5 years of age. Scaling-up hepatitis B birth-dose (HepB BD) vaccination could avert mother-to-child transmission of HBV infection and advance regional progress towards eliminating viral hepatitis.

Objective: To describe whether – *and how* – complexities within the health system or intervention influence the performance of HepB BD vaccination programs in the WHO AFRO.

Methods: Using a complexity perspective, we conducted a qualitative systematic review of literature published between 2009–2022. A Boolean search strategy retrieved relevant literature indexed in PubMed, EBSCOhost databases, Scopus, and Web of Science, with supplementary searches conducted to identify any missed articles. No language restrictions were applied. Data extraction, synthesis and analysis were guided by a systems-based logic model tailored to systematic reviews of complex interventions.

Results: Our search yielded 672 published records. Of these, 28 (26 English, 2 French) were eligible for inclusion. Among the 12 WHO AFRO member states represented, the origin of evidence weighted highest in Nigeria ($n = 12$) and Senegal ($n = 5$). The performance of HepB BD vaccination programs across member states are influenced by underlying complexities across eight cross-cutting themes: (i) availability and interpretation of HepB BD vaccination policies, (ii) capacity of vaccine supply and cold chain systems, (iii) availability of equitable and sustainable financing, (iv) capacity and capability of health care workers (HCWs), (v) immunization monitoring systems and impaired feedback loops, (vi) influence of context vs system design on the timeliness of vaccination, (vii) maternal knowledge and socio-economic factors, and (viii) wider contextual factors (geography, climate, cultural practices).

Conclusion: Countries looking to introduce, or scale-up HepB BD vaccination programs will benefit from careful consideration of components of the intervention design that are dependent on the end-user's context and capabilities in accessing the vaccine; the adherence and interpretation of essential components of the policy; the provision of adequate support of stakeholders specifically HCWs and government ministries; and the need for innovative

approaches to underlying complexities. Lessons offered by these African experiences provide pragmatic approaches to successfully implementing HepB BD vaccination programs in the region.

KEYWORDS

Africa, birth-dose, complexity, health systems, hepatitis B, maternal and child health, vaccine

1 Introduction

Vaccination of newborns within 24 h of life with a single dose of the hepatitis B vaccine is pivotal to preventing mother-to-child-transmission (MTCT) of hepatitis B virus (HBV) infection. Acquisition of HBV infection through MTCT is a major public health concern as this carries a 90% risk of progression to chronic HBV infection, leading to liver cirrhosis, end-stage liver disease, liver cancer and premature death (1). Globally, 254 million persons are chronic carriers of HBV (2). The highest prevalence rates are borne by the World Health Organization (WHO) Western Pacific (5.9%) and African (WHO AFRO) regions (7.5%) (3). Of particular concern within the WHO AFRO is the fact that 2.5% of children under the age of five years currently live with chronic hepatitis B despite it being entirely vaccine preventable (3). This disease burden is unacceptably higher than that in any other region in the world, and without urgent intervention, portends derailment of the global progress towards eliminating viral hepatitis as a significant public health threat by 2030 (4).

Among the available strategies for the prevention of chronic HBV infection, hepatitis B vaccination has been recognized as the most effective (5). Universal hepatitis B infant vaccination initiated at 4 or 6 weeks of age, has long been implemented in all 47 WHO AFRO member states (6), achieving over 70% coverage since 2014 (7). Despite this the region maintains the highest burden of chronic HBV infection among under five-year-olds, surpassing the global prevalence of 0.9% (3). The WHO recommendation on hepatitis B birth-dose (HepB BD) vaccination for the prevention of HBV MTCT has been in place since 2009 (5, 8). Further to this, the World Health Assembly in 2016 endorsed the WHO goal to eliminate hepatitis B as a global public health threat by 2030, in part by achieving 90% coverage of timely HepB BD and infant vaccinations (9, 10). Steady progress has been made in the global arena with 115 of 194 WHO member states adopting national HepB BD vaccination programs, although the coverage rate (45%) remains a concern (2, 9, 11). While the Western Pacific region has been able to attain a HepB BD vaccination coverage of 80% in response to its regional burden of disease, the 18% achieved across the 15 WHO AFRO member states that have thus far adopted HepB BD vaccination policies, is a dismal contrast (2, 11, 12).

Recognizing the inequitable implementation and poor program performance of HepB BD vaccination in Africa, several studies have sought to identify what the contributing determinants are (12). These studies note that the sub-optimal program performance is underpinned by a multiplicity of factors including, weak service delivery and inefficiencies across broader health systems, limited skilled health workforce trained to attend to birth and conduct post-natal visits, and the absence of political will to implement the program (10, 12, 13). Previous evidence syntheses on this research focus have relied on limited empirical data from the African region, which tends to provide limited exploration of attendant complex systemic factors (12, 14, 15).

It has been established that complex interventions are likely to have profound system-wide effects which tend to be more evident in weak health systems (16). Petticrew et al. (17), offer a pragmatic approach to conducting robust systematic reviews of complex interventions. Hepatitis B birth-dose vaccination programs meet the definition of a complex intervention on account of the limited degree of flexibility in the timing of administration of the vaccine (within 24 h after birth) to achieve maximum effectiveness, the occurrence of multiple mediators and moderators of effect throughout the program implementation process, and the presence of feedback loops where changes in behavior among the people at the center of the program (including program implementers, external partners and donor agencies, policy- and decision-makers, and end users) encourage further behavioral change and thereby influence the performance and outcomes of the intervention (17, 18). To support rational reforms to existing policy, practice, and future research, we examine if (*and how*) complexity within the health system and / or intervention influence the performance of HepB BD vaccination programs in the WHO AFRO.

2 Methods

Using a complexity perspective, an exploratory qualitative systematic review study was conducted in two phases aimed at improving our limited understanding of the interaction between HepB BD vaccination programs and health systems in Africa. The first phase involved a scoping review which then informed the research protocol and execution of the qualitative systematic review in phase 2. The protocol is available at the University of Cape Town repository (https://open.uct.ac.za). Phase 1 was essential in gaining an in-depth and up-to-date understanding of the HepB BD vaccination landscape in the region, highlighting the challenges of its implementation in differing contexts (12). Details of this phase are available in the published scoping review (12). A primary outcome thereof was an adapted systems-based logic model for understanding complexities underlying the implementation of HepB BD vaccination programs (18). The themes derived from the logic model were then used to organize and analyze the findings of this systematic review alongside methodological guidance from Petticrew et al. (17) on conducting systematic reviews of complex interventions. Furthermore, this systematic review adopted the Joanna Briggs Institute (JBI) approach to qualitative synthesis (19) and was conducted in line with the updated Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA 2020) guidelines, see Supplementary File 1 (20).

2.1 Literature search strategy

A Boolean search strategy comprising of key search terms and search term synonyms was developed drawing on the target population, intervention, and outcomes. Using this search strategy, peer-reviewed literature was sought from several electronic databases and platforms, namely, PUBMED (including MEDLINE), EBSCOhost (Academic Search Premier, Africa-Wide Information, CINAHL, Health Source: Nursing/Academic Edition, APA PsycInfo), Scopus, and Web of Science (excluding MEDLINE). The complete strategy for each database is provided in Supplementary File 2. Supplementary searches were also conducted by reviewing bibliographies of key articles in order to identify any relevant records that may have been missed by the electronic database searches. Further to this, recommendations on key literature from co-reviewers were obtained and Google Scholar alerts activated to assist in the identification of any upcoming research in the field throughout the review period. Search terms used for Google Scholar alerts included "Hepatitis B birth dose vaccine OR vaccination OR vaccinated," "Africa OR African," "deprived country OR countries OR populations." The final literature search date was 30 September 2022.

2.2 Eligibility criteria

Literature sources were included if they met the following criteria: empirical studies of quantitative, qualitative, or mixed methods study designs involving human participants; primary studies conducted in one or more of the WHO AFRO member states; and research exploring HepB BD vaccination as a primary or secondary outcome measure and its complex interactions with the health system. Only articles with accessible abstracts and full texts were included in this review. The search was limited to literature published between 2009–2022, due to the WHO recommendation of universal HepB BD vaccination for all member states since 2009 (8, 21). This time frame ensured relevant and recent literature sources were retrieved and allowed for the observation of country progress in the adoption and implementation of HepB BD vaccination programs. We did not place any restriction on the language of publication in order to lessen the likelihood of language and publication bias, especially given the multi-lingual context within the WHO AFRO. Literature sources were excluded if they were found to, (i) only measure epidemiological outcomes of vaccination; (ii) only investigate hepatitis B infant vaccination administered from 4 or 6 weeks after birth or vaccination programs other than HepB BD vaccination; and (iii) involve research only conducted in non-WHO AFRO member states. Furthermore, reviews, modelling studies, reports and commentaries were excluded from this systematic review.

2.3 Literature screening and selection

All search results were imported from the respective databases to Mendeley Desktop® reference manager (22). After removal of duplicates in Mendeley®, literature sources were exported to Rayyan®, a web-based application for systematic reviews (23). Further duplicates were then detected and resolved. Thereafter title and abstract screening continued in Rayyan®, guided by the eligibility criteria. Full texts of studies earmarked for potential inclusion were then retrieved and reviewed for relevance and eligibility. The literature search and screening process was conducted by the primary author (TS-R) and the co-reviewers (EA-D and JO). Where discrepancies arose, a decision was made through discussion and consensus among all reviewers.

2.4 Critical appraisal

Following the selection of full texts for inclusion, each eligible study underwent a quality appraisal. Critical appraisal tools developed by the Critical Appraisal Skills Programme (24), the Mixed Methods Appraisal Tool (25) and the assessment scale by Dufault and Klar (26) adapted by Cortes-Ramirez et al. (27) were used as appropriate. The current practice of quality appraisals encourages a description of the judgement of ratings, as opposed to an overall score (24, 25). However, this can be problematic when attempting to report the overall results of multiple appraisal tools applied in a single systematic review. In this systematic review, metrics were developed and used to describe the overall judgement of quality for each study. The Mixed Methods Appraisal Tool scoring was based on the 2011 version (28) and has been used in previous systematic reviews (29, 30). Overall scores were calculated as a percentage of the criteria met (20–100%) (28). In the case of mixed methods studies the percentage of the lowest study component was awarded as the overall score (28). Similarly, we quantified responses to questions in the Critical Appraisal Skills Programme tool (Yes = 1, No = 0, Cannot tell = 0.5) as done in other systematic reviews (31, 32). Overall scores calculated were judged as low-, medium-, or high-quality dependent on their correlated scores within the first-, second- or third- thirds of the total, respectively. The adapted Dufault and Klar assessment scale correlated scores with the overall judgement from low (<5 points) to high (>8 points) relevance (27). Studies considered to be of low quality were not automatically excluded but reviewed and discussed among co-reviewers in order to further evaluate the relevance and value against the quality shortfalls identified. Furthermore, ethical consideration and rigor were assessed by reviewing evidence of author reflexivity and affiliations, transparency on sources of research funding, and declarations of potential conflicts of interest.

2.5 Data extraction

The data extraction process was guided by the adapted systems-based logic model tailored to systematic reviews of complex interventions, developed during the preceding scoping exercise, and drawing on the workings of Rohwer et al., on how to make sense of complexity in systematic reviews (12, 18). A study-specific data extraction sheet was designed using this logic model to identify essential variables and interactions within HepB BD vaccination programs, such as: context, intervention design/delivery/execution, and intermediate/health and non-health outcomes (Supplementary File 3). The data extraction sheet provided a standardized systematic record of the data summaries attained from every literature source, ensuring traceability and validity of the data extracted.

2.6 Data synthesis and analysis

Descriptive, analytical, and qualitative data extracted from eligible studies were synthesized. Relevance and organization of the data was driven by the theoretical model, and broadly categorized as a feature of implementation, intervention, context, or outcomes. An inductive thematic analysis process was then undertaken with the development of codes and relevant themes. Themes were interpreted for underlying complexities of the intervention or through possible interaction with contextual factors in the intervention causal pathway. In studies where national HepB BD vaccination policies have been adopted, an exploration of both enabling factors and constraints to program implementation was done. In those studies where HepB BD pilot interventions or in-depth inquiries have been conducted in the absence of nationwide program adoption, an exploration of anticipated influential factors was performed.

3 Results

The literature search yielded a total of 672 published records. These consisted of 666 articles retrieved via electronic databases, 4 from supplementary bibliographic searches, one from a co-reviewer recommendation and another through a Google Scholar search alert. After deduplication, title and abstract screening, and full text review, 28 articles were judged to be eligible for inclusion in this systematic review, see Figure 1.

3.1 Characteristics of included studies

The 28 studies included in this systematic review reported on findings from 12 WHO AFRO member states namely, Nigeria, Senegal, Uganda, The Gambia, Mozambique, São Tomé and Príncipe, Burkina Faso, Ethiopia, Côte d'Ivoire, Benin, Namibia, and Botswana. Included in this tally was one multi-country study reporting findings from five African countries (Nigeria, Namibia, Botswana, São Tomé and Príncipe, and The Gambia) (33). The evidence distribution weighted greatest in Nigeria ($n = 12$), followed by Senegal ($n = 5$). Two studies reported on global findings with results aggregated by region. Of these findings only those relating to the African region were extracted and synthesized. Of the 28 included studies, 26 were published in English and 2 in French. A member of the research team who is a native French speaker worked closely with the primary

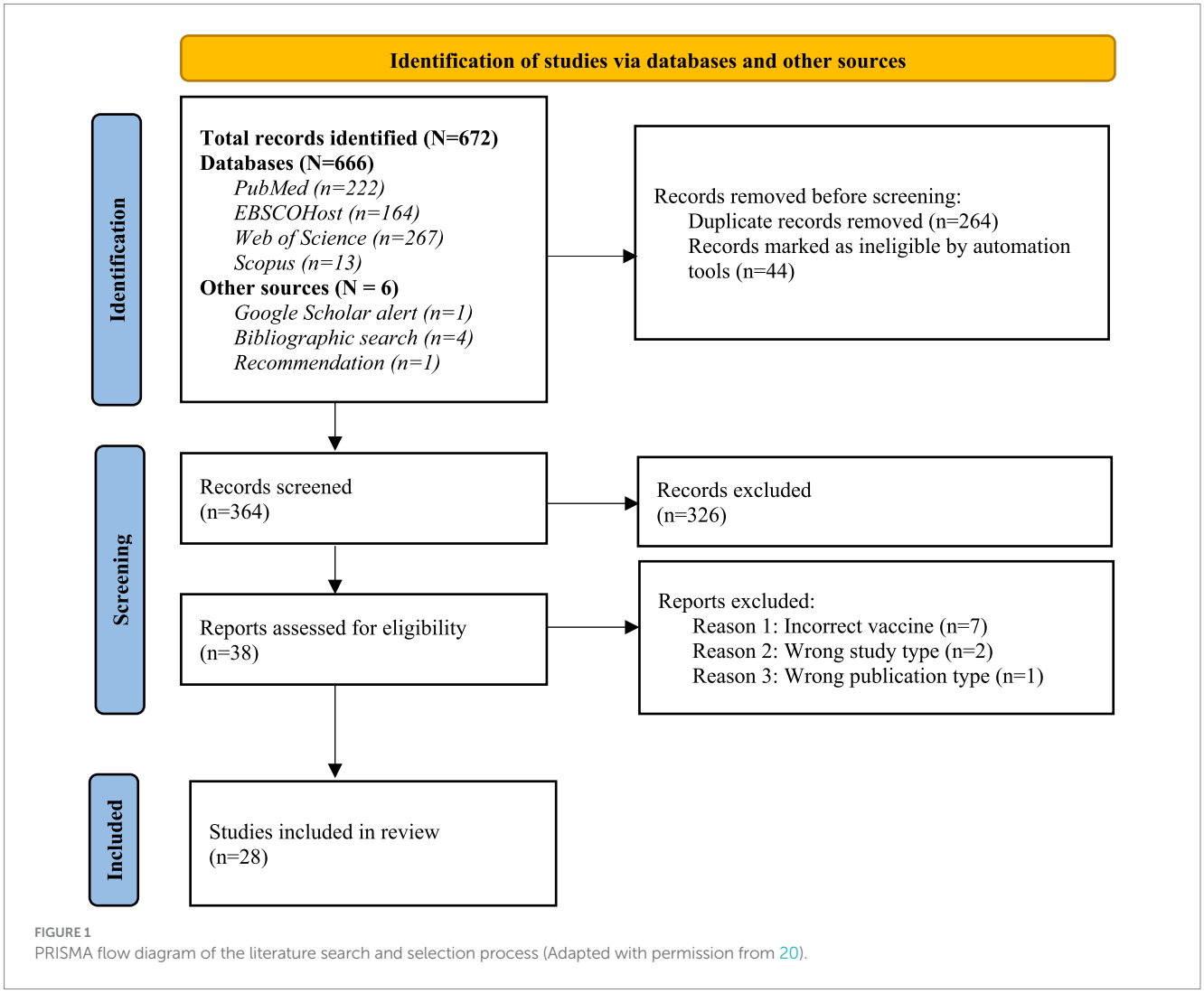

FIGURE 1
PRISMA flow diagram of the literature search and selection process (Adapted with permission from 20).

author (TS-R) to screen, extract and analyze data from these papers with oversight from co-reviewers. A summary of the characteristics of included studies can be seen in Table 1.

Most studies (64.3%; $n = 18$) adopted quantitative cross-sectional designs. The remainder used qualitative ($n = 2$), quantitative cohort ($n = 4$), mixed methods ($n = 3$) and quasi-experimental ($n = 1$) study designs. Based on the methodology, a cross-sectional study was more accurately judged and appraised as having used an ecological study design. One of the qualitative studies included a cost-effectiveness analysis, however for the purpose of this systematic review only the qualitative outcomes were assessed and analyzed. Mothers and mother-infant pairs combined were the largest population group and source of information amongst the studies. Disaggregation of study populations further delineated pregnant women ($n = 4$; 14.3%), mothers ($n = 1$; 3.5%), infants/children ($n = 6$; 21,4%), health care workers (HCWs) ($n = 3$; 10.7%), health facilities ($n = 3$; 10.7%) and countries ($n = 2$; 7.1%). Among those studies involving pregnant women, two were longitudinal studies which provided further information on infants born to these cohorts upon follow-up. Data sources from health facilities and countries included regional experts in the field, informants from the Ministry of Health (MoH), HCWs involved in vaccination services, and partner or stakeholder organizations.

The included studies predominantly focused on identifying factors associated with the performance of HepB BD vaccination

TABLE 1 Summary of characteristics of included studies.

Study characteristics ($N = 28$)	Categories among included studies	No. of studies
Country	Nigeria	12
	Senegal	5
	São Tomé and Príncipe	1
	The Gambia	1
	Uganda	1
	Burkina Faso	1
	Mozambique	1
	Côte d'Ivoire	1
	Ethiopia	1
	Benin	1
	Global	2
	Multi-country (Botswana, Namibia, The Gambia, Nigeria, São Tomé and Príncipe)	1
Publication language	English	26
	French	2
Study design	Quantitative cross-sectional	18
	Quantitative cohort	4
	Qualitative	2
	Mixed methods	3
	Quasi experimental	1
Study population	Mother-infant pairs	9
	Infants/children	6
	Mothers	1
	Health care workers	3
	Pregnant women	4
	Countries	2
	Health facilities	3
Primary focus of study	Factors associated with vaccination program performance	14
	Evaluation of broader immunization-related programs	4
	Efficacy of hepatitis B vaccination program regiments	1
	Knowledge, awareness, perceptions, and practice in key populations	9
Vaccination strategy	Universal	20
	Selective	4
	Universal and selective	1
	Not reported	3

programs (14/28, 50%). Of interest, 9/14 (64.3%) studies specifically focused on adherence to the timeliness of HepB BD vaccination of which 7/9 (77.8%) were conducted in Nigeria. A limited number of studies (4/28, 14.3%) evaluated the performance and outcome of broader routine immunization-related programs, with HepB BD vaccination serving as one of several performance indicators. These studies were able to demonstrate vaccine effectiveness in real-life settings. One other study (1/28, 3.6%) determined vaccine efficacy when comparing HepB BD vaccination followed up by two vs three doses of the hepatitis B vaccine in infancy. The remainder were concerned with knowledge, awareness, practice, or perception of HepB BD vaccination (9/28, 32.1%) among key populations such as HCWs (5/9, 55.3%) and pregnant women or mothers (4/9, 44.4%), see the detailed study characteristics in Supplementary File 4. Of the 28 studies, 25% ($n=7$) were conducted at a time when the relevant countries did not have a national policy for HepB BD vaccination in place. Seventy-one percent of the studies ($n=20$) were conducted in settings that had implemented universal HepB BD vaccination, while 14.3% ($n=4$) employed selective HepB BD vaccination, and 10.7% ($n=3$) did not report their implementation strategy. The multi-country study ($n=1$) reported on both universal and selective HepB BD vaccination programs in the individual countries investigated.

Regarding the quality of included studies, twenty-one studies were appraised using the Mixed Methods Appraisal Tool (25), six using the Critical Appraisal Skills Programme (24) tool and one using the adapted Dufault and Klar assessment scale (26, 27). Three papers were judged as being of lower quality (Table 2). Notably, those employing a mixed method design were inclined to perform better on the quantitative study components compared to the qualitative ones, which brought down their overall quality ratings. The lowest rated study was a cross-sectional study which did not include details on sample representativeness, or control for possible confounding or modifying factors. None of those judged as low quality were excluded as the data still provided considerable value within context. Nevertheless, overall average scores were high (Table 2).

TABLE 2 Quality appraisal of included studies.

Author, year	Appraisal tool	Overall quality judgement
Accrombessi et al. (2020) (55)	MMAT	
Aina et al. (2017) (43)	MMAT	
Allison et al. (2017) (51)	Dufault and Klar	
Bagny et al. (2015) (45)	MMAT	
Bassoum et al. (2021) (58)	MMAT	
Bassoum et al. (2022) (57)	MMAT	
Chang et al. (2019) (47)	MMAT	
Dagnew et al. (2020) (60)	MMAT	
Djaogol et al. (2019) (44)	MMAT	
Goodman et al. (2013) (49)	MMAT	
Guingané et al. (2020) (54)	CASP	
Hagan et al. (2019) (46)	CASP	
Jaquet et al. (2017) (56)	MMAT	
Loarec et al. (2022) (52)	CASP	
Miyahara et al. (2016) (50)	CASP	
Nankya-Mutyoba et al. (2022) (73)	CASP	
Okenwa et al. (2019) (34)	MMAT	
Okenwa et al. (2020) (36)	MMAT	
Olakunda et al. (2021) (37)	MMAT	
Périères et al. (2021) (53)	MMAT	
Sadoh et al. (2014) (41)	MMAT	
Ibrahim et al. (2022) (38, 39)	MMAT	
Ibraheem et al. (2022) (38, 39)	MMAT	
Ibraheem et al. (2019) (35)	MMAT	
Sadoh et al. (2013) (40)	MMAT	
Danjuma (2020) (42)	MMAT	
Bada et al. (2022) (59)	CASP	
Moturi et al. (2018) (33)	MMAT	

Overall judgement of quality: Mixed Methods Appraisal Tool (MMAT) calculated as a percentage of criteria met, mixed method designs awarded an overall score equivalent to the lowest rated study component of the study; Critical Appraisal Skills Programme (CASP) tools overall scores are calculated and then rated as being in the first, second or last third of the total with the overall judgement correlated as low, medium or high quality respectively; Dufault and Klar assessment scale measures overall judgement of relevance from low (<5 points) to high (>8 points) relevance. In this table: red = low quality; yellow = medium quality; green = high quality.

3.2 Sources of complexity in the performance of HepB BD vaccination programs

Eight cross-cutting themes were identified across the included studies. These themes describe the complexity found at the intersection of HepB BD vaccination programs and the health systems that deliver them. These eight themes are listed and further unpacked in Table 3. The "influence of wider contextual factors on timely HepB BD vaccination" was the most frequently identified theme (19 of 28 studies) while that on the "role of immunization monitoring systems and impaired feedback loops" was less frequently researched (11 of 28 studies). A summary of the geographic spread of these themes can be seen in Figure 2.

3.2.1 Availability and interpretation of HepB BD vaccination policies

The influence of policy was not explicitly investigated by any of the studies included in this review. Among the 13 studies briefly touching on the direct or indirect role of policy in the implementation of HepB BD vaccination programs, it was important to note the variations in interpreting global recommendations, often resulting in disparate outcomes. The selective vaccination policy in São Tomé and Príncipe was found to be a principal barrier to achieving high HepB BD vaccine coverage rates in the country (33). In studies conducted in Nigeria, guidelines from the National Primary Health Care Development Agency allowed HepB BD vaccination to be administered up until two weeks after birth (34–37). This guideline was open to misinterpretation, likely misleading both HCWs and mothers into assuming the vaccination between day 0 and 14 would infer the same level of protection or effectiveness against HBV MTCT. The average age at HepB BD vaccination in Nigeria ranged across 6 days (38), 12 days (39), 14.3 days +/− 15.6 days (40), and

TABLE 3 Frequency of themes identified among included studies.

Theme	Frequency of theme (*N* = 28)	Example of theme
Availability and interpretation of HepB BD vaccination policies	13	National policy on HepB BD vaccination allows for the vaccine to be administered up until 14 days post birth (34)
Capacity of HepB BD vaccine supply and cold chain systems	15	Stock outs ranked 3rd in the reasons for delay in vaccine uptake among mothers (42)
Availability of equitable and sustainable financing for HepB BD vaccination programs	17	Pregnant women expressed concerns about unaffordable cost of the vaccine and charges they may incur should the program be implemented in their country (48)
Capacity and capability of HCWs delivering HepB BD vaccination programs	16	~50% of the medical practitioners surveyed in a study thought it safe to administer HepB BD vaccine at birth (56)
Role of immunization monitoring systems and impaired feedback loops	11	Where vaccination records do not include columns for documenting the time of administration of the HepB BD vaccine, it is difficult to establish timeliness (57)
Influence of context vs system design on the timeliness of HepB BD vaccination	16	Mothers identified the lack of vaccine delivery on Friday evenings, weekends, or public holidays among the major reasons for delayed vaccination (59)
Influence of maternal knowledge and socio-economic factors on timely HepB BD vaccination	18	Maternal level of education up to secondary or higher was positively associated with timely vaccine uptake (35)
Influence of wider contextual factors on timely HepB BD vaccination	19	In the primary health care system in The Gambia, village-based traditional birth attendants and HCWs are supervised by community nurses as more than 40% of deliveries occurred at home (50)

28.4 days +/− 40.4 days of life (41), with only one study presenting an average age of 1 day (42). In 2015, Nigeria revised its policy on the Expanded Programme on Immunization (EPI) strategies to emphasize timely HepB BD vaccination within 24 h of birth (33). Although well-meaning, this led to further misinterpretation, with HCWs assuming administration of the birth-dose should only be delivered within 24 h or not at all (43). This revised policy led to an overall 30% drop in coverage of hepatitis B vaccinations across 27 health facilities in one study (43). In a later study (conducted between 2017–2018), 1.3% of mothers from Enugu State in Nigeria recommended the HepB BD vaccination policy should mandate vaccination within 24 h to improve timely uptake (34). Also noteworthy was a similar case of policy misinterpretation in Namibia where the national recommendation on HepB BD vaccination allowed for administration up until 2 weeks post birth (33), although further insights were not provided on the performance of the program in the context of this local policy.

Plausible reasons for the misinterpretation of hepatitis birth-dose vaccination policies at the national level may be drawn from the influence of other birth-dose vaccination policies, such as those for Bacillus Calmette-Guérin (BCG) and oral polio vaccine (OPV). In instances where guidelines state that the birth-dose of OPV should be administered before 2 weeks of life (40) and BCG before 12 months of age (35) it was observed that HCWs in some countries tended to group birth-doses, leading to delays in administering the HepB BD vaccine. Accordingly, in a study conducted by Ibrahim et al. (39), it was suggested that the 14-day policy on administering BCG and OPV birth-doses affects the timely receipt of the HepB BD vaccine in Nigeria, as HCWs often wait to administer them together. In Senegal however, a study exploring the perspective of HCWs on the acceptability and perceived challenges of implementing HepB BD vaccination found that they demonstrated good understanding of the need to vaccinate, the health benefits and the recommended timing (44). One HCW described their approach to home birthed neonates, grouping those presenting before and after 24 h post birth (44). This interpretation of the policy by the HCWs acknowledges their understanding of the time sensitive nature of HepB BD vaccination (44). To the contrary, midwives in Côte d'Ivoire cited "ignorance" on available HBV MTCT prevention strategies as one of their reasons for not administering the birth-dose vaccine (45).

Only two of the included studies addressed the importance of written guidelines or standard operating procedures at the health facility level, especially in instances of vaccinating premature or very low birth weight (VLBW) infants. This includes a study by Moturi et al. (33), which noted that only 26% of facilities in Nigeria and 36% of facilities in Namibia had written protocols, whereas the five health facilities (of differing levels of care) studied in São Tomé and Príncipe did not have any available (46). High HepB BD vaccine coverage rates observed in a Nigerian private hospital was associated with adopting facility guidelines in the form of a discharge checklist which included a HepB BD vaccination check in place (33).

3.2.2 Capacity of HepB BD vaccine supply and cold chain systems

Survey respondents participating in a global study conducted by Chang et al. (47), proposed improvements in vaccine supply, delivery, and storage as an approach to enhance global prevention of hepatitis B. As part of this survey study, local experts addressed the need to improve access to vaccines in hard-to-reach areas in Africa to reduce untimely administration of the HepB BD vaccine to neonates (47). In line with this, interrupted vaccine supply or stockouts were identified by mothers and pregnant women participating in six other studies as contributors to delayed vaccine uptake (34, 38–40, 42, 48). Only two of the six studies rated stockouts as a major reason for delayed birth-dose vaccination (34, 42). Similarly, in three additional studies, HCWs found that unreliable vaccine supply chains, specifically vaccine stockouts, were limitations to the successful implementation of the HepB BD vaccination programs in their settings (44, 45, 49).

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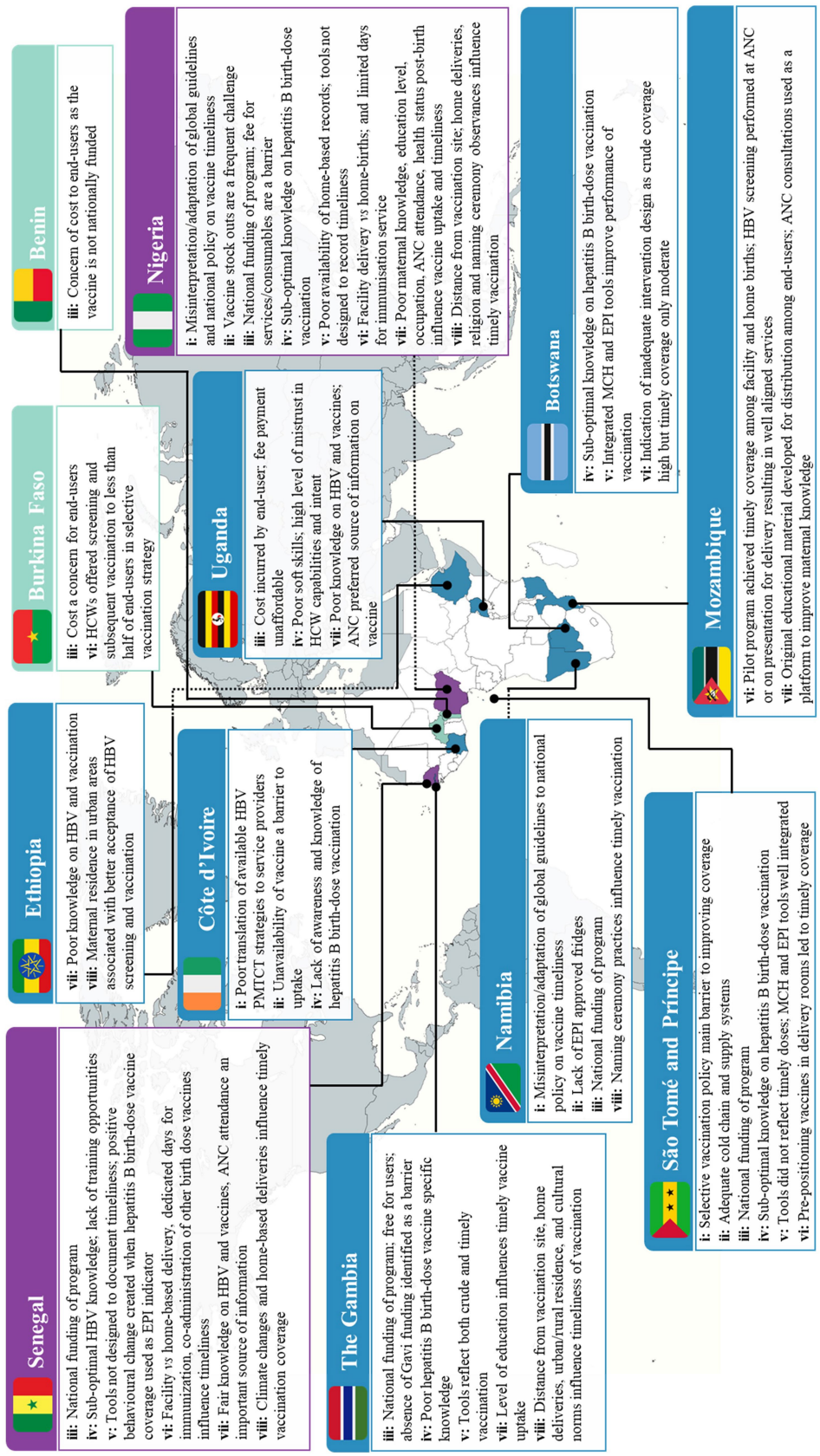

FIGURE 2
Summary of findings on the sources of complexity influencing the performance of HepB BD vaccination programs in the WHO AFRO. Colour key: multiple findings across themes moderate findings across themes Minimal findings across themes. Theme key: **i**: availability and interpretation of HepB BD vaccination policies; **ii**: capacity of HepB BD vaccine supply and cold chain systems; **iii**: availability of equitable and sustainable financing for HepB BD

(Continued)

FIGURE 1 (Continued)
vaccination programs; **iv**: capacity and capability of HCWs delivering HepB BD vaccination programs; **v**: role of immunization monitoring systems and impaired feedback loops; **vi**: influence of context vs system design on the timeliness of HepB BD vaccination; **vii**: influence of maternal knowledge and socio-economic factors on timely HepB BD vaccination; **viii**: influence of wider contextual factors on timely HepB BD vaccination.

While vaccine stockouts have had a negative impact on HepB BD vaccination programs in Africa, improvements in the supply chain have been noted in the region. Only two of 78 facilities investigated across African countries reported experiencing stockouts in one multi-country study (33), whereas findings from another study reported the duration of stockouts lasting less than 2 weeks (46). Multiple studies included in this review indicate that vaccines are supplied by central government (35, 39, 46, 50) in a process coordinated by state or regional health teams. A central area or depot is then accessible for the collection of vaccines to districts and facilities (35, 39, 50). Two studies conducted in Nigeria for example, noted that collection from these central areas by vaccinators take place 2–3 times a week (35, 39). In Kano State, Nigeria, a direct-to-facility-delivery approach was trialed (43). This initiative resulted in a statistically significant decrease in vaccine stockouts and an increase in stock adequacy levels due to reduced bottlenecks at the local government authority cold stores (43). The HCWs participating in this study reported being able to afford more time for direct patient care and health facility management, and less time away from their posts when collecting vaccines (43). A year after the initial roll-out and implementation of the initiative, an increase in vaccine coverage was noted with positive results in the coverage of nearly all vaccinations monitored in Kano (43). However, coverage of the HepB BD vaccine decreased owing to a misinterpretation of the national policy as described previously (43). Explicit information on vaccine supply to private health facilities was not available from the included studies, although one study reported on the exchange between Namibian and Nigerian private facilities and their respective MoH, where vaccine supply was received in exchange for monthly reports including coverage data (33).

Regarding adequate and sustainable storage, it has been noted across the evidence-base that power outages influence the functioning of cold chain systems, leading a HCW in Senegal to suggest the use of solar energy as an alternative power source (44). Accordingly, a study conducted in The Gambia reported the use of solar panels to operate vaccine fridges (50), although no details were provided on whether this improved the cold chain system. The matter of EPI approved fridges was mentioned in two studies as either absent or working well. Moturi et al. (33), note that 52% of Nigerian and 12% of Namibian facilities studied lacked EPI approved fridges while facilities in São Tomé and Príncipe, Botswana, and The Gambia were found to have good quality cold chain systems. Further to this, all five facilities in São Tomé and Príncipe assessed by Hagan et al. (46), possessed EPI approved fridges with vaccines being monitored twice a day.

3.2.3 Availability of equitable and sustainable financing for HepB BD vaccination programs

In-depth exploration of the funding mechanisms for HepB BD vaccination programs was largely absent from the included studies. In one study assessing 62 countries including 13 WHO AFRO member states, it was revealed that 55% had their HepB BD vaccines covered by government funding and 5% by private insurance (47). Miyahara et al. (50), addressed the lack of funding support from Gavi, the Vaccine Alliance, for HepB BD vaccination programs compared to the pentavalent vaccine in eligible countries within Africa. It has been reported that increased national health expenditure *per capita* correlates with higher HepB BD vaccine coverage rates ($p = 0.03$), highlighting the need to strengthen domestic investments to supplement support from external sources (51). In the study assessing direct-to-facility vaccine supply for example, the initiative was reported to have been funded by a tripartite agreement involving the Bill and Melinda Gates Foundation, the Dangote Foundation, and the Kano State Government of Nigeria (43). The inclusion of state funding was aimed at encouraging greater political will and country ownership (43). Similarly, a HepB BD pilot program in Mozambique was reported to have received funding from Médecins Sans Frontières (Doctors Without Borders) in partnership with the national MoH (52).

Where financial accessibility of the HepB BD vaccine is concerned, seven studies reported that HepB BD vaccination was free for users as part of their national immunization schedule, particularly in public health facilities (33, 35, 38, 44, 46, 47, 53). Moturi et al. (33), noted the existence of fee payments for HepB BD vaccination in private facilities in Botswana and Nigeria. End users were required to pay a fee to cover the cost of services, in some instances due to consumable shortages, despite the vaccine itself being free (33, 34, 49). In a quasi-experimental study conducted in Nigeria investigating the perceptions of mothers before and after HCW sensitization, 80% of respondents judged the fees charged to supplement shortages in consumables to be reasonable (49). However, in another study conducted in Nigeria, 6.3% of mothers participating in a study reported fee payment for immunization as their reason for delayed vaccination (34). Some mothers (8.1%) in this study recommended the vaccine should be entirely free of charge in order to improve timely uptake in Enugu State, south-east Nigeria (34). In Uganda pregnant women residing in both urban and rural settings believed the cost of the HepB BD vaccine to be unaffordable, and raised concerns of charges it would carry when implemented (48). Similarly, the pilot study on prevention of MTCT (PMTCT) of HBV in Burkina Faso, reported the cost of the HepB BD vaccine to be 7.76 USD, incurred entirely by the consumer (54). Other costs borne by the consumer included those for HBV screening tests, treatments, and vaccination (54). The authors acknowledge that the costs of all tests, treatments, screening, and vaccines need to be considered in relation to the income levels in Burkina Faso (54). In Benin, Accrombessi et al. (55), also elaborate on the high out-of-pocket expense of HepB BD vaccination, costing 8 USD, given that the vaccine had not been included in the national immunization schedule at the time of the study being conducted. In this same study, it was reported that HCWs recommended HepB BD vaccination to mothers according to their financial means (55). No further details were provided on how HCWs in this study assessed parents' financial capabilities prior to recommending the HepB BD vaccine (55).

3.2.4 Capacity and capability of HCWs delivering HepB BD vaccination programs

A dominating theme within the included studies was the lack of training for vaccinators or other HCWs involved in HepB BD vaccination programs. Two main population groups offered valuable insights on this, end users (mothers or pregnant women) (34, 49), and HCWs themselves (33, 40, 44–47, 56). In the qualitative component of a mixed method study conducted in Senegal, overall attitudes and beliefs among HCWs on HepB BD vaccination was judged to be good (44). However, generally HCWs lacked basic knowledge on HBV and had limited access to HepB BD specific training, although 85% knew the first dose should be administered within 24 h of birth (44). Interestingly, in this same study, those predominantly involved in vaccination services (46%) were more likely to have middle or lower levels of formal education (72%) but were also more likely to have received HBV-specific training (72%) (44). Of those who were mainly involved in antenatal care (ANC) and activities (54%), only 47% had received HBV-specific training (44). In a São Tomé and Príncipe study, 80% of facilities received training on HepB BD vaccination and HCWs in all five sites were aware that administration of the birth-dose should be within 24 h post birth (46). A study conducted to assess the knowledge and attitude among medical practitioners working in an urban setting in Senegal, reported that 21% attained low HBV knowledge scores (56). Among these medical practitioners, a low level of knowledge was attributed to not attending any HBV-specific lectures after basic medical training (odds ratio or OR 6.0 [95% confidence interval or CI 1.4–26.4]) (56). Among the total population of medical practitioners studied, only 51.2% thought it safe to administer vaccines to newborns, of which the rest linked misconceptions of infertility (48%) or neurological disorders (37.8%) to the vaccination (56). In a multi-country study, the lack of training for HCWs specific to HepB BD vaccination ranged from 56% in The Gambia to 88% in Botswana (33). Knowledge of the recommended administration window was high but suboptimal knowledge of contraindications and age-limits were noted (33). False contraindications reported included prematurity, VLBW, and acutely ill but stable infants (33). Additionally, breastfeeding was delayed and discouraged by HCWs according to a São Tomé and Príncipe study until after the HepB BD vaccine was administered for fear of HBV MTCT (33). Similar findings were observed in another São Tomé and Príncipe study where health centers were less likely to vaccinate VLBW, premature, or clinically unstable neonates (46).

In Senegal, immediate hospitalization of neonates was significantly associated with poorer outcomes of timely HepB BD vaccination (adjusted odds ratio or AOR 0.42, [95% CI 0.26–0.68]), whereas weighing neonates increased the chances of timely vaccination (AOR 3.90, [95% CI 1.79–8.53]) (57). Both these practices could be related to the lack of knowledge on contraindications, and the confidence to vaccinate only when the infants' weight suggests a better perceived assessment of health. An alternate and plausible explanation offered relates to reluctance among HCWs to vaccinate hospitalized or VLBW neonates in order to avoid any adverse events being linked to the vaccine or the vaccinators themselves (57). In contrast, a related study in Senegal found that immediate hospitalization of neonates after birth increased the odds of benefitting from co-administration of birth-dose vaccines by 1.74 times, when compared to those not requiring hospitalization after birth (AOR 1.74, [$p = 0.002$]) (58). Weighing the newborn was also associated with better chances of co-administration of birth-dose vaccines ($p = 0.006$) (58). Miyahara et al. (50), discuss the need to improve HepB BD vaccination awareness and training among delivery agents in the Gambia as no difference in timing was found between those delivered in health facilities and those born elsewhere. Similarly, in a Nigerian study, despite frequent contact with the health care system (92.2% of pregnant women attended ANC consultations and 81.1% delivered in a health facility) only 57.7% of women cited receiving information from HCWs on when to commence HepB BD vaccination (40). Furthermore, sources of information on HepB BD vaccination were further disaggregated into nurses (28.1%), ANC visits (20.3%), immunization sessions (17.2%), doctors (1.6%), unspecified HCWs (4.1%) and unspecified hospital activity (10.6%) (40). This finding supports that of a study conducted in Uganda where mothers reported that HCWs provided limited communication regarding vaccination needs, discouraging their involvement in the program (48). In two HBV PMTCT pilot programs conducted in Burkina Faso and Mozambique, training of HCWs on HBV prophylaxis, screening, counselling, and vaccination was conducted prior to rolling out the program (52, 54). In Mozambique, Loarec et al. (52), indicate that training was given to project nurses, MoH nurses and midwives alike, consisting of a 1-day training course or on-the-job training. Despite training of HCWs on HBV prophylaxis, screening, and counselling in the Burkina Faso pilot program, less than half of the pregnant women accessing services during this pilot were offered hepatitis B screening (54). Sub-optimal screening practices led to missed opportunities to identify and timely vaccinate at-risk neonates. Reasons for poor HBV screening and targeted birth-dose vaccination practices reported by midwives in a study conducted in Côte d'Ivoire, include lack of awareness, lack of time, increased workload, and unavailability of vaccines (45). Consequently, 41.4% of midwives reported not performing screening, while 52.3% reported not administering HepB BD vaccination to HBV exposed newborns (45). To mitigate such practices, a study in Nigeria trained HCWs by sensitizing them to improve the quality of immunization services (49). Post-intervention, a significant increase was found among mothers of the study group across two criteria; those who found information provided to them on immunization adequate; and those who correctly identified the number of visits left to complete the immunization schedule (49).

Regarding non-technical skills and communication of HCWs, younger pregnant women in Uganda viewed HCWs as rude and uncaring (48). They were also described as often not providing important information about newborns, including communication on vaccination requirements (48). This discouraged the buy-in of mothers and limited demand for the HepB BD vaccine, leading to missed opportunities for vaccination (48). Delayed vaccination was also linked with mistrust of HCWs (48). Pregnant women expressed concern about HCWs handling their newborns and administering injectables (48). They instead preferred oral vaccines over injectables as it reduced the risk of HCWs making errors when administering vaccines (48). The quasi-experimental study in Nigeria on the other hand, found that pre-intervention, 80% of women in both study and control groups felt that HCWs treated them with respect, were approachable and polite (49). Further to this, a statistically significant increase was observed among respondents in the study group post-intervention who rated HCWs approachable ($p < 0.05$) (49). Lastly, another aspect of the capability of HCWs explored in the evidence-base was the importance of delegating duties. Across facilities studied

in five African countries, senior oversight by medical practitioners was not required in order to deliver HepB BD vaccination, allowing midwives and other qualified cadres of HCWs to administer vaccinations without undue delays (33).

3.2.5 Role of immunization monitoring systems and impaired feedback loops

Of the 28 included studies, 11 touched on data collection and information systems, with multiple studies referring to reliance on vaccination cards to monitor the administration of HepB BD vaccines (33, 34, 36, 37, 41, 46, 50, 52, 53, 57, 58). The monitoring process should serve as an active feedback loop, encouraging improvements as vaccine coverage outputs guide future operations of the program. However, if monitoring systems are inaccurate or data collection tools are inadequately designed (i.e., not fit for purpose), feedback loops are unlikely to be effective in improving programs and broader systems functioning. In the HBV PMTCT pilot program in Mozambique, reference to the suboptimal quality and completeness of data was accepted as a characteristic of the real-world setting (52). The dilemma in monitoring the accuracy of HepB BD vaccination coverage was recurringly linked to the reliance on home-based immunization records. In studies conducted in Nigeria, only 27.3% of children had their immunization cards available in one study (41) while 44% of mothers in another offered verbal confirmation of vaccination due to unavailable or ambiguous home-based records (37). The reliability of vaccination history recall is of course questionable as was demonstrated in a study conducted in Senegal which noted disparities between HepB BD vaccination coverage based on reports by mothers/caregivers versus that recorded in home-based or facility records (57). Overall, vaccination coverage reported by mothers/caregivers in this study was approximately 10% less than that recorded in home-based or facility vaccination records (57). In another study conducted in Senegal, the availability of home-based records was found to be associated with high co-administration rates of birth-dose vaccines, with those having home-based records reported to be 6.88 times more likely to receive co-administered birth-dose vaccines compared to those without (AOR = 6.88, [$p = 0.006$]) (58).

Health facility records have frequently been used to correlate the accuracy of vaccination coverage or to determine the timeliness of HepB BD vaccine administration (34, 36, 57). Again, in Senegal, Bassoum et al. (57), found that HepB BD vaccine coverage rates were largely concordant between home-based records (82.3%) and health facility registries (84.1%), with similar trends noticed in coverage of other birth-dose vaccines. However, in the absence of columns dedicated to documenting the time of vaccination, establishing timeliness required calculation of the difference between the date of birth from health facility records and the date of HepB BD vaccine administration (34, 36, 57). This was instrumental in determining the large discrepancy between crude HepB BD coverage (88.5%) and valid timely doses (42.1%) (57). In São Tomé and Príncipe, although all 5 study sites provided written documentation, the date of HepB BD vaccination was not recorded and therefore establishing timeliness was not possible (46). Practices among facilities in The Gambia included adapting EPI records to reflect both timely and crude HepB BD vaccination (33). These studies underscore the need for clear and appropriate policies and guidelines, without which information systems cannot be designed to be fit for purpose, disrupting feedback processes, and rendering data, like vaccine coverage and timeliness less useful, for appropriate action.

In the multi-country study conducted by Moturi et al. (33), facilities in all five participating countries (Nigeria, Namibia, Botswana, São Tomé and Príncipe, and The Gambia) reported having designated columns for recording HepB BD vaccination in their EPI reporting and recording tools, although older versions of these tools (without these columns) were still circulating in some facilities. In addition, tally sheets and reporting forms at facilities were routinely updated, but none of the maternity registers were modified with columns to record receipt of HepB BD vaccines (33). In health facilities in São Tomé and Príncipe, maternal child health (MCH) and the EPI tools were integrated, facilitating collaboration on implementing the HepB BD vaccination program (33). Similarly, health facilities in Botswana recorded data on HepB BD vaccination in both EPI tools and delivery registries (33). One study described a possible knock-on effect of monitoring, where timely HepB BD vaccination was used as an EPI performance indicator and may have encouraged better timely coverage of the vaccine when compared to other birth-dose vaccines in the study (BCG = 13.9%; OPV = 30%; HepB BD vaccine = 42.1%) (58).

3.2.6 Influence of context vs system design on the timeliness of HepB BD vaccination

Twelve of the included studies explored timeliness of HepB BD vaccination. Even among those studies where measurement of timely vaccine administration or factors associated with delayed HepB BD vaccination were not the primary focus, timeliness emerged as an important challenge. Frequently reported determinants of timely vaccination among the studies reviewed ranged from institutional deliveries and health facility type, inaccessibility of immunization services and vial dosage and co-administration of birth-dose vaccines. Across the evidence-base, a valid or timely dose was often defined as vaccination on the day of birth or the day thereafter. However, time frames used to assess timeliness of HepB BD vaccination differed across countries and studies but frequently fell within day 0–1, day 0–7, and day 0–14, although in a study conducted in The Gambia, birth-dose vaccinations were recorded even after 6 and 12 months after birth (50). The summarized data presented in Table 4 reflects two key findings on the timeliness of HepB BD vaccination in the region; (i) that the vaccination was typically recorded between days 0–1 or 0–7 after birth with wide coverage rates ranging between 1.1% – ~92.4%, and (ii) that generally, vaccine coverage rates tend to increase with increasing age, with the highest rates frequently recorded from day 0–14 and over.

Ibraheem et al. (38), report that in Nigeria, the HepB BD vaccine performs the poorest when comparing crude coverage rates of all three birth-doses: 75.1% vs. 91.2% for BCG and 82.1% for OPV, respectively. More importantly, this study observed that 20.6% of infants presented for all three birth dose vaccinations beyond day 28, with the majority (78.8%) not presenting on day 0–1 (38). This finding is in line with those from previous studies conducted by Sadoh et al. (40), which showed poor adherence to timely birth-dose vaccinations in Nigeria, where only 1.3% of neonates presented within 24 h of birth in one study and 56.1% of children received their HepB BD vaccine beyond day 28 in the other (41). In contrast, two other studies conducted in Nigeria reported better compliance to timely

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TABLE 4 Timeliness and coverage of the HepB BD vaccine in WHO AFRO member states.

Study (Author, year)	Country	HepB BD vaccination coverage (%)							[†]Median/ mean age at receipt of vaccine
		Crude	*Day 0–1	Day 0–7	Day 0–14	Day 0–28	6 m	12 m	
Bassoum et al. (2022) (57)	Senegal	88.1	42.1	–	–	–	–	–	–
Périèras et al. (2021) (53)	Senegal	71.5	54.4	58.2	–	–	–	–	–
Okenwa et al. (2019) (34) and Okenwa et al. (2020) (36)	Nigeria	–	26.2	–	–	–	–	–	–
Ibrahim et al. (2022) (39)	Nigeria	–	11	26.3	68.5	–	–	–	12 days
Miyahara et al. (2016) (50)	The Gambia	–	1.1	5.4	–	58.4	93.1	93.3	24 days
Loarec et al. (2022) (52)	Mozambique	83.4	89.4	–	–	–	–	–	–
Guingane et al. (2020) (54)	Burkina Faso	–	78.3	–	–	–	–	–	–
Sadoh et al. (2014) (41)	Nigeria	–	–	31.7	39.0	43.9	–	–	28[†] days ± 20.4 days
Ibraheem et al. (2022) (38)	Nigeria	75.1	20.5	~52.4	~68.1	~79.4	–	–	6 days
Sadoh et al. (2013) (40)	Nigeria	–	1.3	43.1	70.6	89.5	–	–	9 days
Danjuma et al. (2020) (42)	Nigeria	–	~53.8	~92.4	-	-	–	–	1 day
Ibraheem et al. (2019) (35)	Nigeria	~100	~49.8	~87.8	~94.6	~100	–	–	2 days
Bada et al. (2022) (59)	Nigeria	99	33	91	–	–	–	–	–
Olakunde et al. (2021) (37)	Nigeria	53	–	–	–	–	–	–	–
Moturi et al. (2018) (33)	The Gambia	84	7	–	–	–	–	–	11 days
	Nigeria	23	13	–	–	–	–	–	–
	Botswana	94	74	–	–	–	–	–	–

*Defined as vaccination on the day of birth or the day thereafter. – Timeframe not recorded. ~ Approximation of HepB BD vaccination coverage value as disaggregated coverage among the 3 birth-doses (OPV, BCG, HepB BD) was not available in the respective study. [†]Mean age at receipt of vaccine.

administration of HepB BD vaccination as the majority in one study presented (49.8%) within one day after birth and only 5.4% of infants beyond 14 days (35), while in the other study, 53.8% of infants received their birth-dose vaccinations within 24 h after birth with nearly a third presenting between day 1–7 (42). Despite reporting the highest crude coverage estimates (98%) of HepB BD vaccination, the Kweneng District of Botswana in fact had the lowest timely estimates (62%) compared to other districts in the country (33). A noteworthy knock-on effect of untimely HepB BD vaccination is the further delay in uptake of hepatitis B infant vaccination, as highlighted in studies from Senegal, Nigeria and globally (41, 47, 53).

The influence of institutional delivery on access to the HepB BD vaccine emerged as a prominent sub-theme under timely administration. Institutional delivery rates in WHO AFRO was positively and significantly associated with optimal coverage of the HepB BD vaccine (rho = 0.89; $p = 0.04$), as reported by Allison et al. (51). More specifically, among other included studies, seven found an association between institutional delivery and timely administration of the HepB BD vaccine (33, 35, 36, 38, 40, 53, 57). Neonates in a Senegalese study where most pregnant women (68.8%) delivered at a health facility, were 1.62 times more likely to receive timely HepB BD vaccination compared to their counterparts who were born elsewhere (AOR 1.62; [$p = 0.046$]) (57). In Nigeria, hospital delivery increased the odds of timely vaccination by 6-fold (OR 6.36, [95% CI 1.33-30.38]) (35) and was a determinant of vaccination by day 0–1 compared to those presenting after day 1 (35). Despite most mothers (95.1%) delivering at a health facility in another Nigerian study, only 26.9% of the infants studied were administered timely doses, however the authors still observed a significant association between delivery at a health facility offering immunization services and the timely receipt of the HepB BD vaccine (36). This was advantageous to those delivering at such a health facility compared to those who did not (AOR 5.39, [95% CI 2.45-11.87]) (36). Another study used a 1-week metric and reported that 50% of those delivering at a health facility and only 20.7% of those delivering outside of health facilities presented within this time frame for birth-dose vaccination (40). Though not a statistically significant finding, Bassoum et al. (58), found high facility delivery (71.8%) in Senegal to be an enabling factor for the co-administration of birth-dose vaccines. Similarly in another Senegalese study, being born at home as opposed to a health facility was significantly associated with non-adherence to timely administration of the HepB BD vaccine at the 10% threshold (AOR 2.02, [$p = 0.077$]) (53). Furthermore, HCWs in Senegal who were interviewed as part of a study by Djaogal et al. (44), expressed their view of home deliveries being a barrier to timely vaccination and suggested sensitizing women to give birth in health facilities.

When stratified by health facility type, public facilities were favored over private ones where timely administration of the HepB BD vaccine was concerned (36, 42). Danjuma et al. (42), for example, found that private health facilities in North-Central Nigeria were more likely to delay HepB BD vaccination by 2-fold compared to public health facilities [AOR 2.616; $p = 0.003$]. Another Nigerian study investigating the influence of the place of birth on the receipt of the

HepB BD vaccine among 12-24-month-old children found the odds of vaccination were low in private facilities (AOR 0.77, [95% CI 0.59-0.99]) and home deliveries (AOR 0.48, [95% CI 0.36-0.63]) (37). Further to this, the odds of vaccination among neonates delivered at home when compared to those delivered at a private health facility was also found to be significantly lower in this study (AOR 0.62, [95% CI 0.43-0.88]) (37). Among reasons offered by mothers for delayed vaccination, 8.5% listed having delivered at a private hospital, 3% having delivered at home and another 3% delivered at church (35). In comparison, 91.3% of mothers participating in the study by Okenwa et al. (34), identified the unavailability of the vaccine at the delivering facility more than the actual place of delivery as the reason for delayed vaccination. In this study, 95.05% of mothers delivered at health facilities, with the majority delivering at private health facilities (53.5%) and public primary level care facilities (24.7%), but only 63.77% delivered at a place where the vaccine was offered, inferring that birthing facilities did not always offer birth-dose vaccination (34). Contrary to the aforementioned studies, two other studies found minimal influence of the place of delivery on the timely administration of the HepB BD vaccine (50, 52). In the Gambia, while 59.7% of neonates were delivered at a health facility, only 0.6% had been vaccinated by day 1 and 3.8% by day 7 (50). Such coverage rates were not much higher than those recorded for the 40.3% of infants delivered outside of health facilities (day 1 = 1.3%; day 7 = 5.2%) (50). Similarly, comparable coverage rates of timely vaccination between home births (80%) and facility delivery (75.4%) were recorded in the HBV PMTCT pilot program in Mozambique, although the proportion delivering at home ($n = 5$) was much lower than those who delivered in health facilities ($n = 199$) (52). It is important to note, that during this pilot program, follow-up processes were integrated into routine ANC consultation where women who missed appointments were contacted by phone and those presenting for delivery were screened and their HBV exposed infants vaccinated as soon as possible by midwives (52).

Another key sub-theme was the accessibility of immunization service and its influence on timely uptake of HepB BD vaccination. This emerged across findings from 11 included studies (33–35, 38–40, 42, 50, 53, 57, 59). Most frequently cited as a barrier to accessing timely HepB BD vaccination was the allocation of immunization services on certain days of the week. In Nigeria, vaccination services were reported to only be available from Monday to Friday, excluding weekends and public holidays (35, 38, 39), or on Tuesdays and Thursdays in other facilities (42, 59). Exceptions were made when the number of deliveries were large enough to warrant vaccination on days other than the two routine vaccination days (42). In relation to this, mothers across six studies identified the lack of vaccine delivery on Friday evenings, weekends, or public holidays among the major reasons for delayed vaccination (38–40, 42, 59). Further reasons proffered by mothers for delayed vaccination included having fixed days for immunization clinics (4.2%) (35), not delivering (75.6%) (34) or presenting on a routine facility immunization day (31.2%) (42), being given a later date to return for vaccination (11.2%) (39) or waiting for the day of BCG immunization services (30.3%) (40). In a study by Ibrahim et al. (39), where vaccination services were available Monday to Friday from 8:00 – 15:00, delivery on specific days of the week was not found to have any statistically significant association with timely receipt of the HepB BD vaccine.

Further to the discourse on service accessibility, other studies provide useful insights into how the design of broader services influence the performance of HepB BD vaccination programs within the African region. In The Gambia, reproductive and child health clinics responsible for vaccinations take place once or twice a week, and a set schedule of supplementary outreach clinics take place on the other days of the week (50). Périères et al. (53), report that four health care posts found in the most rural areas in Senegal provide vaccination services on a particular day of the week and offer outreach to the villages furthest from the post. This contrasts with the situation across the five health facilities studied in São Tomé and Príncipe where daily birth-dose vaccination services were routinely offered without any supplementary outreach services (46). High timely HepB BD vaccination coverage was recorded in São Tomé and Príncipe, particularly among facilities that store HepB BD vaccines in labor wards (33). This was confirmed by findings from Hagan et al. (46), where health facilities in São Tomé and Príncipe provided HepB BD vaccination in delivery rooms. Maternal recommendations for improving timely vaccination in a Nigerian study echoed these insights, suggesting pre-positioning vaccines in labor rooms (22.7%) and making the vaccine available at all birthing health facilities (14.8%) (34). In addressing the design of services and wider systems, it is also important to highlight the role of vaccine technologies. Of the 28 studies, four addressed the use of multi-dosage vials for the three commonly administered birth-dose vaccines within the WHO AFRO (38, 39, 50, 57). Hepatitis B birth-dose vaccines supplied in a 10-dose vial are valid for use up to 4 weeks once opened under the correct storage conditions (57). In contrast, BCG is supplied in 20-dose vials and only valid for use for up to 6 h after opening (57). As such, vials are unlikely to be opened unless 10–12 neonates present for vaccination. Should they be born on a day BCG is not administered, they are unlikely to receive the BCG vaccine on day 0–1 as reported by a study conducted in Senegal (57). This was considered as one of the contributing factors to the better performance of HepB BD vaccination compared to BCG and even OPV (42% vs 13.9 and 30%, respectively) in this study (57). However, these practices may limit feasibility of timely administration at the time of delivery as found in Miyahara et al. (50), where multi-dose vials were a barrier to integrating all three birth-dose vaccination programs within broader maternal and neonatal health services.

3.2.7 Influence of maternal knowledge and socio-economic factors on timely HepB BD vaccination

Maternal factors emerged as a prominent theme across the included studies. These factors included maternal awareness and knowledge of HBV and vaccination, ANC attendance, the health and well-being of mothers and infants' post-birth, maternal level of education, maternal occupation, and maternal wealth. In terms of maternal awareness and knowledge of HBV and hepatitis B vaccination, this was found to have a statistically significant effect on the adherence to timely receipt of the HepB BD vaccine as demonstrated in three studies (35, 36, 40). Among them, timely vaccination was 2.4 (AOR 2.36, [95% CI 1.38–4.03]) (36) and 3 (OR 3.06, [95% CI 1.16–8.23]) (35) times more likely among infants born to mothers with good overall knowledge on HBV and vaccination. In a study focusing on the co-administration of birth-dose vaccines, knowledge of co-administration and vaccine timeliness among mothers was found to be associated with better co-administration rates, it also predisposed neonates to receive all birth-dose vaccines on

the same day (58). Studies surveying maternal reasons for delayed presentation frequently identified the lack of knowledge on the timing of vaccination (34, 38, 40). In one of these studies, poor knowledge, and awareness on the timing of vaccination was the third highest reason for delayed presentation as cited by 72.8% of mothers (34). In support of this trend, findings from Ethiopia demonstrated that 89.6% of pregnant women attained poor overall scores on HBV knowledge, performing poorly in categories on the viral origin (87%), MTCT (87%) and the existence of a vaccine (85%) (60). Similar themes emerged from a qualitative study conducted in Uganda which found sub-par knowledge among pregnant women participating in focus group discussions, contributing to their poor overall understanding of HBV and vaccination (48). A notable observation was that both these studies were from countries yet to adopt HepB BD vaccination as part of their EPI. In Senegal and Nigeria where the HepB BD vaccine is part of the EPI, mothers were found to perform well when assessed on their knowledge of commencement of the vaccination schedule, the benefits and co-administration of birth-dose vaccines (58), vaccine timeliness, HBV MTCT, and disease awareness (36).

Additional factors influencing maternal knowledge and awareness of HepB BD vaccination include place of residence, access to media, improved socio-economic status, gravidas, and level of education. In Nigeria, residing in rural areas was a negative predictor (AOR 0.55, 95% CI [0.34-0.89]) of good maternal awareness and knowledge of HBV (36), whereas in Senegal, mothers with access to television were 1.7 times more likely to receive timely HepB BD vaccination compared to those without (57). This was likely due to better access to information and information sharing mediums (57). Dagnew et al. (60), further showed that in Ethiopia, increased monthly income and primigravida were positively associated with good HBV knowledge; those earning >4,000 Ethiopian Birr were 3.2 times more likely to have good HBV knowledge than those earning <2000 Ethiopian Birr, and primigravidae were 2.9 times more likely to have good HBV knowledge than multigravidas. In addition, maternal education at both primary and secondary levels was associated with good HBV knowledge in this study (60). Good knowledge of HBV was then further associated with better attitudes towards HBV treatment, screening, and vaccination, as 57% of pregnant women were willing to have their babies vaccinated against HBV while 53% demonstrated favorable attitudes toward vaccination, screening, and hepatitis B treatment (60). A Nigerian study also demonstrated the positive effect of maternal tertiary education (AOR 2.10, 95% CI [1.28-3.46]) on good maternal knowledge and awareness of HBV (36). In Senegal, HCWs found that mothers or pregnant women tend to experience difficulties in understanding the concept of HBV when they had no formal education (44). A survey of global experts suggests inclusion of education on hepatitis B in public education campaigns with the aim of increasing public awareness and motivation to vaccinate (47). Accordingly, as part of the pilot program in Mozambique, original educational material was developed as well as advice given during screening to improve knowledge and awareness among women (52). This practice supports maternal recommendations to educate mothers and caregivers on HBV and available vaccinations as a means to improving the performance of HepB BD vaccination programs in Senegal (34).

Summary findings on the association between maternal education and timely HepB BD vaccination are presented in Table 5. Of the 18 studies providing information on maternal level of education, five studies found a positive relationship between educated mothers and timely receipt of the HepB BD vaccine, while five other studies found no association, and eight did not compare these two variables. Across the five studies that found significant associations between educated mothers and those without any formal education (35, 38–40, 50), the most frequent positive correlation was found between mothers with a post-secondary education and HepB BD vaccination by day 7 post-birth (35, 40, 50). These mothers were two (AOR 2.43, 95% CI [1.17–5.07]) and three times (OR 3.29, $p = 0.02$) more likely than uneducated mothers to present within 7 days for vaccination in The Gambia and Nigeria, respectively (35, 50), with one other Nigerian study observing a strong significant relationship between these variables ($p = 0.0001$) (40). Additionally, the odds of timely HepB BD vaccination by day 0–1 was higher among mothers with a post-secondary education (OR 3.6, $p = 0.013$) (35). In a Nigerian setting, mothers with a primary level of education were 17 times more likely (AOR 16.95 $p = 0.026$) to receive timely HepB BD vaccination within 24 h post-birth when compared to those with no formal education, followed by those with secondary (AOR 5.9 $p = 0.033$) and tertiary (AOR 7.7 $p = 0.029$) education (39). Health care workers in a Senegalese qualitative study believed uneducated pregnant women or mothers were less compliant with vaccination schedules (44). Overall, findings from these studies suggest that any level of formal education among pregnant women and mother may have a positive influence on the performance and outcomes of HepB BD vaccination programs in the WHO AFRO.

Both neonatal and maternal health concerns post-birth were reported to influence delayed HepB BD vaccination. The proportion of mothers identifying their ill health as a reason for delayed presentation for vaccination ranged from 7.6% (35), 12.3% (40) to 16.2% (38), whereas those who identified having undergone a caesarean section as their reason ranged from 5.9% (35) to 6.1% (39). In Uganda women felt they needed to recover from the stress of childbirth before their newborns could be safely vaccinated, while others who underwent an operation suggested delaying vaccination till the day of discharge (48). Superseding maternal ill health was the health and well-being of the neonates. The baby's ill health was cited among reasons for delayed HepB BD vaccination in five studies (35, 39, 40, 42). The proportion of mothers identifying their neonates' ill health as a deterrent to timely vaccination ranged from 5.8% (42), 9.7% (35), 10.5% (39), 11.6% (40), to 24.4% (38) across included studies. Among these studies, a lesser proportion of mothers identified prematurity as their reason for delayed vaccination (4 and 0.8% in two studies) (35, 42).

Where maternal socio-economic determinants of timely HepB BD vaccination were addressed, maternal occupation was found to be significantly associated with timely vaccination in three studies, all of which were conducted in Nigeria (38–40). In a study conducted by Ibrahim et al. (39), types of occupations were categorized into five groups, with group 1 being the higher end comprising of occupations like senior civil servants, and group 5 the lower end representing those who were students or unemployed. Group 2 (non-academic professionals like nurses, medium size business owners, secondary school teachers, intermediate grade public servants) was negatively associated with timely receipt of the HepB BD vaccine within 24 h (AOR 0.14, 95% CI [0.037-0.554]) (39). Another study found that the likelihood of vaccination by day 0–1 among petty traders and teachers was 4 and 1.5 times higher, respectively, than that among the

TABLE 5 Summary findings on the association between maternal education and timely HepB BD vaccination.

Study (Author, year)	Country	Participants (*N*)	Maternal level of education (%)				Association between education and timely vaccination	Summary findings
			No education	Primary	Secondary	Tertiary		
Okenwa et al. (2019) (34)	Nigeria	344	1.2	7.6	61.1	30.2	Not measured	37.2% of participants recommended improving HBV education of mother's caregivers
Okenwa et al. (2020) (36)	Nigeria	366	1.2	7.6	61.1	30.2	Tertiary education was associated with valid birth-dose (COR = 1.7; AOR = 1.2)	Tertiary education was associated with good maternal knowledge of HBV infection and vaccination
Olakunde et al. (2021) (37)	Nigeria	6,143	43.1	14.3	33.4	9.3	Not measured	Level of maternal education was positively associated with receipt of vaccination when delivered at home and in public facilities
Périères et al. (2021) (53)	Senegal	241	66.5	20.1	13.4[a]	a	Level of maternal educational was not associated with non-adherence to birth-dose schedule ($p = 0.363$)	Level of maternal education was not significantly associated with non-adherence to birth-dose schedule
Sadoh et al. (2014) (41)	Nigeria	150	2.7	27.7	23.6	45.3[b]	Not measured	Overall low timely birth-dose coverage. Age, sex and socioeconomic status found not to be associated with hepatitis B seropositivity.
Ibrahim et al. (2022) (39)	Nigeria	400	3.4	8.3[c]	49.0	39.3	Education and timeliness AOR: primary = 17; secondary = 5.9; tertiary = 7.7	The level of maternal education associated with timeliness. Primary level education showed the biggest association compared to mothers with no education
Ibraheem et al. (2019) (35)	Nigeria	480	1.7[d]	[d]	34.2	64.2	Post-secondary education and presenting on day 0-1: OR = 3.6; day 2-7 OR = 3.29	Post-secondary education was significantly associated with valid timely dose of HepB BD
Danjuma et al. (2020) (42)	Nigeria	355	2.3	5.9	23.9	67.9	No significant correlations at any level (primary: $p = 0.95$; Secondary: $p = 0.11$; Tertiary: $p = 0.65$)	Level of maternal education was not significantly associated with delayed birth-dose vaccination
Bada et al. (2022) (59)	Nigeria	409	33.2[d]	[d]	66.8[a]	[a]	Level of education ≤ elementary schooling or ≥ secondary schooling was not associated with timely birth-dose ($p = 0.63$)	No association found between maternal level of education and timely birth-dose
Ibraheem et al. (2022) (38)	Nigeria	1952	6.3%	4.3%	51.2%	38.1%	Tertiary education and presentation within day 1: OR = 1.6; ($p = 0.028$)	Tertiary education was significantly associated with presentation for vaccination within day 1 post-birth
Bassoum et al. (2021) (58)	Senegal	726	57.4%	42.6%[e]	[e]	[e]	Not measured	Factors associated with co-administration of birth-dose vaccinations did not include maternal education

(Continued)

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TABLE 5 (Continued)

Study (Author, year)	Country	Participants (*N*)	Maternal level of education (%)				Association between education and timely vaccination	Summary findings
			No education	Primary	Secondary	Tertiary		
Bassoum et al. (2022) (57)	Senegal	832	54.1	45.9[e]	[e]	[e]	Educated vs uneducated mothers and vaccination within 24 h: $p = 0.503$	No significant association between education level and vaccination within 24 h
Dagnew et al. (2020) (60)	Ethiopia	1,121	27.5[f]	15.4	26.9	29.5	Not measured	Education was significantly associated with good HBV knowledge and attitude among pregnant women
Goodman et al. (2013) (49)	Nigeria	300	Study = 36.7; Control = 37.7	Study = 39.3 Control = 41.4	Study = 16.7 Control = 14.0	Study = 7.3 Control = 7.3	Not measured	No multivariate analysis was done
Guingané et al. (2020) (54)	Burkina Faso	2,220	35.6	21.9	37	5.5	Not measured	Interestingly a ≥ secondary level of education of both parents was significantly associated with better retention to care (more so in fathers than mothers)
Miyahara et al. (2016) (50)	The Gambia	10,851	15.8 67.1[g]	10.5	6.7	–	Higher educated mothers and vaccination by day 7 compared to uneducated mothers: AOR 2.43 ($p = 0.02$)	Vaccine coverage by day 7 was significantly higher in children born to mothers with higher levels of education
Sadoh et al. (2013) (40)	Nigeria	153	[d]	72.5[d]	27.5[a]	[a]	≥ Secondary education more likely to present within the first week of life ($p = 0.0001$)	Mothers educated beyond secondary level more likely to present for vaccination within the first week after birth
Nankya-Mutyoba et al. (2021) (48)	Uganda	70	–	48.6[h]	51.4[h]	–	Not measured	Participants were grouped by residence and education level. No other insights drawn on maternal education level

[a]Combined secondary and tertiary education.
[b]Combined university degree or equivalent (and school certificate with teaching/other professional training).
[c]Combined primary and Islamic education.
[d]Combined no education and primary education.
[e]Combined primary, secondary, and tertiary education.
[f]Combined no education and basic literacy.
[g]Koranic education.
[h]Purposive selection of education level for qualitative inquiry.

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unemployed (39). Sadoh et al. (40), applied a social class variable which combined ratings assigned for both parents' occupation and education level, with social class 1 being the lower end and class 4 the higher end of the spectrum. High social class was found to have a statistically significant association with presentation for vaccination within the first week after birth (40).

Closely related to maternal occupation, the influence of maternal wealth on the receipt of HepB BD vaccine was reiterated among studies. In three studies assessing the relationship between these variables, women's level of wealth was categorized in one of 5 quintiles, with the upper end being the richest and the lower end the poorest (37, 50, 58). No marked difference in the distribution of the population among the wealth quintiles were found in all three studies (37, 50, 58). Two of the three studies found no statistically significant correlation between maternal wealth and vaccination by day 7 (50), or co-administration of birth-dose vaccines (58). Contrary to this, Olakunde et al., found that wealthier mothers had higher odds of receiving HepB BD vaccination when compared to the poorest category (AOR richest =3.05, richer =2.17, middle =1.55) (37). Noteworthy were the findings on maternal unemployment despite secondary education attainment. Most mothers in one Nigerian study were unemployed (48.7%) despite the majority attaining a secondary level of education (51.2%) (38). Similar findings in Nigeria demonstrate 50% of mothers with at least a secondary level education but high unemployment (59%), additionally the majority (47.8%) belonged to the middle class (39).

Among the included studies, maternal history of ANC attendance was another determinant of timely HepB BD vaccination. Antenatal services or facilities were also frequently identified as the preferred location or medium of attaining knowledge on HBV and vaccinations, see Table 6. In Nigeria, women who attended ANC consultations were 10 times more likely to present for vaccination by day 0–1 (AOR 9.55, 95%CI [1.75–52.12]) and nearly 6 times more likely to present by day 2–7 (OR 5.78, 95%CI [1.27–26.28]) compared to those who did not attend ANC (35). Across other WHO AFRO member states, HepB BD vaccine coverage rates were shown to be high in instances of high ANC attendance (33). Similar correlations between ANC attendance and timely administration of the HepB BD vaccine were however not demonstrated in other studies (38, 39, 53). Pregnant women in Uganda preferred getting information on HBV and vaccines at their ANC consultations as opposed to via post or electronic media (43). In an exploration of the source of health information available to mothers, the health system was identified as the main source specifically on commencement of birth-dose vaccination (57.7%), of which 20.3% of mothers named ANC sessions as their source (40). Similarly, 82.2% of mothers received advice on vaccination during ANC consultations and 85.3% received advice during post-natal visits which was associated with higher odds (AOR 1.72, $p = 0.01$) of co-administration of birth-doses (58). In a related study, an increased proportion of mothers in Senegal received advice on vaccination at post-natal visits (87.2%) compared to during ANC consultations (82.4%) (57). Although paternal factors were assessed in six of the included studies, an association with HepB BD vaccination or delayed vaccine uptake was not reported (38, 39, 53, 54, 57, 58). Only the pilot program in Burkina Faso cited the level of education among fathers as being significantly associated with retention to care and HBV DNA testing among mothers, see Table 5 (54).

3.2.8 Influence of wider contextual factors on timely HepB BD vaccination

It is critical to address how HepB BD vaccination programs perform in the local contexts where they are delivered. From our review of the evidence-base we identified key factors that influence, to varied degrees, how HepB BD vaccination programs function. These include geographical factors, cultural and religious beliefs or observances underpinning decision-making around home deliveries and post-birth practices, parental decision-making authority on a child's health, concepts around maternal marital status and birth order of children, and the local historical or current political climate. With regards to geographical factors, physical distance, and climate issues such as seasonal weather conditions were highlighted in several studies as influencing the timeliness of HepB BD vaccination. In Nigeria for example, mothers attributed delayed HepB BD vaccination to an increased distance between their place of residence and vaccination sites, often requiring unaffordable transportation costs (34, 35, 38). Miyahara et al. (50), report that in The Gambia, increased distances of ≥2 km from the vaccination site decreased likelihood of vaccination by day 7 (AOR 0.41 [$p < 0.0001$]) but those residing in rural areas were more likely to be vaccinated by day 7 compared to those from urban or peri-urban areas (West rural AOR 6.13; East rural AOR 6.72 [$p < 0.001$]). Even when assessing correlation of vaccination by day 1, rural areas faired significantly better than urban or peri-urban areas (AOR 4.61, 95% CI [2.27-9.36]) in this study (50). Two health system design factors were advantageous to this Gambian cohort; 50% of infants lived within 1 km of vaccination clinics and village HCWs performed an active role in informing rural mothers of the dates of outreach clinics (50). Unlike their counterparts in The Gambia, pregnant women residing in urban areas in Ethiopia were two times more likely than rural residents to have good attitudes towards HBV transmission, screening, and vaccination (60). By adopting a service delivery structure involving three strategies, fixed, advanced, and mobile strategies, Senegal has been able to expand access to vaccination services (57, 58). The fixed strategy is designed to provide vaccination services at fixed health centers to those living within a 5 km radius, while the advanced strategy targets those staying between 5–15 km from health centers with services rendered at health huts or sites by the staff from the main health centers. The mobile strategy on the other hand, targets those living >15 km from the health centers (57). With this service model, Bassoum et al. (58), observed that 66.1% of mothers lived within 5 km from a health center and this was found to be an enabling factor for co-administration of birth-dose vaccines. Interestingly, in another study by Bassoum et al. (57), findings showed that although 70.1% of the sample population lived <5 km from a health center, this was not associated with HepB BD vaccination within 24 h of life. In addition to physical distance, it has been demonstrated that being born in the dry season is associated with a 1.97 times higher likelihood of non-adherence to the HepB BD vaccination schedule when compared to those born in the wet season (53). Reasons proffered in a Senegalese study for this outcome include migration during the dry seasons which reduced the likelihood of adherence to the vaccination schedule (53).

TABLE 6 Summary findings on ANC attendance and HepB BD vaccination.

Study (author, year)	Country	Participants (*N*)	Antenatal care attendance (%)	Summary findings
Périères et al. (2014) (53)	Senegal	241	96.2	Not attending ANC visits was not significantly associated with non-adherence to birth-dose schedule [$p = 0.8$]
Ibrahim et al. (2022) (39)	Nigeria	400	96.5	No correlation between ANC attendance and timely administration
Sadoh et al. (2013) (40)	Nigeria	153	92.2	20.3% of mothers who identified the health system as their source of information on HBV and vaccination received their information from ANC visits
Ibraheem et al. (2022) (39)	Nigeria	1952	94.7	ANC attendance was not significantly associated with vaccination at day 0-1 [p = 0.63]
Ibraheem et al. (2019) (35)	Nigeria	480	93.5	Women attending ANC were 10 times more likely to receive vaccination by day 0-1 and nearly 6 times more likely to present by days 2-7 when compared to those who did not attended ANC
Bassoum et al. (2021) (58)	Senegal	726	47.5 [<4 visits] 52.5 [≥4 visits]	82.2% of mothers received advice on vaccination during ANC visits
Bassoum et al. (2022) (57)	Senegal	832	46.4 [0-4 visits] 53.6 [≥4 visits]	82.4% of mothers received advice on vaccination during ANC visits.
*Moturi et al. (2018) (33)	Namibia	N/A	97	No comment on association between coverage and ANC attendance in these two countries
	Nigeria	N/A	61	
	Botswana	N/A	94	In these 3 countries with high coverage rates of the HepB BD (high rates of ANC attendance are recorded. ANC provides an opportunity to educate on HBV and encourage facility delivery)
	The Gambia	N/A	86	
	São Tomé and Príncipe	N/A	98	
Nankya-Mutyoba et al. (2021) (48)	Uganda	N/A	n/a	Pregnant women prefer receiving HBV education during ANC consultations

ANC, antenatal care; N/A, not applicable; *data regarding ANC attendance was derived from UNICEF 2016 report (www.data.unicef.org).

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With regards to home birthing practices, a survey conducted among African experts found that 92% reported limited vaccine resources for neonates born outside of health facilities (47). In this same study, ~22% of participating African countries reported that the proportion of deliveries outside of health facilities was in the region of 40% or higher (47). In a Nigerian study where the majority of participants were rural residents (60.5%), over 50% of women delivered at home with a high rate of unskilled birth attendants (54.1%) (37). Thirty-three percent of those who delivered at home received HepB BD vaccination whereas the vaccine coverage rate among neonates delivered in both private and public health facilities was over 75% (37). It is also worth noting that of those who did not receive their HepB BD vaccine, majority (69.5%) were delivered by unskilled birth attendants (37). Home deliveries in Senegal were also associated with non-adherence to the HepB BD vaccination schedule (AOR 2.02, $p = 0.07$) (53). In The Gambia, home deliveries (40.3%) and assistance by traditional birth attendants or TBAs (29.8%) are prominent components of the broader health system (50). In this primary health care system, village based TBAs and village HCWs are supervised by community nurses (50). Contrary to findings from Nigeria and Senegal, timely vaccination in The Gambia has been shown to favor those infants born at home. While coverage remains unacceptably low, relatively higher vaccine uptake by day 0–1 for home deliveries (1.3%) compared to deliveries in health centers (0.8%) and hospitals (0.5%) likely reflect the health systems design in The Gambia which accommodates the local realities of home deliveries (50). There is clear demand for designing vaccination systems that make careful considerations for long-established birthing practices rather than dismantling them altogether.

While we anticipated that ethical norms, cultural practices, and religion would be important considerations for timely uptake of the HepB BD vaccine, such topics were rarely addressed in the evidence-base. Some of the limited data available highlighted how mothers from some core northern states in Nigeria were discouraged from leaving their homes with their babies before the name giving ceremony held on day 7 post-birth (38). Accordingly, it was reported that 6.4% of mothers delayed vaccination until after the naming ceremony (38) as did those participating in another Nigerian study where 6.5% of the mothers delayed presenting for vaccination as they were "waiting for after the naming ceremony" (39). This was also highlighted as a cultural practice in both Nigeria and The Gambia in the multi-country study (33). Additionally, waiting to circumcise male babies seven days after birth was given as a reason by 3.2% of mothers in a study conducted in Nigeria (40). In Uganda, a study investigating maternal perceptions and preferences of HepB BD vaccination highlighted participants' belief that newborns should not be out of the mothers' sight in order to remain protected. Mothers suggested the handling of newborns be done in their presence, especially during vaccination (48). Another cultural perspective cited in two of the included studies was the decision-making authority within the household. Only 0.6 and 1.1% of mothers participating in the two studies proffered paternal non-consent as a reason for delayed presentation for HepB BD vaccination (38, 39). Another study identified the unavailability of husbands among reasons for delayed presentation for HepB BD vaccination (40). In Senegal, one study found that 97.5% of decisions concerning the child's health were made by the mother, or both the mother and father, as opposed to somebody other than the parent (58).

Findings from a long-term observational study in The Gambia noted participants from the Fula ethnicity had significantly lower odds (AOR 0.60, 95%CI [0.40-0.91]) of receiving the HepB BD vaccine by day 7 compared to the majority Wollof ethnicity (50). In Senegal, among the Serer ethnic population, HBV was likened to a dietary problem commonly managed by traditional medicine (44). In Ethiopia, HBV is known as "Yewefe Bashita" and thought to be transmitted through bat feces and urine, and as such, the local population was unaware of the importance or need for clinical treatment or prevention (60). Religion as a contextual determinant was assessed in three studies, two of which found a significant association with HepB BD vaccination. Infants born to Christian mothers in Nigeria had twice the odds of vaccination by day 0–1 than those born to Muslim mothers (38). Another Nigerian study found that religion was a significant determinant for home births (37), where the odds of receiving HepB BD vaccination were 0.66 times lower among Muslims when compared to Christians (37). A noteworthy related finding is the fact that 61.3% of the population in the latter study prescribed to the Islamic faith (37).

In terms of birth order, findings appeared inconclusive among three Nigerian studies reporting on the determinant of timely vaccination (38, 39, 59). One study demonstrated higher birth order (3rd born) increased the likelihood of HepB BD vaccination within 24 h by 6-fold when compared to the first born (39). To the contrary, lower birth order (between 2nd–4th born) was associated with 1.5 times the odds of timely vaccination when compared to the 5th born in another study (39), whereas no association between parity and timely vaccination was found in the other study (59). In Loarec et al. (52), authors discuss concerns of the high fertility rate in Mozambique (4.85 births per female in 2018) which when considered together with high home birth rates in some non-urban settings has important implications for access to timely vaccination. Globally, the increasing number of live births per woman was found to be inversely proportional to HepB BD vaccination coverage ($p = 0.01$) (51). In this regard, discussions in this publication centered around higher birth rates likely overwhelming the health system and thereby impacting the capacity to provide timely birth-dose vaccines (51). Lastly, only two studies addressed the influence of conflicts or unrest on the performance of HepB BD vaccination programs. In examining the low coverage and timeliness of HepB BD vaccination in 2018 compared to that in 2017 in Senegal, Périères et al. (53), found that a HCW strike which took place between April–December 2018 had a considerable effect on national immunization services. Aina et al. (43), on the other hand, highlighted the insecurities across the north-eastern parts of Nigeria which caused migrations to stable states like Kano in the north-western parts of the country, and thereby negatively impacting on timely uptake of HepB BD vaccination.

4 Discussion

With 2030 drawing close, more countries within the WHO AFRO plan to introduce selective or universal hepatitis B birth dose vaccination programs as part of national viral hepatitis elimination strategies (4). We contribute synthesized evidence on the complexities influencing the performance of hepatitis B birth dose vaccination programs with the aim of informing the strengthening of future and existing programs in the region.

Where the intervention itself is concerned, the source of complexity lies with the permitted degree of flexibility in the timely administration of the HepB BD vaccine for optimal PMTCT of HBV (17). This further interacts with complexities prevalent across the causal pathway of the vaccination program. This is demonstrated in the dynamics involved in the translation of policy or guidelines into practice (17). We found impaired feedback loops created by misinterpretation of policy encouraged multiple stakeholders to continue a pattern of non-adherence to timely vaccination. When national policies allow for a 0–14-day timeframe for the receipt of the HepB BD vaccine (33–37), HCWs are likely to interpret the upper limit as inferring the same protection as a dose received within 24 h. This misinterpretation would impact on their decisions and practices which in turn influences the health seeking behaviors of mothers leading to a cascade of delayed behaviors. Consequently, mothers presenting for vaccination within 14 days was the most frequent timeframe noted in this review (38–40). Policy makers should take care to not compromise effective program performance when adapting international guidelines to local contexts. Similar complexities have been noted with birth-dose co-administration practices serving convenience or wastage aversions in some settings (50). Reasons for delaying HepB BD vaccination while awaiting pairing with OPV or BCG (39, 50) need to be further investigated in order to formulate pragmatic solutions that do not compromise vaccine effectiveness. Although our findings demonstrate that deficits in supply are not the sole reason for poor program performance, it remains as an important source of complexity (34, 38–40, 42, 48). This has also been demonstrated in other reviews on the performance of HepB BD vaccination programs (6, 14, 15). Establishing a sustainable supply of the HepB BD vaccine decreases the likelihood of untimely or missed vaccination (6). It might be that more innovative strategies, like direct-to-facility supply, could avoid bottlenecks and improve effective program performance (43).

The design of the intervention was also observed as an important point of complexity. Most infant vaccination programs are delivered on allotted days at immunization centers or clinics (35, 38, 39, 42, 59, 61). Though this has allowed for the delivery of essential vaccines as part of the EPI globally (62, 63), this design feature is not the best fit for HepB BD vaccination programs as it leads to poorly accessible services. This is further compounded by several influential maternal and wider contextual factors such as maternal knowledge and awareness of the risk and prevention of HBV MTCT (35, 36, 40), health status of mothers and infants post-birth (35, 39, 40, 42), cultural and religious practices (33, 37–39), geographical factors and seasonal changes (34, 35, 38), home birthing preferences (37, 50, 57) and maternal occupation and level of education (35, 38–41). These characteristics act as mediators or moderators of the intervention (17). Aligning HepB BD vaccination with birth delivery services would be an important step in overcoming this complexity, allowing for a more responsive intervention design that encourages effective vaccination practices. Such efforts should include, pre-positioning of vaccines in delivery rooms (34, 46); ordering of single dose vials or compact pre-filled auto-disable injections (CPADs) for use in delivery centers and during home births (64), the use of mobile vaccination initiatives combined with the use of the vaccine outside the cold-chain (65), training TBAs or village HCWs on the use of CPADs for countries with high volumes of home births (64), and formulating policies that shift responsibility of vaccine administration to the birthing facility or agent as opposed to immunization centers (65, 66). These strategies have proven useful in other settings with similar contexts (64–66).

Further to changes aimed at the design of the intervention, changes in the moderators of effect, like maternal and contextual factors, could provide systemic change in the performance of the vaccination program. Where cultural or religious practices such as naming ceremonies and male circumcision influence delayed uptake of the HepB BD vaccine, explorations of these socio-cultural practices should be conducted and carefully accommodated as part of the vaccination program in order to establish trust from local communities. This calls for strategic planning and social mobilization, engaging community, cultural, and religious leaders to negate misconceptions, raise awareness and improve acceptance of the vaccination program. These cultural considerations are not unique to the WHO AFRO. A previous study suggests that mothers in Indonesia are encouraged to remain indoors with their newborns during the first 40 days of life (64). In this study it was reported that health promotion activities like face-to-face educational sessions during ANC visits, health promotion material such as handouts and mass media campaigns via radio communication improved acceptance of the vaccination program among local communities in Indonesia (64). Further to this, our review noted the pivotal role of village HCWs and TBAs who are essential in raising awareness on outreach immunization services and improving timely uptake of HepB BD vaccine in rural settings with substantial home birthing practices (50). Similar strategies have been used in Papua New Guinea where village HCWs are critical to raising awareness (67).

When considering the broader health system, sources of financial resources described as contributing to vaccine coverage include government health spending, donor funding or development assistance for health, out-of-pocket and prepaid private health spending (68). Among low-income countries, an increase in total health expenditure does not always translate into better health outcomes or optimal vaccine coverage (68, 69). In contrast, national or government health spending *per capita* and government spending per birth on routine vaccines, have been proven as positive predictors of vaccination coverage (68, 69). A steady increase in national funding for new vaccine introductions, like the HepB BD vaccine, in the WHO AFRO is likely to improve coverage. This review highlights how inadequately resourced HepB BD vaccination programs can result in exorbitant out-of-pocket payments which are important constraints to end-user buy-in and uptake of services. In addition, these findings give impetus to the ongoing calls for relevant stakeholders, including global partners like Gavi, to further their pivotal role across the region and honor their financial commitments to support the strengthening of existing programs while expanding roll-out of nationwide HepB BD vaccination programs across the region (70, 71). In 2018, as part of their investment strategy, Gavi committed to providing support for HepB BD vaccination by 2021 but due to the COVID-19 pandemic, these intentions were deferred, although currently being reconsidered following an impressive global movement (70). Even with Gavi support, it is imperative that national governments mobilize domestic investments as this has been shown to strengthen country ownership and secure the sustainability of the vaccination program above dependence on donor funding (68). The China-Gavi project is an example of one such collaboration that helped to convince the Chinese government to introduce and fully fund HepB BD vaccination after attaining 75% coverage in 80% of Gavi project counties (72).

We also found that the level of HBV specific knowledge among HCWs created behavioral change in end-users and HCWs themselves. The poor level of HBV specific knowledge among HCWs manifested in delayed vaccination, lenient practices when screening for selective vaccination, and inaccurate or poor knowledge transfer from providers to mothers and pregnant women (45, 48, 52, 56). This emphasizes the importance of increasing the basic knowledge among all HCWs, especially those involved with MCH activities as they are the first point of contact for pregnant women and the preferred source of HBV-related information (48, 58). Improving the level of knowledge about HBV among HCWs is likely more feasible when training is integrated with other disease training models, like that of HIV (73). This serves as a low-cost intervention towards HBV elimination (74). Future research directions should include exploring potential gaps in tertiary or formal training of HCWs in order to advise the Ministry of Education in adapting the curriculum to local contexts. Dedicated educational sessions and training on HBV among HCWs in Tanzania and Uganda have seen improvements in HBV knowledge but call for ongoing efforts to sustain improved basic knowledge among HCWs (73, 74). Elloker et al. (75), highlight the importance of embracing the 'tangible software' like knowledge, skills, systems and procedures, as well as the "intangible software" such as values, norms, power, communication, and relationships. In our review, knowledge and awareness (tangible software) among HCWs were investigated more frequently than their values, norms, communication, or relationships (intangible software). However, we found dynamics of trust and power (intangible software) evident between HCWs and mothers in the handling of newborns and administration of vaccines (48, 49). It would be premature to draw conclusions on this potentially rich source of complexity based on our limited findings given the gap in research. Further research is needed to better explore these dynamics and how they influence the performance HepB BD vaccination programs.

5 Strengths and limitations of this review

To the best of our knowledge, this qualitative systematic review is the first to explore how key underlying complexities influence the performance of HepB BD vaccination programs in the African region. We retrieved and critically appraised literature sources published in both English and French and indexed in multiple electronic databases and repositories. By applying a systems-based logic model developed in a preceding scoping exercise and tailored to systematic reviews of complexity, we enhanced the reliability and validity of our data collection, synthesis, and analysis. Limitations in the generalizability of the review findings lie in the underrepresentation of other WHO AFRO member states while studies from countries like Nigeria and Senegal dominated the knowledgebase. However, it is important to consider that only 15 member states have so far adopted national HepB BD vaccination policies. In addition, research capabilities and appetites may vary even across those same countries. Systematic review designs are subject to the biases and confounders inherent in component studies, and this should be considered when interpreting the findings of this review.

6 Conclusion

This systematic review draws on the complex links between the design of hepatitis B birth dose vaccination programs and the broader health systems that deliver them, providing complex explanations as to why simply introducing the vaccine may not lead to timely uptake or improved coverage. Owing to the complexity of the hepatitis B birth dose vaccination program, or the complex interaction with the health system, findings and recommendations on strengthening program performance are expected to be multifaceted. Our findings underscore five major considerations for scaling up HepB BD vaccinations in the WHO AFRO. Firstly, the misinterpretation of policy significantly contributed to poor program performance. This produces a cascade of adaptations and behavioral changes along the chain of relevant stakeholders which negatively influences timely vaccine uptake and may ultimately derail HBV PMTCT efforts. Research exploring the non-adherence to policy guidelines is largely lacking despite its systemic effect on implementation and control of HBV in Africa. We therefore encourage further investigation of this focused topic in order to inform interventions that enhance HCW adherence and maximize the benefits of HepB BD in the region. Secondly, the existing design of the program including information systems and supply chains may be inadequate in meeting the needs of an intervention with complex requirements like the HepB BD vaccination program. Innovative and context-specific approaches are required in order to ensure programmatic success. Thirdly, acknowledging the contextual underpinnings and multiple influencing factors of end-users is pertinent when designing and implementing this program. Fourthly, recognizing the role of various cadres of HCWs as a reliable source of information, vaccine administrators, and as complex individuals themselves, is essential to providing tailored support and improving the delivery of the program. Lastly, national governments' buy-in in mobilizing financial resources and maintaining intersectoral collaboration among MoH, education and social development would provide a sustainable basis for programmatic success within the region.

Ultimately, countries within the WHO AFRO looking to introduce, or scale-up HepB BD vaccination programs will benefit from carefully considering components of the intervention design that require responsiveness and flexibility (vaccine accessibility and delivery), or inflexibility (policy interpretation); which stakeholders require further support (HCWs and government ministries); and where innovation is required (information systems and supply chains). Lessons learned from the experiences of the various African countries clearly demonstrate that successful introduction and implementation of HepB BD vaccination programs across the region is achievable with careful consideration of complexities within the broader health system.

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.

Author contributions

TS-R: Writing – original draft, Writing – review & editing, Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Validation, Visualization. JO: Supervision, Writing – review & editing, Methodology, Validation. EA-D: Conceptualization, Supervision, Visualization, Writing – review & editing, Formal analysis, Funding acquisition, Validation.

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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

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2024.1389633/full#supplementary-material

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Effectiveness of financial incentives for control of viral hepatitis among substance users: a systematic review and meta-analysis

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Background: Hepatitis B virus (HBV) poses a significant global health challenge in substance users who are at a higher risk of infection. Financial incentives have been proposed as a strategy to enhance vaccine uptake among high-risk groups. This meta-analysis aims to assess the effectiveness of financial incentives in increasing HBV vaccination rates among substance users.

Methods: A literature search across various databases was done for randomized controlled trials (RCTs) and non-randomized trials evaluating the impact of financial incentives on HBV vaccination rates in substance users. Six studies with a total of 3,886 participants were included. The GRADE approach was used to assess the quality of evidence, and a random-effects meta-analysis was done to calculate pooled risk ratios (RRs) for vaccination uptake.

Results: Financial incentives were associated with a significant increase in the HBV vaccination uptake rates among substance users, with pooled RR of 2.261 (95% CI: 1.327–3.851), despite considerable heterogeneity ($I^2 = 93.7\%$). Sensitivity analysis confirmed the robustness of these findings. However, GRADE assessment indicated a very low quality of evidence, primarily due to risk of bias, inconsistency, imprecision, and potential publication bias, highlighted by a significant Luis Furuya–Kanamori (LFK) index of 6.42.

Conclusion: Financial incentives significantly improve HBV vaccination rates among substance users, underscoring their potential as a public health intervention in this high-risk population. Low quality of evidence calls for further high-quality RCTs to confirm these results and explore the most effective incentive strategies.

Systematic review registration: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42024505277, identifier CRD42024505277.

KEYWORDS

hepatitis, incentives, meta-analysis, substance abuse, systematic review

Introduction

Viral hepatitis, especially hepatitis B (HBV), represents a significant global public health challenge, particularly among populations with high-risk behaviors such as substance users (1). The World Health Organization (WHO) identifies viral hepatitis as a leading cause of liver disease and mortality worldwide (2). HBV infections are particularly prevalent among

substance users due to behaviors such as the sharing of needles and other drug paraphernalia, which significantly increase the risk of transmission (3). Since HBV is associated with substantial morbidity, mortality, and socioeconomic burden, there is a pressing need for effective strategies to control its spread within high-risk populations (4).

Substance users face numerous barriers to accessing healthcare services, including stigma, lack of awareness, financial constraints, and the transient nature of this population (5, 6). As a result, rates of hepatitis testing, vaccination, and treatment uptake among substance users is significantly lower compared to the general population (7, 8). Therefore, innovative approaches, such as financial incentives, may potentially increase the participation of substance users in hepatitis prevention and treatment programs (9). Financial incentives, including cash or vouchers, are provided to individuals as a reward for engaging in health-promoting behaviors, like completing vaccination series (10–12). The general idea is that such incentives can motivate behavior change by providing a tangible reward for actions that these individuals might otherwise neglect due to various barriers (10, 13).

The concept of using financial incentives to influence health behaviors is supported by theories of behavioral economics, which suggest that individuals are more likely to engage in health-promoting behaviors when provided with immediate rewards (10, 14). Nevertheless, despite the potential of financial incentives to improve health outcomes, their effectiveness in controlling HBV in substance users is still unclear. While some studies have reported positive outcomes, including increased rates of vaccination, others have found limited or no impact (15–17). This review aims to assess the value of financial incentives in improving the uptake of HBV vaccination among substance users.

Methods

Eligibility criteria

Population: We included studies conducted on patients who are current substance users, defined as individuals actively using substances at the time of the study. Studies focusing on other populations, such as former substance users or those not using substances, were excluded.

Intervention: The intervention of interest was the provision of financial incentives aimed at increasing HBV vaccination rates. Financial incentives could include cash payments, vouchers, or other monetary rewards given to participants for receiving the HBV vaccine. Studies needed to clearly define the type, amount, and delivery method of the financial incentives to be included in the analysis.

Comparison: The comparator was the usual care arm, which included standard practices for encouraging HBV vaccination without additional financial incentives. Usual care could involve educational interventions, reminders, or other non-monetary methods.

Outcome: The primary outcome of interest was HBV vaccination coverage, defined as the proportion of the target population that received one or more doses of the HBV vaccine.

Study Design: We included parallel-arm individual randomized controlled trials (RCTs), cluster RCTs, and non-RCTs.

Publication status: Only full-text studies published in peer-reviewed journals were included to ensure the reliability and validity of the findings. Studies needed to provide sufficient methodological detail to allow for quality assessment and data extraction. Abstracts, conference proceedings, and unpublished data were excluded to avoid the inclusion of incomplete or non-peer-reviewed information. Additionally, studies published in languages other than English were excluded due to resource limitations for translation.

Information sources

Through search was conducted in Medline Ovid, Scopus, EMBASE, Cochrane library, ClinicalTrials.gov, and the WHO trials registries.

Search strategy

Terms such as "Hepatitis B," "Financial Incentives," "Conditional Cash Transfer," "Randomized Controlled Trial," and "Hepatitis B vaccine" were utilized in various combinations across all the databases mentioned, from their inception until January 2024, with no publication language restrictions. Detailed search for each of the databases are provided in Supplementary file 1. The search strategy was designed to increase the sensitivity and comprehensiveness by including a broader range of synonyms and relevant terms for each concept (Hepatitis B, financial incentives, and study design). By incorporating both controlled vocabulary (MeSH terms) and free-text terms, the strategy aims to capture all relevant studies, including those that might not use standard terminology.

Reference lists of retrieved studies were then manually searched for additional relevant articles. Study authors were contacted in cases where clarification or additional information was required. Two authors (WW and LZ) independently conducted the search.

Selection process

The study selection process was also conducted independently by two investigators (WW and LZ). Titles and abstracts of all identified studies were searched for possible inclusion, and full-texts of relevant articles were the assessed independently by primary and secondary investigators for eligibility (WW and LZ). All disagreements were resolved through consensus.

Data collection process.

General information, methods section containing design, details of the participants, and setting, total sample in each group, baseline, endline values, and criteria, interventions related details, and outcomes was extracted. Data related to outcome measures were independently extracted by primary and secondary investigators. In case of studies with multiple arms in a single trial, only the relevant arms were included in the analysis.

Study risk of bias assessment

Study quality was assessed by two reviewers using the Cochrane Collaboration's Risk of Bias 2 (RoB-2) tool for RCTs (18), and the risk of bias tool for non-randomized trials (ROBINS-I) (19). Based on this

assessment, studies were classified as 'low,' 'high,' or 'some concerns' in terms of the bias risk.

Effect measures and synthesis methods

STATA software, version 14.2 was used for analysis. Given that the data were dichotomous, the risk ratio (RR) and its 95% confidence interval (CI) were calculated based on the frequency of events observed in the intervention and control groups, offering a comparative assessment of the intervention effects.

To accommodate the variability across studies, a random-effects model was applied, using the inverse variance method (20). Heterogeneity was assessed by the inspection of confidence interval overlaps in forest plots, chi-square tests, and by I^2 statistic (20). A sensitivity analysis was carried out to determine the impact of individual studies on the overall results.

Reporting bias assessment

Due to the smaller number of studies (less than 10), traditional methods for publication bias analysis, like Egger's test and funnel plots, were not feasible. The Doi plot and the Luis Furuya Kanamori (LFK) index were used as alternative approaches to explore and quantify potential publication bias (21). The LFK index ranges from-1 to +1, indicating no publication bias (perfect symmetry). Values between-1 to-2 or + 1 to +2 suggest minor asymmetry, while values less than-2 or greater than +2 indicate major asymmetry.

Certainty assessment

Grading of Recommendations Assessment, Development, and Evaluation (GRADE) involves a systematic evaluation of the quality of evidence across several domains (22). This includes:

Risk of Bias: Potential biases that could affect the validity of the findings were assessed. The Cochrane risk of bias tools were used for this purpose.

Inconsistency: Examination of heterogeneity across study results, including statistical measures such as I^2 and Cochran's Q, to assess variations in effect sizes.

Indirectness: Evaluation of the directness of the evidence in addressing the research question, including the applicability of the study populations, interventions, and outcomes to the context of interest.

Imprecision: Analysis of the confidence intervals around the effect estimates to determine the certainty of the findings.

Publication Bias: Investigation of the potential for publication bias, using statistical tools like the LFK index, to identify asymmetry in the meta-analysis that could indicate missing studies or small study effects.

Based on these domains, we classified the quality of evidence into four levels: high, moderate, low, or very low. These levels reflect our confidence in the effect estimate: the higher the quality, the more likely it is that the true effect lies close to the estimate of the effect.

Results

Study selection

A total of 1,322 records were retrieved from all the databases. Of them, 890 records remained after deduplication, and underwent primary screening. Full-texts of 53 studies were screened for eligibility, and finally, six studies were included in the analysis (Figure 1) (15–17, 23–25).

Study characteristics

As shown in Table 1, all six studies reported the efficacy of financial incentives in promoting hepatitis B vaccination among substance users. Of them, five were RCTs and one was a non-randomized trial. Studies were done in the United States, Australia, and the United Kingdom. Participant age ranged from 18 to 65 years, and the sample sizes varied from 13 to 1,158 in the intervention arms, and from 13 to 2023 in the control arms. The interventions involved monetary incentives of varying amounts and forms, aiming to enhance vaccination uptake. Gender distribution across studies showed a higher prevalence of male participants.

Risk of bias in studies

Among the five RCTs, all of them were assessed to have a low risk with respect to randomization domain. Confounding was assessed in one non-RCT showed some concerns, while participant selection indicating high risk and classification of intervention had lower risk of bias. For deviation from the intended intervention, four studies had low risk, two had some concerns. Missing outcome data was low risk in three studies and high risk in three studies. Outcome measurement showed low risk in three studies, high risk in two studies and some concerns in one study. Selective outcome reporting was low risk in one study, some concerns in one study, and high risk in four studies. Two studies had a high risk of bias, one study had a low risk of bias, and the remaining studies had some concerns or not specified (Table 2).

Results of individual studies

The individual studies included in this review present a comprehensive analysis of financial incentives on hepatitis B vaccination uptake among substance users. Seal et al. (2003) conducted a randomized controlled trial comparing monetary incentives to outreach methods for hepatitis B vaccine adherence in IDUs (15). They found that 69% of participants in the incentive group completed the vaccine series compared to only 23% in the outreach group, demonstrating a significant positive effect of monetary incentives on vaccine adherence. Trubatch et al. reported that offering monetary incentives to IDUs in Anchorage, Alaska significantly increased hepatitis B vaccination rates, with 48% of incentivized participants receiving their first dose compared to 7% without incentives (16). Similarly, Stitzer et al. showed that prize-based incentives improved adherence to a 6-month hepatitis B vaccination protocol among cocaine users, with 74% of injections

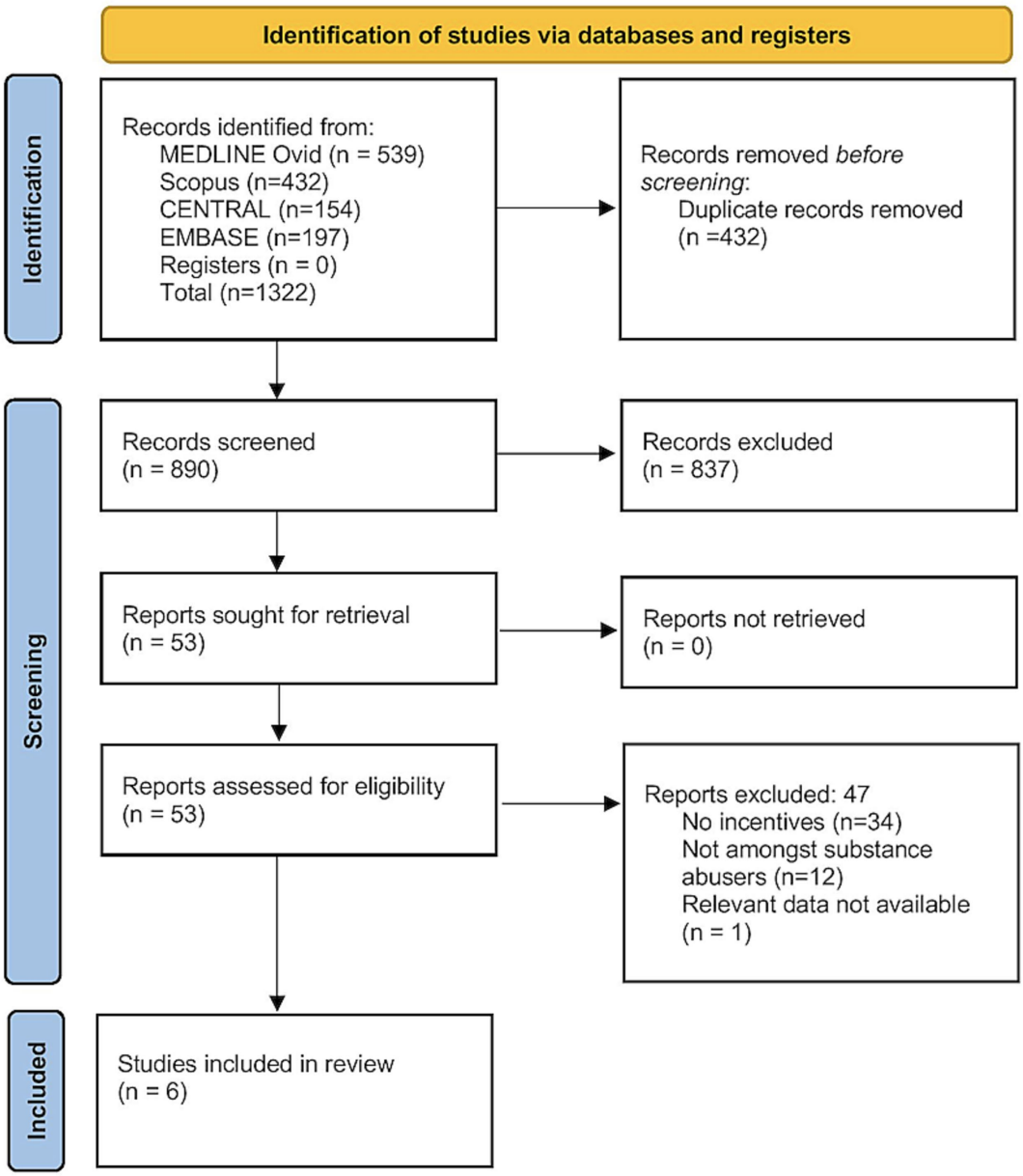

FIGURE 1
PRISMA flowchart.

received on schedule in the incentive group compared to 51% in the control group (23). Campbell et al. highlighted the effectiveness of financial incentives in promoting health behaviors, showing substantial improvements in vaccination rates and suggesting a scalable approach for public health interventions (17). Topp et al. further corroborated these findings by demonstrating that incentivized participants had significantly higher vaccination uptake rates (24). Finally, Weaver et al. underscored the importance of tailored incentive programs to address the specific needs and barriers faced by substance users, enhancing overall public health outcomes (25). Together, these studies underscore the robust impact of financial incentives on improving hepatitis B vaccination rates among high-risk populations, suggesting their potential utility in broader public health strategies.

Results of synthesis

Hepatitis vaccination coverage

The meta-analysis of data from six papers with a total of 3,886 participants, showed an overall pooled RR of 2.261 (95% CI: 1.327 to 3.851), indicating a significant effect of financial incentives on hepatitis B vaccination uptake among substance users (Figure 2). Heterogeneity across studies was high ($I^2 = 93.7\%$, Cochran's $Q = 79.48$, $p < 0.0001$), underscoring considerable variability in study outcomes. The overall effect test was statistically significant ($z = 3.002$, $p = 0.003$), supporting the effectiveness of financial incentives in improving vaccination rates.

Subgroup analysis based on type of outcome shows that the pooled RR for the single dose outcome was 2.372 (95% CI: 0.319–17.618, $p = 0.398$), and for completion of the vaccination schedule, it

TABLE 1 Characteristics of the included studies in the meta-analysis.

Author and year	Study design	Location	Study participants	Sample size	Outcome details	Intervention details	Usual care details	Gender distribution	Age in years
Stitzer et al. 2009	Randomized Controlled Trial	United States	Participants included aged 18–64 years, meets diagnostic criteria for cocaine abuse or dependence, agrees to a 6-month regimen of the HBV vaccine, and reads English.	I = 13\u00B0C = 13	Completed the vaccination schedule	Participants are randomly assigned to incentive or control conditions and expected to meet with research staff for 1 h each week for 24 weeks. Maximum incentives that can be earned in intervention arm is $751 and $20 for completing study procedures	Usual care participants received only $20 for completing study procedures	21 Males and 5 Females	Average age was 45 years. Incentive (mean = 48) and control (mean age = 41, SD = 11.7)
Topp et al. 2013	Randomized Controlled Trial	Australia	Participants aged 16 years and above and injected drugs in the preceding 6 months with no previous HBV infection and a maximum of one previous vaccination dose, or unknown infection and vaccination status and willing to be randomized, to undertake vaccination, and to attend follow-up 12 weeks post-randomization.	I = 74\u00B0C = 65	Completed the vaccination schedule	$30 Australian Dollars cash following receipt of vaccine doses two and three ('incentive condition') and $20 shopping voucher for study completion	$20 shopping voucher for study participation only	107 males and 32 females	Mean age of 33.1 years (SD 8.4)
Weaver et al. 2014	Cluster randomized trial	United Kingdom	Participants with previous, current, or future risk of injecting drug use and agreed to receive vaccination, participate in the trial, and provided written informed consent.	I = 143\ u00B0C = 67	Completion of vaccination schedule within 28 days	Escalating value contingency management (£5, £10, and £15 vouchers)	Offered vaccination without any incentive	167 males and 43 females	18–65 years
Trubatch et al. 2000	Non-randomized trial	United States	Street-recruited IDUs who are participating in a National Institute on Drug Abuse–funded study are offered hepatitis B vaccination	I = 172\ u00B0C = 140	Receipt of first Hepatitis B vaccination	Monetary incentive of $10 in the incentive arm	No incentive and treatment as usual	Not mentioned	Not mentioned
Campbell et al. 2007	Randomized Controlled Trial	United States	Those who injected drugs in the past 6 months, willing to provide locator information and a blood specimen for serologic testing, spoke English and had no plans to move in the following 12 months	I = 1,158\ u00B0C = 2023	Receipt of one or more dose of Hepatitis B vaccine	Participants received standardized HIV and viral hepatitis pre-test counseling, and were offered free vaccination, on a flexible 0-, 1-, 6-month schedule and monetary incentives of $5 per dose	Treatment as usual without incentive	Not mentioned	18–30 years
Seal et al. 2003	Randomized Controlled Trial	United States	Those who lacked all three HBV seromarkers and those with antibodies to HBV core antigen (anti-HBc) only were offered enrolment.	I = 48\u00B0C = 48	Complete vaccination schedule	Participants were randomized to either the monetary incentive or outreach arms and received the first dose of hepatitis B. Monetary incentive arm received a modest cash incentive ($20) each month for 6 months.	Maintain weekly contact with outreach worker	69 males and 27 females	Mean age = 43 Years

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TABLE 2 Risk of bias assessment.

Author and year	Randomization process	Confounding	Participant selection	Classification of intervention	Deviation from intended intervention	Missing outcome data	Outcome measurement	Selective outcome reporting	Risk of bias
Stitzer et al. 2009	Low	NA	NA	NA	Low	Low	Low	Some concerns	Some concerns
Topp et al. 2013	Low	NA	NA	NA	Some concerns	High	Low	Some concerns	High
Weaver et al. 2014	Low	NA	NA	NA	Low	Low	Low	Low	Low
Trubatch et al. 2000	NA	Some concerns	High	Low	Low	Low	Some concerns	Some concerns	High
Campbell et al. 2007	Low	NA	NA	NA	Some concerns	High	High	High	High
Seal et al. 2003	Low	NA	NA	NA	Low	High	High	Some concerns	High

NA, not applicable.

was 2.299 (95% CI: 1.233–4.289, $p = 0.009$; Supplementary Figure 1). Between-group heterogeneity was not significant ($p = 0.977$), indicating no significant difference in the effect sizes between these two outcome types.

Subgroup analysis also examined two types of incentives: incentive for each dose or regular incentive (RR: 1.582, 95% CI: 0.690–3.630, $p = 0.279$) and different incentive pattern (RR: 3.526, 95% CI: 1.018–12.220, $p = 0.047$). Between-group heterogeneity was not statistically significant ($p = 0.293$), suggesting that the type of incentive did not result in significantly different effects on vaccination uptake (Supplementary Figure 2).

The sensitivity analysis, excluding one study at a time, yielded combined estimates ranging from 1.77 to 2.90, consistently supporting the effectiveness of financial incentives in increasing hepatitis B vaccination rates among substance users (Figure 3).

Reporting biases

The LFK index of 6.42 suggested a major asymmetry, indicative of a potential publication bias or other small-study effects (Figure 4).

Certainty of evidence

The GRADE assessment of evidence certainty is provided in Table 3.

Risk of Bias: There was a mixed levels of bias risk across studies, with some studies having high risk and others low or some concerns, suggesting an initial downgrade in the quality of evidence.

Inconsistency: The high degree of heterogeneity ($I^2 = 93.7\%$, $p < 0.0001$) suggests significant inconsistency across studies, which may lead to a further downgrade in evidence quality.

Indirectness: We found that the studies directly address the research question and populations, interventions, and outcomes as applicable, this domain has not led to a downgrade.

Imprecision: The wide confidence intervals in some study estimates could indicate imprecision, potentially leading to a downgrade depending on the overlap and the width of these intervals.

Publication Bias: The LFK index of 6.42 points to substantial publication bias or small study effects, necessitating a downgrade in the quality of evidence.

Given these considerations, the GRADE assessment for the overall quality of evidence on the effectiveness of financial incentives for hepatitis B vaccination among substance users has been classified as very low.

Discussion

Our meta-analysis, incorporating six studies with a total of 3,886 participants, revealed a significant effect of financial incentives on hepatitis B vaccination uptake in substance users, with an overall pooled RR of 2.261 (95% CI: 1.327 to 3.851). This finding underscores the potential of financial incentives to substantially enhance vaccination rates in this high-risk group. However, a considerable heterogeneity and a significant LFK index suggest substantial variability among study outcomes and potential publication bias or small-study effects. The GRADE assessment resulted in a very low quality of evidence due to concerns regarding risk of bias, inconsistency, imprecision, and publication bias.

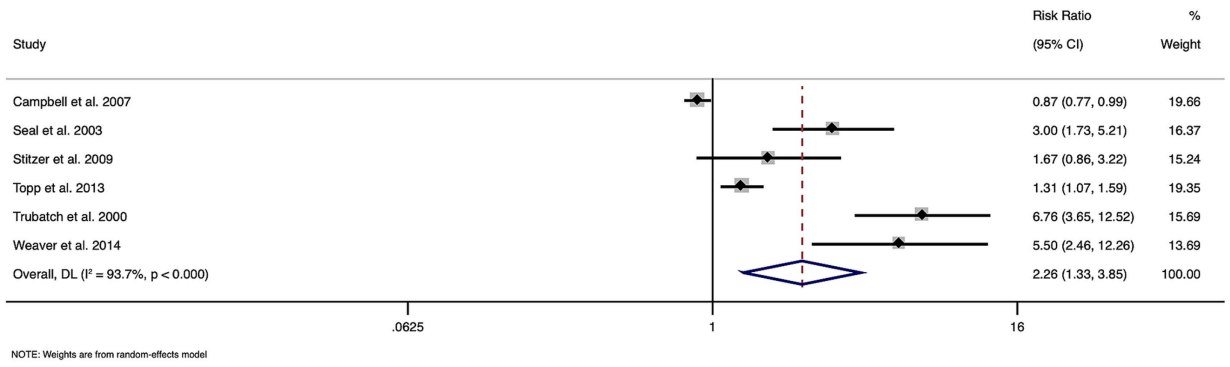

FIGURE 2
Forest plot showing the effectiveness of financial incentives for improving hepatitis vaccination coverage.

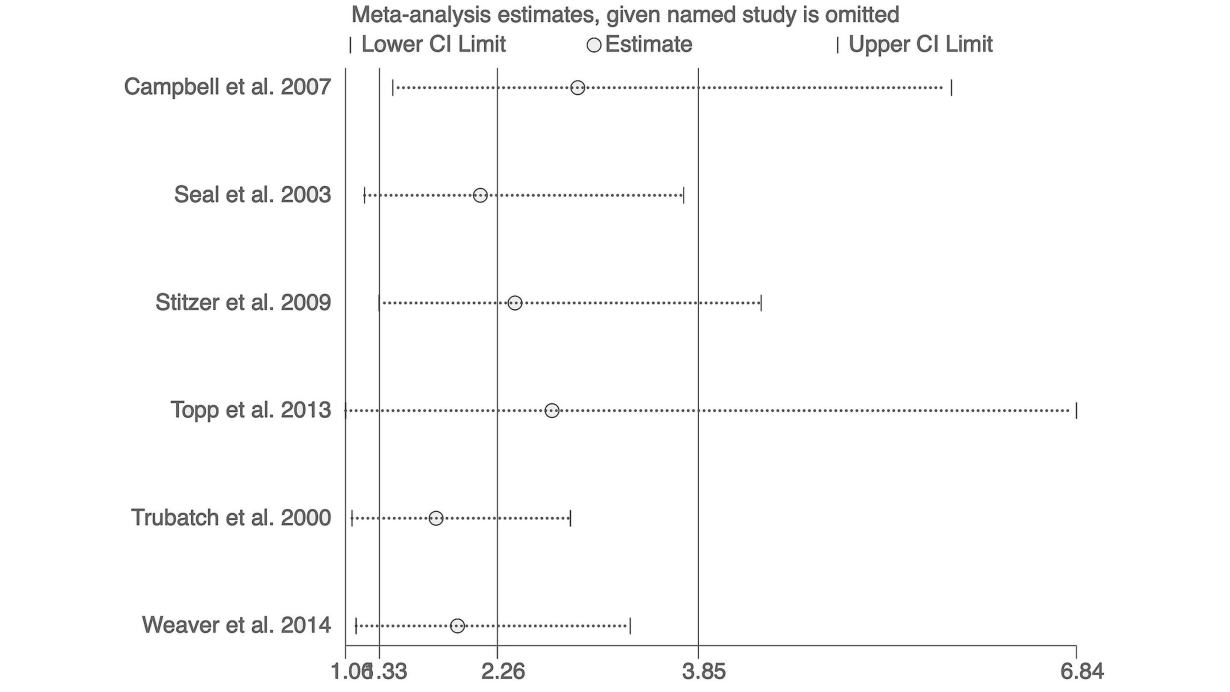

FIGURE 3
Sensitivity analysis plot.

Our findings align with the broader literature, which suggests that financial incentives can be effective in promoting health-related behaviors among high-risk populations, such as substance users (26–28). Previous studies have indicated that financial incentives were effective in increasing rates of screening, vaccination, and treatment adherence for various health conditions (26–30). However, the degree of effectiveness reported in our study exceeds some prior estimates, highlighting the specific efficacy of financial incentives in HBV vaccination uptake. The significant heterogeneity observed in our analysis is consistent with previous meta-analyses in similar fields. We may speculate that this heterogeneity is due to the variability in how financial incentives are implemented and their impact across different settings and populations.

Our analysis offers critical insights into the scalability of financial incentives as a public health intervention. By comparing our findings with existing literature, we can infer that the effectiveness of such incentives may vary not only by demographic factors but also by the nature of healthcare systems and societal norms across different regions (26–30). This variation underscores the need for tailored approaches in implementing financial incentives, suggesting that a one-size-fits-all strategy may not be universally effective. Together with previous research, our results imply that the success of financial incentives hinges on the perceived value of the incentive by the target population, indicating the importance of cultural and economic contexts in shaping responses to such interventions.

TABLE 3 Grade assessment.

Certainty assessment							Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	
6	randomized and non-randomized trials	serious[a]	very serious[b]	not serious[c]	serious[d]	serious[e]	⨁◯◯◯ Very Low

[a]High risk of bias in fewer studies.
[b]Substantial heterogeneity.
[c]No indirectness found in the parameters.
[d]Confidence interval is broad.
[e]Significant publication bias.

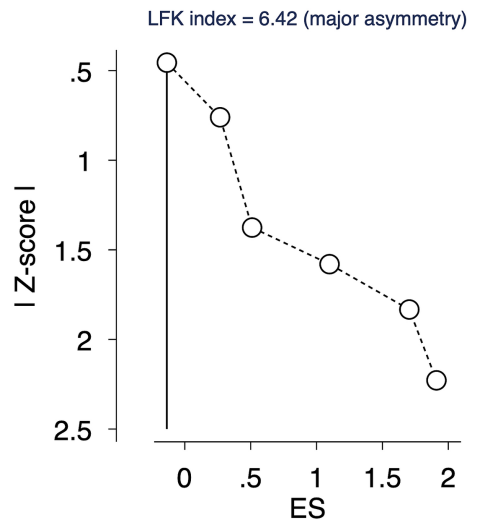

FIGURE 4
Doi plot for assessing the publication bias.

The effectiveness of financial incentives can be attributed to several factors. Behavioral economic theory suggests that immediate rewards can significantly influence health behaviors, making financial incentives a potent tool for encouraging vaccination uptake among substance users, who may face barriers to accessing healthcare services (31). The variation in effectiveness across studies could be due to differences in the size of incentives, the method of delivery, or the contextual factors unique to each study's setting.

This variability emphasizes the complexity of human behavior in health-related decision-making. The decision to accept vaccination, influenced by financial incentives, may be affected by factors such as individual health beliefs, perceived susceptibility to the disease, and trust in medical institutions (32). While financial incentives may address the immediate barriers of access and motivation, they still need to be part of a broader strategy that includes education and outreach to account for these deeper, underlying factors (10). This is particularly important for designing interventions that are not only effective but also sustainable in promoting health behavior change over the long term.

Our study's primary strength lies in its comprehensive approach. We included a wide range of studies and a substantial participant pool, which provides a robust analysis of the effectiveness of financial incentives on HBV vaccination rates. Additionally, the use of GRADE methodology enhances the reliability of our evidence quality assessment.

However, there are several limitations. The very low quality of evidence, as determined by GRADE, reflects significant concerns about risk of bias, heterogeneity, imprecision, and potential publication bias. The high I^2 value indicates considerable variability in the study outcomes, which could limit the generalizability of our findings. Moreover, the presence of publication bias, suggested by the LFK index, may have influenced the overall effect size, potentially overstating the effectiveness of financial incentives.

Despite these limitations, our findings have important implications for public health policy and practices. They suggest that financial incentives could be a valuable tool in increasing HBV vaccination rates in substance users, a group traditionally hard to reach with conventional public health interventions. Implementing financial incentives in targeted vaccination campaigns could, thus, contribute to reducing the prevalence of HBV and its associated health burdens in this vulnerable population.

Moreover, the potential of financial incentives to make a significant impact on public health extends beyond HBV vaccination to other areas where behavioral change is crucial for disease prevention and health promotion. For instance, financial incentives may provide substantial public health benefits in populations, affected by the current opioid epidemic and associated health complications, including hepatitis C and HIV. This strategy would contribute to a more holistic approach to managing health risks among substance-using populations, emphasizing the need for integrated healthcare solutions that address a range of interrelated health issues.

Future research should aim to address the limitations identified in this study. Specifically, there is a need for high-quality RCTs with rigorous design and reporting standards to minimize bias and improve the precision of effect estimates. Studies should also explore the impact of different incentive structures and amounts on vaccination uptake to identify the most cost-effective strategies. Additionally, research should focus on understanding the mechanisms through which financial incentives influence behavior change among substance users and the potential long-term effects on HBV prevalence and health outcomes in this population. Cost-effectiveness studies should aim to determine whether the short-term financial outlay associated with incentive programs yields long-term savings in healthcare costs through the prevention of disease. This economic perspective is crucial for policymakers and public health officials in allocating resources effectively to combat public health challenges. As we advance, integrating behavioral economic principles with epidemiological research could revolutionize our approach to disease prevention, particularly in hard-to-reach populations where traditional public health strategies have been less effective.

Conclusion

Our meta-analysis indicates that financial incentives significantly increase HBV vaccination rates in substance users. Although the evidence in this study is of very low quality due to factors such as heterogeneity, and publication bias, financial incentives still present a promising strategy for public health interventions aimed at increasing vaccination coverage in high-risk populations. More rigorous research is needed to confirm our findings, determine the most effective incentive strategies, and ensure that such interventions can be efficiently integrated into broader public health programs.

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.

Author contributions

WW: Conceptualization, Data curation, Methodology, Software, Validation, Writing – original draft, Writing – review & editing, Formal analysis. LZ: Conceptualization, Data curation, Methodology, Project administration, Software, Supervision, Validation, Visualization, Writing – original draft, Formal analysis.

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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.2024.1394164/full#supplementary-material

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Vaccination of pregnant women: an overview of European policies and strategies to promote it

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Maternal immunization is a valuable tool for protecting mother and unborn child from vaccine-preventable diseases. However, the implementation of strategies for vaccinating pregnant women has only recently gained traction. This work is aimed at providing an overview of European vaccination strategies and gathering evidence on interventions enhancing vaccination knowledge, attitudes, and behaviors (KAB) in pregnant women. To summarize current pregnancy vaccination strategies in Europe, we consulted literature, institutional national health system websites, and the ECDC Vaccine Scheduler. The review of evidence on interventions targeting pregnant women's vaccination KAB was performed by searching primary studies on PubMed and Web of Science. The 27 EU member states offer various vaccinations in pregnancy, but only 10 recommend all of these: tetanus, pertussis, diphtheria, influenza, and COVID-19, albeit with different administration schedules. The literature review included 7 studies, 3 from Italy and 4 from other European countries (UK, Netherlands, Greece, Poland, and Ukraine). They were conducted in various settings such as childbirth preparation courses, prenatal visits, and online platforms, and all included educational interventions providing information on vaccine safety and efficacy during pregnancy. Knowledge about vaccines and vaccine-preventable diseases, generally low in the pre-intervention period, increased post-intervention, with a rise in awareness of the risks associated with infectious diseases and the recommended vaccines, a reduction in vaccine-related misinformation, and a greater propensity to vaccinate both newborns and themselves. Furthermore, there was a significant increase in adherence to recommended vaccinations, particularly among those with higher educational levels. However, vaccine hesitancy persisted, influenced by factors such as fear of adverse events and the lack of recommendations from healthcare providers. Variations in pregnancy vaccination strategies across Europe emphasize the importance of establishing a unified framework to optimize maternal and fetal health outcomes through evidence-based policies. Educational interventions may positively impact pregnant women's KAB, therefore promoting vaccination uptake.

KEYWORDS

vaccination, vaccine policies, knowledge, behavior, pregnancy

1 Introduction

Throughout pregnancy, the immune system undergoes significant modulation alongside physiological adaptations aimed at maintaining maternal homeostasis and facilitating optimal fetal development. These alterations make women more vulnerable to both viral and bacterial infections (1–3), consequently heightening the likelihood of severe complications for the mother and the potential transmission of pathogens to the developing fetus (4–6).

Due to the immaturity of their immune system in the first months of life, neonates are notably susceptible to the onset of potentially severe or fatal infections until they reach the age suitable for vaccination and complete the vaccination cycle (7).

Vaccinating pregnant women has been identified as an optimal strategy for safeguarding the health of the mother, fetus, and infant, resulting in a triple benefit. This intervention affords pregnant women, protection against vaccine-preventable diseases (VPDs) such as influenza, diphtheria, tetanus, pertussis, and COVID-19 (8, 9). Furthermore, a vaccine against Respiratory Syncytial Virus (RSV) has been recently approved in pregnant women for the protection of infants from lower respiratory tract diseases (10).

Therefore, vaccination in pregnancy is widely recognized as an essential component of the comprehensive antenatal care package aimed at enhancing maternal and child health (11, 12).

In this light, many European countries followed the guidance provided by the World Health Organization (WHO) (13–15) and the Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (CDC) (16, 17), routinely advocate for maternal immunization to prevent influenza, diphtheria, pertussis, tetanus, and COVID-19, often through fully subsidized vaccine offerings, as evidenced by a comprehensive review of vaccination policies specific to pregnant women in Europe published in 2021 (18). These vaccines have been demonstrated safe, immunogenic, and effective (19). Nevertheless, vaccine coverage in Europe among pregnant women exhibits substantial discrepancies in terms of both monitoring and data (20). The 2018 ECDC report indicated that only nine European Union Member States (21), reduced to four in the most recent 2023 report (22), monitored pregnant women's adherence to seasonal influenza vaccination. The highest influenza vaccination rates were observed in Northern Ireland (58.6%) and England (44.9%) during the 2016–2017 influenza season, while Ireland reached 62% in 2017–2018 (21). A wide variability in influenza vaccination coverage, ranging from 1.7 to 61%, was indeed shown in 2020–2021 (22). Significant variability was evident also in respect to other vaccinations, such as pertussis, with high vaccination coverage in Spain, Denmark, and Belgium (88.5, 69, and 64.3%, respectively), in stark contrast to the low ones observed in the Czech Republic and Slovenia (1.6 and 6.5%) in 2023 (23).

Regarding SARS-CoV-2 during the 2023–2024 season, only Ireland (19.6%) and Spain (7.8%) have published official data (24), emphasizing the considerable efforts still required, not only to achieve adequate vaccination coverage in this at-risk population but also to ensure effective monitoring.

The substantial variability in vaccination coverages and their unsatisfactory level can be partly attributed to "vaccine hesitancy" (25), which is defined by the WHO's Strategic Advisory Group of Experts on Immunization (SAGE) (26) as the inclination to postpone or decline vaccination despite its availability and is currently recognized as one of the top ten threats to global health (27, 28).

Several studies have explored the factors that influence vaccine hesitancy in pregnancy. These investigations have consistently identified some elements in the literature, namely vaccine-specific factors, such as fear of adverse events and lack of confidence in vaccine safety, and lack of recommendation from healthcare professionals. Disease-related perceptions as well as previous vaccination behavior have also been shown to have an impact on vaccine uptake (9, 29, 30).

This evidence underscores the imperative need to address the determinants influencing maternal immunization, including knowledge, attitudes, and beliefs about maternal and childhood vaccines, through educational interventions (19, 31–34). Such measures are crucial to promoting behavioral changes in pregnant women and their families, enhancing adherence to vaccination protocols, and thus reducing vaccine hesitancy in pregnancy (35, 36).

This review aims to provide an updated overview of pregnant women's vaccination policies across Europe and of current evidence regarding educational interventions aimed at promoting knowledge, attitudes, and behaviors related to recommended vaccinations for pregnant women in the European context. Based on the identified issues and problems the paper seeks to explore potential avenues for optimizing maternal and fetal health outcomes within diverse European settings.

2 Materials and methods

To procure a contemporaneous assessment of extant vaccination strategies tailored for pregnant women in Europe, we consulted the "Vaccine Scheduler" of the ECDC (37). Additionally, we examined the recommendations provided by national health systems, as available on their institutional websites, or reported in the comprehensive review of pregnancy vaccination policies in Europe published in 2021 (18).

Moreover, a review focusing on educational interventions aimed at promoting knowledge, attitudes, and behaviors regarding recommended vaccinations among pregnant women, namely influenza, diphtheria, tetanus, pertussis, and COVID-19, was conducted. Educational interventions have been considered in various formats, including, for example, expert-led information sessions, digital campaigns, and distribution of themed information materials. The primary objective of the search was to identify studies that assessed the impact of these interventions on pregnant women's knowledge, attitudes, and behaviors toward vaccination recommended in pregnancy. To achieve this objective, we employed a search string and adhered to the PICOS criteria, although we did not intend to conduct a systematic review. The evidence retrieval was conducted by consulting two databases (MEDLINE/PubMed, and Web of Science) up to 21 May 2023. Search terms related to pregnancy, vaccination, immunization, knowledge, attitudes, and behaviors regarding vaccination were included. Only language filters were applied to include articles in English, French, and Italian.

The entire search strategy is reported in Table 1.

The inclusion criteria for studies were based on the PICOS framework (38), as described below: (P) Population: European pregnant women during any trimester of pregnancy; (I) Intervention: any intervention involving education, training, or vaccination awareness initiatives; (C) Comparison: not applicable; (O) Outcome:

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TABLE 1 Search strategy.

Search engine	Search strategy
PubMed	(strategy[Title/Abstract] OR intervention[Title/Abstract] OR program[Title/Abstract]) AND (vaccination[Title/Abstract] OR immunization[Title/Abstract]) AND (pregnancy[Title/Abstract] OR pregnant[Title/Abstract] OR antenatal[Title/Abstract] OR ante-partum[Title/Abstract]) AND (knowledge[Title/Abstract] OR attitudes[Title/Abstract] OR behaviour[Title/Abstract] OR belief[Title/Abstract] OR coverage[Title/Abstract] OR uptake[Title/Abstract] OR trust[Title/Abstract] OR mistrust[Title/Abstract] OR perception[Title/Abstract] OR hesitancy[Title/Abstract] OR confidence[Title/Abstract] OR acceptance[Title/Abstract] OR adherence) [Title/Abstract]
WoS	(TS = (strategy OR intervention OR program)) AND (TS = (vaccination OR immunization)) AND (TS = (pregnancy OR pregnant OR antenatal OR ante-partum)) AND (TS = (knowledge OR attitudes OR behaviour OR belief OR coverage OR uptake OR trust OR mistrust OR perception OR hesitancy OR confidence OR acceptance OR adherence))

knowledge, attitudes, and behaviors of women toward vaccinations; (S) Study design: primary studies with experimental or quasi-experimental designs, including randomized and non-randomized trials, and observational studies.

The PICOPortal platform (39) was used for screening and for identifying duplicates. Records underwent initial screening by two reviewers, with a third reviewer resolving equivocal cases. The full texts of selected articles were independently reviewed by two reviewers for eligibility.

Within the scope of this narrative review, a qualitative synthesis was conducted. Information about the study setting, the study population, the sample size, the type of intervention, and the tools used to assess the impact of the intervention were extracted by each study by a researcher and cross-checked by a second one. Data about pregnant women's knowledge, attitudes, and behaviors were also collected from each study and reported descriptively highlighting any significant difference due to the intervention. We employed the NIH quality assessment tools, specifically the "Quality Assessment Tool for Before-After (Pre-Post) Studies With No Control Group" and the "Quality Assessment of Controlled Intervention Studies" to evaluate the quality of the included studies (40). The former tool evaluates pre-post studies by examining 12 aspects such as the clarity of study objectives, the inclusion of pre-specified outcome measures, the appropriateness of statistical analysis, and the consideration of potential confounding factors. Three distinct categories were identified based on the scoring: 0–4 as poor, 5–8 as fair, and 9–12 as good. The second tool assesses controlled intervention studies based on 14 key criteria such as randomization, allocation concealment, blinding, completeness of outcome data, selective reporting, and other sources of bias. Also in this case, three quality categories were identified based on the scoring: 0–4 as poor, 5–9 as fair, and 10–14 as good.

3 Results

3.1 Overview of vaccination policies in Europe

Despite the diversity of vaccination programs, several European countries implement tailored vaccination policies for pregnant women (18), following guidelines outlined by the WHO (13–15). Nevertheless, strategies exhibit variability across European Countries (17, 32).

An examination of the most recent directives from 39 states, including European Union member states, revealed that 97% (38) of such states advocate for the administration of the influenza vaccine during the gestational period. Furthermore, 77% (30) endorse vaccination against pertussis, with 38% (15) advocating for the tetanus vaccine, 28% (11) for the diphtheria vaccine, and 56% (22) for vaccination against COVID-19. Lastly, 26% (10) endorse the entirety of the aforementioned vaccinations for women in a pregnant state (Table 2) (18, 37).

Thirty-eight European countries advocate for administering the influenza vaccine to pregnant women, though with different timings (18, 37). Notably, Belgium, Bulgaria, the Netherlands, Portugal, and Sweden recommend influenza vaccine in the 2nd–3rd trimester. Austria, Denmark, Germany, Malta, Norway, and Russia also stipulate that influenza vaccination is advisable for pregnant women in the 2nd to the 3rd trimester (18, 41–45), but extend their recommendation to include vaccination from the onset of the 1st trimester in pregnant women with high-risk conditions or during epidemics (18, 37). Twenty-seven out of the 38 countries (Albania, Belarus, Croatia, Cyprus, Czech Republic, Estonia, Finland, France, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Liechtenstein, Lithuania, Luxemburg, Monaco, Poland, Romania, Serbia, Slovakia, Slovenia, Spain, Switzerland, Ukraine, and the United Kingdom), recommend influenza vaccination between the 1st and 3rd trimester (18, 37).

Pertussis vaccination is also advised during pregnancy in numerous European countries, with notable variations in the timing and condition of recommendation. Luxembourg and Switzerland recommend vaccination between the 13th and 26th weeks, Sweden and Finland from the 16th week, Portugal between the 20th and 36th week, Denmark and Belgium between the 24th and 32nd week, the Netherlands from the 22nd week, Slovenia and Norway from the 24th week and Austria, Bulgaria, Cyprus, Czech Republic, Germany, Greece, Italy, Poland, Serbia, Spain and Ukraine from the 27th week (18, 37, 46–54). In Denmark, as well as in Germany, vaccination is extended at the beginning of the 2nd trimester if premature labor is expected (18, 37, 52). Estonia, Iceland, Ireland, and the United Kingdom recommend vaccination between the 2nd and 3rd trimester, as well as Romania if more than 10 years have elapsed after the last dose (18, 37, 55, 56). In Liechtenstein, pertussis vaccination is advocated during the 2nd trimester (18). Few countries recommend the vaccination in response to prevailing epidemiological trends, such

10.3389/fpubh.2024.1455318

TABLE 2 Vaccination programs for pregnant women in Europe.

Country	Influenza	Pertussis	Coronavirus	Tetanus	Diphtheria
Belgium[EU]	2nd–3rd trimester	24th–32nd week	1st–3rd trimester	24th–32nd week	24th–32nd week
Spain[EU]	1st–3rd trimester	From 27th week	1st–3rd trimester	From 27th week	From 27th week
Bulgaria[EU]	2nd–3rd trimester	27th–36th week		2nd–3rd trimester	2nd–3rd trimester
Ireland[EU]	1st–3rd trimester	2nd–3rd trimester	1st–3rd trimester	2nd–3rd trimester	2nd–3rd trimester
Italy[EU]	1st–3rd trimester	3rd trimester	1st–3rd trimester	3rd trimester	3rd trimester
Finland[EU]	1st–3rd trimester	From 16th to 32nd week	1st–3rd trimester		
Estonia[EU]	1st–3rd trimester	2nd–3rd trimester			
Croatia[EU]	1st–3rd trimester	2nd–3rd trimester			2nd–3rd trimester
Germany[EU]	2nd–3rd trimester*	2nd–3rd trimester	2nd trimester		3rd trimester**
Norway	2nd–3rd trimester*	From 24th week	2nd–3rd trimester	2nd–3rd trimester	2nd–3rd trimester
Denmark[EU]	2nd–3rd trimester*	24th–32nd week**	1st–3rd trimester		
Netherlands[EU]	2nd–3rd trimester	From 22nd week		From 22nd week	From 22nd week
Luxemburg[EU]	1st–3rd trimester	13th–26th week	From 10th week		
Portugal[EU]	2nd–3rd trimester	20th–36th week	1st––3rd trimester		
Iceland	1st–3rd trimester	2nd–3rd trimester	1st–3rd trimester		
Switzerland	1st–3rd trimester	13th–26th week	From 13th week		
Sweden[EU]	2nd–3rd trimester	From 16th week	From 12th week		
Austria[EU]	2nd–3rd trimester*	27th–36th week	2nd–3rd trimester		
Czech Republic[EU]	1st–3rd trimester	3rd trimester	From 13th week		
France[EU]	1st–3rd trimester	2nd–3rd trimester	1st–3rd trimester		
Romania[EU]	1st–3rd trimester	2nd–3rd trimester			
Ukraine	1st–3rd trimester	3rd trimester			
Cyprus[EU]	1st–3rd trimester	27th–36th week			
Greece[EU]	1st–3rd trimester	27th–36th week			
Poland[EU]	1st–3rd trimester	27th–36th week			
Liechtenstein	1st–3rd trimester	2nd trimester			
Slovenia[EU]	1st–3rd trimester	From 24th week			
United Kingdom	1st–3rd trimester	2nd–3rd trimester			
Serbia	1st–3rd trimester	3rd trimester			
Lithuania[EU]	1st–3rd trimester		1st–3rd trimester		
Slovakia[EU]	1st–3rd trimester		1st–3rd trimester		
Malta[EU]	2nd–3rd trimester*		From 12th week		
Moldova		3rd trimester			
Albania	1st–3rd trimester				
Belarus	1st–3rd trimester				
Hungary[EU]	1st–3rd trimester				
Latvia[EU]	1st–3rd trimester				
Monaco	1st–3rd trimester				
Russia	2nd–3rd trimester*				

Dark grey: Recommended for all pregnant women. Light grey: Recommended in specific situations: epidemics or at-risk conditions. *extended to 1st trimester only in women with high-risk conditions ** extended to 2nd trimester only in women with increased risk of premature birth.

as Moldova (recommended in the 3rd trimester during epidemics or high-risk conditions), France (recommended in the 2nd–3rd trimester in the epidemic territory), Croatia (recommended in the 2nd–3rd trimester in light of the ongoing pertussis epidemic) (37).

As far as diphtheria vaccination is concerned, in Bulgaria and Ireland it is recommended between the 2nd and the 3rd trimester of pregnancy, along with tetanus vaccination (18, 37). In the Netherlands, the diphtheria vaccination is advised from the 22nd

week of pregnancy, in Belgium between the 24th and 32nd week, in Spain and Italy in the 3rd trimester, ideally from the 27th week and at the 28th week, respectively (18, 37). In these countries, tetanus vaccination is also recommended in the same time window (18, 37, 57–61). In Finland, vaccination against diphtheria is recommended for all pregnant women, preferably at the end of pregnancy (18). In Germany, vaccination against diphtheria is advocated at the beginning of the 3rd trimester, and extended at 2nd in women at risk of pre-term birth (41), while in Estonia it is recommended for women presenting specific risk conditions (18); furthermore, in these countries, as well as in Finland, Denmark, Moldova, Romania, and Ukraine, tetanus vaccination is recommended for pregnant women who are either unvaccinated or incompletely vaccinated, as well as for pregnant women following exposure to potential tetanus risks (18). In Norway, the consideration for administering the diphtheria vaccine arises if clinically warranted; it is prudent to defer vaccination until the 2nd–3rd trimester rather than administering it during the initial trimester (18). Additionally, Norway recommends tetanus vaccination between the 2nd and the 3rd trimesters, specifically during epidemics or for individuals with risk conditions (18).

Croatia temporarily advises diphtheria and tetanus vaccination for all pregnant women during the 2nd–3rd trimester, along with vaccination for all close contacts of newborns (37).

COVID-19 vaccination is recommended for pregnant women across all trimesters in 14 European countries (Belgium, Bulgaria, Croatia, Denmark, Estonia, Finland, France, Iceland, Ireland, Italy, Lithuania, Portugal, Slovakia, Spain) (18, 37). On the contrary, in Luxembourg, it is suggested starting from the 10th week of pregnancy (62), while in Malta and Sweden, the recommendation begins from the 12th week (63, 64). In the Czech Republic, COVID-19 vaccination during pregnancy is deemed particularly appropriate for women exhibiting high-risk conditions predisposing them to infection or severe manifestations of COVID-19; the vaccination protocol stipulates that inoculation during pregnancy should be scheduled after the completion of the 12th week of gestation, hence commencing anytime from the onset of the 13th week of pregnancy (65), as well as in Switzerland (66). Austria and Norway recommend COVID-19 vaccination between the 2nd and 3rd trimesters (54, 67), while Germany during the 2nd (68). Bulgaria, Estonia, and Croatia recommend COVID-19 vaccination generally for all pregnant women (69–71).

A summary of the main vaccinations offered during pregnancy in Europe is provided in Table 2.

The heterogeneous landscape of vaccination policies across European nations underscores the complex interplay between epidemiological variables, healthcare infrastructure, and regulatory paradigms. Tailored vaccination initiatives, informed by WHO directives, are progressively being enacted to address the unique requirements of the pregnant women cohort. Ranging from trimester-specific recommendations to individualized strategies in response to epidemic circumstances, national protocols underscore the necessity for adaptive vaccination approaches. Considering the heterogeneity observed in pregnancy vaccination initiatives across European nations, it becomes imperative to delineate a cohesive framework aimed at ensuring optimal maternal and fetal health outcomes via evidence-informed and collaborative policy formulations.

3.2 Evidence on interventions aimed at promoting pregnant women's knowledge, attitudes, and behaviors in respect to vaccination

The initial search across MEDLINE/PubMed and Web of Science resulted in the identification of 3,186 studies. Following the removal of 1,470 duplicates and the exclusion of 1,406 studies based on the screening of titles and abstracts, a thorough full-text evaluation of the remaining 310 studies was conducted to assess their eligibility. Ultimately seven studies were included in the review, comprising three conducted in Italy (72–74), one in the Netherlands (75), one in Poland and Ukraine (76), one in Greece (77) and one in the UK (78). They encompassed a variety of research designs, including five before-after cross-sectional (72–74, 76, 77), one prospective (78), and one experimental (75) study. Four studies were conducted within hospital settings (72, 73, 76, 77). In particular, in the Italian studies, the Department of Obstetrics and Gynecology (72) and the Department of Women's and Children's Health and Public Health (73) organized and conducted antenatal courses; in Poland and Ukraine (76), as well as in Greece (77), the Perinatal Center and the Outpatient Clinic of the hospital carried out the perinatal visits. On the other hand, researchers in the Netherlands and in UK used online platforms for their studies (75, 78). Another Italian study adopted a hybrid approach combining hospital and online modalities due to the COVID-19 pandemic.

The recruited population across the studies comprised pregnant women participating in antenatal classes, those engaged in prenatal diagnostic consultations for congenital anomalies (72), or those attending routine prenatal visits (76, 77). The participants in the two studies conducted online were, in one case, pregnant women who signed up to the Qualtrics online panel to express interest in taking part in research activities (78), and, in the other case, pregnant women recruited through advertisement on social media (75). Sample sizes ranged from 119 (73) to 2,012 women (75), and included women between 18 and 40 years old (Table 3).

3.2.1 Methodological quality assessment (risk of bias)

One of the included quasi-experimental studies reported a score of 5 out of 12 (64), three a score of 6 out of 12 (59, 60, 65), and two a score of 7 out of 12 (61, 63), showing all fair quality. The only experimental study included in the review (62) reported a score of 7 out of 14 being of fair quality too.

3.2.2 Intervention characteristics

The educational interventions carried out exhibited heterogeneity across the studies. In five studies (72–74, 76, 77), interventions involved participant engagement with healthcare professionals. Among these, three (72–74) were conducted during antenatal classes held at varying frequencies, featuring educational sessions about vaccination and vaccines lasting 30–60 min and facilitated by highly qualified healthcare practitioners, with expertise in vaccinology. Since April 2020, one of these antenatal classes has been delivered online through digital platforms due to the COVID-19 pandemic (74).

Two interventions (76, 77) were integrated during routine prenatal visits. In the study conducted in Poland and Ukraine (76), participants were briefed on the safety, efficacy, and health benefits

TABLE 3 Study characteristics.

Author, year	Study setting and period	Study design	Population	Sample size	Objective	Intervention	Intervention setting	Intervention tool	Tool used to assess the impact of intervention	Main results	Additional results
Januszek et al., 2022 (76)	Poland and Ukraine-Hospital-from June to August 2021	Before-after cross-sectional study	Pregnant women who attended routine pregnancy visits	300 pregnant women, including 150 Polish and 150 Ukrainian	To describe the level of vaccination acceptance, to find the factors that most influence the decision to vaccinate, and to describe the scale of changes in vaccination acceptance influenced by medical information on the safety, efficacy, and benefits of COVID-19 vaccination among pregnant women.	Physicians updated patients on current COVID-19 vaccination recommendations, safety, efficacy, and health benefits during the visit.	Medical consultations by 11 gynecologists during routine pregnancy visits were carried out at the Provincial Clinical Hospital No. 1 in Rzeszów and at the Khmelnytsky Perinatal Perinatal Center.	NA	A questionnaire, marked with a number, was administered before and after the intervention. The pre-intervention questionnaire included 30 questions around demographic details, childbirth history and miscarriages, as well as aspects related to vaccination such as safety, efficacy, side-effects severity, and frequency, vaccination status, future vaccination intentions and reasons for vaccine refusal. The post-intervention questionnaire included 18 questions that were consistent with those in the pre-intervention questionnaire, excluding the data that remained unchanged, such as age, number of deliveries, and miscarriages. Descriptive and inferential statistics were used to analyze the results.	Before physician consultations 16.7 and 35.3% of Ukraine and Poland women expressed an intention to undergo vaccination. Subsequent to gynecological consultations, there was a significant increase in the proportion of patients inclined toward vaccination, with figures rising to 46 and 72.6%. Following consultation with a gynecologist, patients exhibited significantly increased awareness of the severity of COVID-19 in pregnancy, perceived their post-vaccination immunity as better than that following infection, recognized the safety of COVID-19 vaccination during pregnancy, and expressed greater confidence in its safety. Consequently, fewer patients reported fear about receiving the COVID-19 vaccine during pregnancy.	The main factors influencing the acceptance of vaccinations were the fear of harming the fetus (OR 0.119, CI 0.039–0.324 $p < 0.001$), complications in pregnancy (OR0.073 CI 0.023–0.197 $p < 0.001$), and poor vaccination opportunities due to limitations in the vaccination program (OR0.026 CI0.001–0.207 $p < 0.001$)

(Continued)

10.3389/fpubh.2024.1455318

TABLE 3 (Continued)

Author, year	Study setting and period	Study design	Population	Sample size	Objective	Intervention	Intervention setting	Intervention tool	Tool used to assess the impact of intervention	Main results	Additional results
Maltezou et al., 2019 (77)	Greece-Hospital-from October to December 2017	Before-after Cross-sectional study	Pregnant women who attended the Outpatient Clinic	304 pregnant women	To evaluate the knowledge about influenza and influenza vaccine and the adherence to recommendations for influenza vaccination of pregnant women	A leaflet with information about the complications of influenza was distributed to pregnant women Pregnant women also discussed with their obstetrician their concerns about vaccination.	Waiting room of the outpatient clinic at Alexandra General Hospital.	A leaflet with information about the complications of influenza during pregnancy and infancy and the efficacy and safety of influenza vaccine was distributed to pregnant women	Before the intervention, a standardized form was used to collect information about age, area of residence, immigrant, education level, number of household members, number of children <5 years old, underlying disease, number of parities, gestational age, pregnancy complications, scheduled cesarean section, smoking, intention to breastfeed, history of influenza vaccination in the past, awareness of recommendations for influenza vaccination. After the intervention a questionnaire with 11 questions was used to assess participants' knowledge about the impact of influenza on pregnant women, neonates, and young infants and the safety of the influenza vaccine was administered. Descriptive and inferential statistics were used to analyze the results. The rate of knowledge regarding influenza and influenza vaccine was computed as [(number of correct answers)/11]*100.	39.5% of women reported that they were already informed about the recommendations to get vaccinated against influenza. Their obstetrician was the prevalent source of information (58%), followed by internet/newspaper/TV (25.5%), other healthcare professionals (25%), and friends or relatives (9.5%). 57% of pregnant women stated that they intended to get vaccinated and received a prescription; 31% of those pregnant women were not vaccinated and their main reason for not being vaccinated was "being sick" (81%)	Fear of adverse events was a frequently reported reason (27%) among women refusing vaccination followed by the perception of uselessness of vaccination (18.5%) and of being at low risk of influenza (13%). Overall, 19.5% of participating pregnant women were vaccinated against influenza at a mean gestational age of 24.6 weeks (range: 12–37 weeks, SD: 7.5 weeks)

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TABLE 3 (Continued)

Author, year	Study setting and period	Study design	Population	Sample size	Objective	Intervention	Intervention setting	Intervention tool	Tool used to assess the impact of intervention	Main results	Additional results
Buursma et al., 2023 (75)	Netherlands-Online-from April to June 2020	Experimental study	Pregnant Women within 20th week, speaking Dutch language, who are hesitant about accepting MPV and experience negative affect concerning the decision	382 pregnant women (151 cognitive reappraisal,107 acceptance, 124 control)	To assess whether cognitive reappraisal and acceptance are effective emotion regulation strategies to decrease the influence of negative affect on intention to accept maternal pertussis vaccination (MPV) among pregnant women	After an online baseline questionnaire (t0), two intervention groups and a control group were established. Women in the first intervention group – the cognitive reappraisal group - had to describe how they experienced the decision about MPV by trying to focus on the positive aspects of MPV decision itself. In the second intervention group - the acceptance group - women had to describe how they experienced the decision about MPV by focusing on their emotions and figuring out which emotions were triggered and why. Participants in the control group received general instructions to think about MPV decision without any specific emotion regulation instructions;	Online context	Online instructions for Cognitive reappraisal, Acceptance and Control group in English and Dutch	After the intervention participants completed a 1st post-test survey (t1); seven days later, participants were invited via e-mail to respond to the 2nd follow-up survey (t2). At all three time points (t0, t1, t2), measurements included negative affect toward the decision about MPV, attitude toward MPV, and intention to accept MPV. The impact of interventions on negative affect over time was assessed using multilevel regression	All three groups showed a significant decrease in negative affect between baseline and the follow-up, but no significant differences were found between the cognitive reappraisal, acceptance, and the control groups in changing negative affect from baseline to the first and second follow-up	NA

(Continued)

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TABLE 3 (Continued)

Author, year	Study setting and period	Study design	Population	Sample size	Objective	Intervention	Intervention setting	Intervention tool	Tool used to assess the impact of intervention	Main results	Additional results
Costantino et al., 2021 (74)	Italy- Hospital From October 2019 to March 2020, online platform from March 2020 to October 2020	Before–after Cross sectional study	Pregnant women attending childbirth preparation courses	326 pregnant women	To evaluate the efficacy of an educational intervention to improve vaccination adherence during pregnancy	Participants took part in an educational intervention focused on maternal immunization during pregnancy, life course immunization, and vaccination recommended on the Italian Immunization Plan, conducted by healthcare professionals. At the end of the educational intervention, which usually lasted one hour, participants had the opportunity to express any doubts or concerns about the topics covered, and further vaccination counseling "on demand" was provided if requested.	Childbirth class at University of Palermo	A copy of the Vaccination Schedule of the Sicilian Region prepared by the Scientific Board of "VaccinarsinSicilia" was offered to all participants.	At baseline, participants filled in a 36 items-questionnaire, divided into five sections (demographic information and educational level; pregnancy history; self-knowledge about immunity status to Measles, Rubella, and HBV; knowledge and attitudes about influenza and DTPa vaccination during pregnancy and vaccination on early childhood). 30 days after interventions, adherence to influenza and DTPa vaccination of pregnant women was evaluated through contact by text and/or WhatsApp messages or by email address. Descriptive and inferential statistics were used to analyze the results.	After the intervention, among the responding pregnant women 47.8% received influenza vaccination (+44.8% compared to the period before the childbirth preparation course), 57.7% DTPa vaccination (+50.7% compared to the period before the childbirth preparation course) and 64.2% at least one of the two vaccinations recommended (+54.8% compared to the period before the childbirth preparation course)	A significant association was found between pregnant women who received at least one vaccination and higher educational level (graduation degree/master's degree), employment status (employed part/full-time), and influenza vaccination adherence during past seasons (at least one during last five years)
Bruno et al., 2021 (73)	Italy- Fondazione Policlinico Universitario Agostino Gemelli IRCCS (FPG)-From October 2019 to January 2020	Before–after Cross sectional study	Women from the 4th month of pregnancy attending childbirth preparation courses	119 pregrnant women	To increase awareness and attitudes to vaccination in pregnant women, to evaluate the effectiveness of the on-site influenza vaccination offer to pregnant women (and their partners).	a 30–40 min vaccination session was held addressing the definition and mechanism of vaccines, vaccine components and classifications, adverse reactions, prevalent misconceptions, vaccination schedules during pregnancy, and access to vaccination services through the Italian National Health System, the vaccination calendar, and the mandatory vaccines in Italy.	The antenatal classes at hospital FPG	NA	Before and following the training session, participants completed a voluntary anonymous questionnaire assessing their knowledge, awareness, of vaccination, and their compliance through flu vaccination. Descriptive and inferential statistics were used to analyze the results.	Significant differences were noted in participants' knowledge regarding the severity of infectious diseases before and after the intervention. Awareness of the severity of Hib increased from 35.63 to 54.05%, knowledge of poliomyelitis rose from 68.82 to 88.46%, and understanding of diphtheria improved from 40.45 to 61.84%. A significant change was observed in the preferences for tetanus vaccinations between the pre-and post-intervention questionnaires. During the study, 40.34% of participants received the influenza vaccination	The number of participants believing that there is no relationship between vaccination and autism rose from 41.05% in the pre-intervention to 72.97% in the post-intervention

(Continued)

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TABLE 3 (Continued)

Author, year	Study setting and period	Study design	Population	Sample size	Objective	Intervention	Intervention setting	Intervention tool	Tool used to assess the impact of intervention	Main results	Additional results
Bechini et al., 2019 (72)	Italy- Obstetrics and Gynecology Department-From October 2017 to May 2018	Before–after Cross sectional study	Pregnant women attending childbirth preparation courses a/o prenatal diagnostic counseling on congenital defects	210 pregnant women	To evaluate pregnant women's knowledge of and attitudes toward vaccination, their sources of vaccine information, and the impact of an educational intervention carried out by experts on vaccination	A 30-min intervention session focusing on vaccine prevention, conducted by vaccination experts Topic intervention: definition and mechanism of vaccines, concept of herd immunity, contraindications and associated risks of vaccination, detailed explanation of the National Vaccine Plan Prevention, efficacy of vaccines, recent epidemic trends, debunking of false myths, considerations regarding vaccination during pregnancy, legal aspects of compulsory vaccinations, and guidance on accessing reliable information sources.	Childbirth preparation courses or prenatal diagnostic counseling on congenital defects at the Obstetrics and Gynecology Department at the University of Florence	The intervention was supported by a set of slides, the paper version of which was then distributed to each participant	A pre-intervention questionnaire comprising sections on knowledge and attitudes toward vaccinations and the Italian vaccination program, alongside personal information including age, country of origin, and qualification was administered and followed by a post-intervention questionnaire identical to the pre-intervention. Descriptive and inferential statistics were used to analyze the results	After the intervention, there was a significant decrease from 43 to 13% in responses signifying a low level of knowledge about vaccines. A significant increase in knowledge of vaccines such as diphtheria, tetanus, pertussis, poliomyelitis, Hib was found between pre and post intervention. The average pre-intervention score for items related to women's intentions regarding vaccination during pregnancy and vaccinating their children was 35.46 (95% CI 33.62–37.30), which increased to 42.57 (95% CI 41.31–43.82) post-intervention	The primary source of information regarding vaccines and vaccinations was reported to be word of mouth, followed by family doctors and mass media
Parson et al., 2022 (78)	UK-Online-from October to November 2019-form March to April 2020	Prospective before-after study	Pregnant women living in England, and not having received the flu vaccination during that flu season	411 pregnant women	To evaluate if the intervention effectively increased pregnant women's intention to undergo influenza vaccination during pregnancy and influenza vaccine adherence	A 4-min animation was used to inform pregnant women about the risks of flu to themselves and their unborn babies, the effectiveness of the flu vaccination and its ease of administration.	Qualtrics survey software-online	4-min animation provided simple visual demonstrations of the processes involved in the pathogen infecting pregnant women, and how the flu vaccination works to disrupt it. Descriptions of the vaccine component, and how it works to protect pregnant women and unborn babies were also provided, to rectify any misconceptions, and reassure pregnant women about the safety and effectiveness of the vaccination	Before receiving the intervention and immediately afterward participants completed a short anonymous survey measuring illness risk appraisals. Six months later, a further short survey was administered to measure vaccination behavior and attitudes. Descriptive and inferential statistics were used to analyze the results	67 participants completed the follow-up survey at six months of follow-up. Of those no longer pregnant (43), 53.5% reported receiving the vaccination, while 46.5% had not. Among the 24 participants still pregnant, 62.5% had received the vaccination, while 37.5% had not, with 33.3% expressing no intention (44.4%) being uncertain, and (22.2%) intending to receive it. Additionally, of those with a higher intention to receive the vaccination 57.1% proceeded to receive it.	Participants' perceptions of the likelihood and severity of flu during pregnancy significantly increased after viewing the animation

10.3389/fpubh.2024.1455318

associated with COVID-19 vaccination by gynecologists, In the study conducted in Greece (77) participants were provided with an informational leaflet on influenza and influenza vaccination while in the waiting room of the clinic (77), followed by consultations with midwives (77).

In the study carried out in the Netherlands (75) pregnant women were randomly assigned to one of the 3 online groups (cognitive reappraisal intervention group, acceptance intervention group, and control group) to evaluate the influence of negative affect on intention to accept maternal pertussis vaccination (MPV). The cognitive reappraisal group was instructed to describe their experience relating to the decision regarding MPV, with specific attention to its positive aspects. The acceptance group received instructions to describe their emotional experience related to the MPV decision, trying to identify the emotions triggered and their causes. Finally, the control group received general instructions to reflect on the decision regarding MPV, without a specific focus on emotion regulation.

In another study (78), carried out online, the intervention comprised a 4-min animated video designed to inform pregnant women about the risks posed by influenza to both themselves and their unborn babies, as well as to elucidate the efficacy of the flu vaccine and its ease of administration.

3.2.3 Tools for assessing the impact of intervention

In all the studies, questionnaires were used to evaluate the impact of the interventions. One Italian study (73) used a pre-and post-intervention questionnaire adapted from a validated tool (79) to assess knowledge, awareness of vaccination, and compliance to influenza vaccination. In another Italian study (72), a pre-and post-intervention non-validated questionnaire was employed, encompassing demographic details (age, country of origin, and educational attainment) alongside inquiries about participants' knowledge and attitudes toward vaccinations, as well as their awareness of the Italian vaccination schedule. The pre-post intervention questionnaires in both studies (72, 73) included questions about participants' knowledge and attitudes toward vaccinations; however, the specific focus and detail of these questions differed between studies. In the third Italian study (74), the pre-intervention survey was performed through a questionnaire validated in a preliminary pilot study, while the post-intervention assessment was performed by text message and/or WhatsApp message or e-mail contact and was aimed to evaluate adherence to flu vaccination and/or diphtheria–tetanus–pertussis acellularis (DTPa), as well as the main reasons for refusing vaccination.

Also, the studies conducted in Poland and Ukraine (76) and the UK (78) adopted a pre-post-intervention non-validated questionnaire survey, measuring safety, efficacy, side-effects severity, and frequency of vaccinations (76) and illness risk appraisal (78) respectively; both studies explored vaccination attitudes, one conducting the assessment immediately following the educational intervention (76) and the other six months after the intervention (78). In the investigation undertaken in Greece (77), a standardized non-validated questionnaire with 11 questions was employed to assess pregnant women's understanding of influenza and their compliance with influenza vaccination after the educational intervention. The study undertaken in the Netherlands employed a survey administered at baseline, alongside two subsequent post-intervention surveys, to assess the impact of negative affect on the intention to accept MPV (75).

3.2.4 Results

3.2.4.1 Effects on knowledge

Pregnant women's knowledge about vaccines and vaccine-preventable diseases was assessed in six (72–74, 76–78) of the included studies.

The evidence showed that the main sources of vaccination information were obstetricians (58%) (77), independent research (52.9%) (73), word of mouth (friends, family members, etc.) (9.5–50%) (72, 77), traditional mass media (TV, radio, and newspapers, internet) (19.5–35.7%) (72–74, 77), health professionals, particularly family doctors (25–45.7%) (72, 74, 77). Specialists such as pediatricians and gynecologists were consulted less frequently (16.2–21.4%) (72). Additionally, within a study carried out in Italy (73), post-intervention questionnaires revealed that 64.6% of respondents (51/79) deemed the prenatal course highly beneficial for information acquisition, showing a significant increase compared to the pre-intervention questionnaire results (30.3%, 27/89 respondents).

The level of knowledge regarding the recommendation for influenza vaccination during pregnancy exhibits considerable variability among pregnant women. In a study conducted in Italy (74), in the pre-intervention, approximately 70% of the interviewees were aware of the recommendation for influenza vaccination during pregnancy, but only 23.9% demonstrated awareness that influenza vaccination during pregnancy could be administered throughout all trimesters of gestation. Furthermore, 58.6% were aware of the recommendation of DTPa vaccination during pregnancy, but 54.6% did not know the correct timing for vaccination during pregnancy, while only 32.8% knew about the necessity of receiving a DTPa vaccine booster in each pregnancy. In a study conducted in Greece (77), in the post-intervention, 39.5% of the participants reported being already informed about the recommendations for influenza vaccination. The same study found that the average knowledge score on influenza and influenza vaccination, after the intervention, was 87% (77). However, neither the Italian nor the Greek studies evaluated the impact of the intervention on knowledge through a pre-post comparison (74, 77).

Furthermore, regarding information on vaccine-preventable diseases, in the study carried out in Poland and Ukraine (76), only 28.1% of the participants in the pre-intervention declared having received information regarding COVID-19 vaccination from their healthcare provider.

The evidence shows a low level of general knowledge about vaccinations against infectious diseases in the pre-intervention, as demonstrated by 43% of responses indicating poor or insufficient level of knowledge (72); following the educational intervention there was a notable 30% decrease in responses indicating a low level of knowledge in the vaccination field (72).

In terms of understanding the risks associated with infectious diseases, the findings indicate that, before the educational intervention, only 36.5% of participants were aware of the possible complications resulting from pertussis in newborns, and as many as 42.9% were uninformed about the potential repercussions of severe complications of influenza on both the mother and the fetus, as well as the newborn (74).

Moreover, it was revealed that 35.63% of respondents in the pre-intervention questionnaire, perceived influenza as quite serious, while almost 54% of the women in the post-intervention

questionnaires shared this perception (73), with a notable increase. A significant increase in participants' perception of the severity of influenza during pregnancy was also found following the educational intervention conducted in the British study (78).

The data showed that before the intervention, a notable proportion of women (40.5%) regarded diphtheria infection as very severe (73). Following the intervention, there was a significant increase in the proportion of women (61.8%) who perceived the infections as highly severe (73). Furthermore, after medical consultation, participants exhibited significantly heightened awareness regarding the severe clinical manifestations of COVID-19 infection (76).

Regarding vaccine safety, during the pre-intervention of one of the Italian studies (72), 15% of participants reported direct or indirect personal experiences with one or more post-vaccination adverse effects, including severe conditions such as autism, meningitis, deafness, polio, and acute leukemia. However, following the intervention, there was a reduction in this percentage, suggesting that the instances reported in the pre-intervention survey were possibly influenced by unsubstantiated beliefs or misinformation rather than genuine personal experiences.

Two studies conducted in Italy (72, 73) revealed a significant rise in the percentage of individuals who disregarded the existence of a causal association between vaccines and autism after the intervention, escalating from 43.8% (72) and 41% (73) during the pre-intervention to 84% (72) and 73% (73) during the post-intervention.

After the educational intervention, there was a significative increase in the proportion of individuals expressing a lack of concern regarding the adverse effects associated with vaccination (pre-intervention 33.3%, post-intervention 57.2%), believing that vaccines have mild side effects (pre-intervention 77.5%, post-intervention 97.40%) (73), and holding the belief that administering multiple vaccines simultaneously does not pose harm to the health of their offspring (pre-intervention 15.2%, post-intervention 70.1%) (72).

Noteworthy is the significant increase also in general knowledge regarding recommended pediatric vaccines, including diphtheria, tetanus, pertussis, poliomyelitis, and HIb, following the intervention (72).

In conclusion, these studies revealed a significant impact of educational interventions on pregnant women's knowledge about vaccines and vaccine-preventable diseases. These interventions led to increased awareness of vaccination recommendations, decreased misinformation, and improved understanding of the severity of vaccine-preventable diseases.

3.2.4.2 Effects on attitudes

Six (72, 73, 75–78) out of the seven studies included in the analysis provided insights into the attitudes of pregnant women toward vaccination for themselves.

In an Italian study (72), the mean score quantifying the inclination to vaccinate during pregnancy was 35.46 (95% CI: 33.6–37.3) before the intervention and 42.57 (95% CI: 41.3–43.8) after the intervention. Considering that the score was calculated assigning a value of "0" to responses indicating opposition to vaccination, a value of "1" to neutral or hesitant responses, and a value of "3" to responses showing a support to vaccination, the results showed a shift toward a greater support to vaccination (72).

In another study conducted in Italy, an examination of the expressed preferences for vaccinations against individual infectious diseases revealed a significant surge in the inclination toward tetanus vaccination, with an increase from 80.77 to 91.14% (73).

Following the educational intervention, a notable increase was discerned in the responses concerning women's intentions to undergo several vaccinations for themselves, including diphtheria and pertussis (72, 73).

A significant increase in the inclination to undergo influenza vaccination during pregnancy was highlighted in the study conducted in the UK (78) at the first follow-up assessment after the educational intervention. Moreover, within this study, both the probability of contracting influenza during pregnancy and the intention to receive the influenza vaccine emerged as significant positive predictors of influenza vaccination (78). Among the cohort of 411 participants in this study (78), 67 individuals completed the second follow-up. Within this subset, 57.1% of the participants who exhibited an increased intention to undergo vaccination (with a score of $\geq$6 out of 10) during the initial follow-up, subsequently received the vaccine (78).

In the investigation conducted in Greece (77), 57% of the participants expressed the intent to receive the vaccine and were accordingly prescribed it. However, despite the expressed intention and prescription, a substantial portion, comprising 31% of the individuals, did not proceed with vaccination. The predominant reason cited for non-adherence was "being sick," as reported by 81% of women who had not been vaccinated.

A significant escalation in the intention to receive vaccination is evidenced also in the study conducted in Poland and Ukraine (76). Before medical consultations, 35.3% of patients in Poland and 16.7% of patients in Ukraine indicated their plans to undergo COVID-19 vaccination. Following medical consultations, the percentage of patients expressing willingness to receive vaccination surged to 72.6% in Poland and 46% in Ukraine. The data also showed that participants with higher education exhibited significantly greater level of vaccination acceptance compared to women with lower one (76). The investigation additionally underscored that heightened resistance to vaccination and incidence of patient-perceived post-vaccination complications corresponded with the diminished likelihood of altering the decision regarding COVID-19 vaccination after medical consultation (76). Predictors of reduced likelihood of vaccination included apprehension regarding fetal harm, perceived post-vaccination complications, and limitations in vaccinations program offered (76).

The study carried out in the Netherlands (75) demonstrated that an elevated magnitude of negative affects is markedly linked to a diminished inclination to embrace pertussis vaccination. Furthermore, within this study, all 3 groups, cognitive reappraisal intervention group, acceptance intervention group and control group, exhibited a noteworthy decrease in negative affect, with no notable disparities observed among them (75). Furthermore examining the written responses provided by participants across all groups, the adoption of emotional acceptance emerges as a promising approach in alleviating the influence of negative affect on the intention to accept pertussis vaccination (75).

In conclusion, the studies results revealed a notable shift toward greater acceptance and intention to vaccinate among pregnant women, influenced by educational interventions, medical consultations and emotional regulation strategies.

3.2.4.3 Effects on behavior

Following the educational intervention, a notable increase in adherence to influenza vaccination was observed across four studies (73, 74, 77, 78).

In two studies, conducted, respectively, in Italy (74) and Greece (77), 47.8% of respondents in the follow-up (74) and 19.5% of participants (77) reported having been vaccinated post-intervention, compared to 3.1% (74) and 10.53% (77) in the pre-intervention, indicating a significant increase (Figure 1).

In two studies conducted in Italy (73) and the UK (78), respectively, 40.34% of participants (73) and 57% of respondents (78) reported receiving influenza vaccination after the educational intervention.

The empirical findings suggest that after the implementation of the educational intervention, a significant augmentation in adherence to DTPa vaccination was observed, with rates escalating from 7.4 to 57.7% (74).

Factors influencing vaccination behavior were also addressed in the included studies. In two of them (74, 77) a significant association was also found between adherence to recommended vaccinations and a higher level of education. Indeed, findings from a study conducted in Italy emphasized that individuals with a higher level of education (bachelor's/master's degree) exhibited notably greater adherence to recommended vaccinations in comparison to counterparts with lower educational attainment (high school/primary-secondary school diploma) (adjusted OR = 3.12; 95% CI 1.25–4.67) (74). The aforementioned findings are corroborated by those from the investigation undertaken in Greece, wherein a demonstrably significant correlation was established between higher educational attainment (college-university level) and heightened compliance with vaccination protocols (77).

Evidence also indicated that a thorough understanding of influenza and influenza vaccine, and prior influenza vaccination history, were significantly associated with an increased likelihood of receiving influenza vaccination during pregnancy [respectively OR from 1.69 (74) to 17.8 (77), and from 3.6 (77) to 4.12 (74)], in contrast to individuals lacking adequate knowledge regarding influenza and the flu vaccine, as well as those who have not received vaccinations in preceding years.

Despite the implementation of educational interventions, various factors contributed to women's reluctance to undergo vaccination during pregnancy, as evidenced by findings from three studies (74, 76, 77).

In the study conducted in Poland and Ukraine (76), participants cited concern about fetal harms and post-vaccination complications/adverse reactions, with fear being a key emotional driver influencing their decision to avoid the COVID-19 vaccine. These concerns decreased significantly after the intervention.

Additionally, in two separate studies (74, 77), post-intervention data revealed that 47.6% (74) and 27% (77) of participants who cited reasons for refusing influenza vaccination identified fear of adverse events as the main deterrent. In a study conducted in Italy (74) the secondary predominant reason for vaccine refusal was the absence of recommendations from gynecologists/obstetricians, highlighting the pivotal role of healthcare professionals in addressing vaccination hesitancy. Additionally, the belief that influenza vaccination is unnecessary and that the risk of contracting the flu is low has been cited as additional reason for vaccine refusal (77).

In conclusion, the educational intervention led to a significant increase in vaccination adherence across several studies. Higher education levels were associated with greater adherence to recommended vaccination regimens. However, despite these positive outcomes, vaccine hesitancy persists among pregnant women, emphasizing the continued need for interventions and the crucial role of healthcare professionals in addressing concerns.

4 Discussion

The primary objective of this investigation was to provide an examination of the latest national vaccination policies for pregnant women in European countries and to ascertain the effects of educational interventions targeted at pregnant women on their knowledge, attitudes, and behaviors regarding vaccination within the European setting.

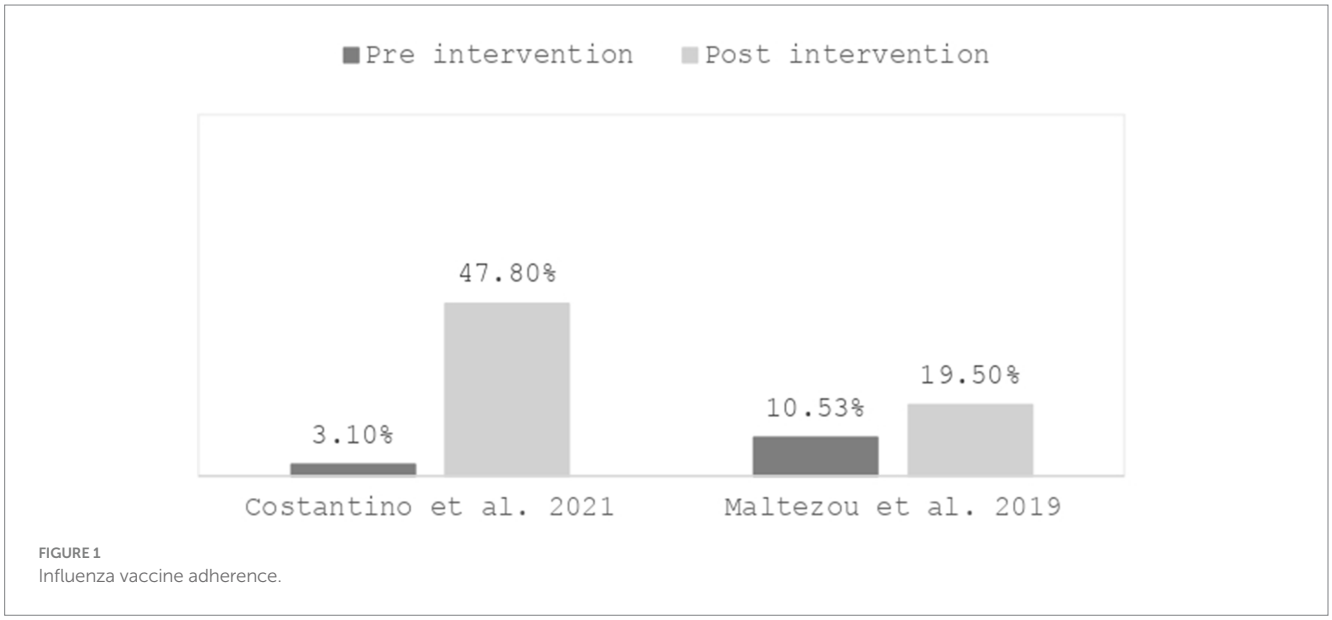

FIGURE 1
Influenza vaccine adherence.

In each country, vaccination policies may be shaped by disparities in the incidence of vaccine-preventable diseases, vaccination adherence rates, costs, and criteria used to issue recommendations and assess potential reimbursement (80, 81). Vaccine characteristics, such as efficacy or effectiveness and safety, are critical in shaping vaccination policies, as they directly influence public health outcomes and disease prevention strategies (81). Equally important is vaccine acceptability, which affects public uptake and the success of vaccination programs. If a vaccine is not widely accepted, its impact may be limited despite its efficacy (81). Additionally, vaccination policies must consider alternative interventions, such as public health campaigns or treatments, to ensure a balanced approach to disease prevention (81). The complex interaction between these factors could be reflected in the diversity in vaccination policies between European countries (18, 37, 62–65, 82–84). Despite this, following WHO guidelines (13–15), tailored vaccination programs are increasingly being implemented. From trimester-specific recommendations to personalized strategies during epidemics, national protocols highlight flexible vaccination approaches in pregnancy.

However, given the European decreasing confidence in vaccines (85), it would be useful to establish cohesive and harmonized pregnancy vaccination strategies across European countries to promote optimal outcomes in terms of maternal and fetal health. A viable approach to harmonize vaccination recommendations across Europe, while accounting for national variations, would involve the establishment of a transparent and common, yet adaptable, European framework to identify a core set of priority recommended vaccines while allowing individual countries to integrate additional vaccines according to their specific epidemiological circumstances. In this light, ongoing and systematic monitoring would facilitate timely adjustments to the core set of recommended vaccines, ensuring it remains responsive to evolving epidemiological conditions, also in relation to specific cases. Furthermore, ensuring that information regarding vaccination schedules and local updates is readily accessible and understandable to both healthcare professionals and the public is crucial to guarantee the equity and continuity of vaccination offer, particularly for individuals traveling between countries. Transparency and standardization in decision-making processes, coupled with a thorough and regular assessment of vaccination policies are imperative to allow harmonization.

In this context, governments assume a central role in structuring and implementing evidence-based vaccination policies and strategies tailored to pregnant women and capable of responding to any specific epidemiological situation, such as a potential high circulation of the pathogen, but also to integrate with existing vaccination recommendations in the general population.

In order to enhance vaccine uptake it is of utmost importance to also address knowledge and attitudes as foundations of individual behaviors. Our review encompassed seven studies addressing these aspects through educational interventions in pregnant women. Comparability across studies was restricted owing to variations in the contexts and nature of interventions implemented, as well as the criteria and methodologies used for evaluating results. Furthermore, the generalizability of the results can be influenced by the specific context of each country. For example, countries such as the United Kingdom, Greece, Poland, and Ukraine have similar vaccination policies for pregnant women, including recommending pertussis and influenza vaccines, as highlighted in our research (18, 37). In these countries, educational interventions have been implemented (76–78) specifically to raise awareness of influenza and pertussis vaccination. Therefore, given the existing vaccination awareness promoted by national policies, one might hypothesize that an educational intervention developed in one of these countries could have similar effectiveness when implemented in another. However, substantial heterogeneity in vaccination policies across countries, coupled with variations in national health cultures and health systems, complicates the prediction of the effectiveness of educational interventions developed within one national context when applied in another. This highlights the need for a more nuanced assessment of the adaptability and effectiveness of such interventions in accordance with the unique conditions of each country. Nevertheless, we contend that a favorable inference can be derived from the findings of the studies we reviewed, albeit challenges remain also in particular with respect to the reproducibility of interventions and methodology to assess their impact.

A relevant aspect that emerged from the collected evidence is concerning primary sources of information for pregnant women that mostly encompass obstetricians and healthcare practitioners (72–74, 77). In this respect, the absence of recommendations from gynecologists/obstetricians emerged as a pivotal determinant influencing vaccine refusal from one study conducted in Italy (74). In a recent Italian survey, about one-third of gynecologists expressed safety concerns about administering the influenza vaccine during the first trimester whereas Tdap vaccination is recommended in the third trimester with less safety concern (86). Furthermore, most participating gynecologists had themselves low influenza and Tdap vaccination rates, which might have affected their confidence in recommending vaccines (86, 87). Indeed, gynecologists/obstetricians are regarded as trusted healthcare professionals during pregnancy in Italy (85), therefore their advice was shown to play a crucial role in influencing decisions regarding vaccination uptake (88). This also aligns with the evidence of the fundamental role of healthcare professionals in combating vaccination hesitancy (29, 89–92). Nonetheless, albeit vaccinations should be addressed during antenatal care, it is not certain that this is done constantly and in a standardized way. The increasing prevalence of healthcare workers declining vaccination for themselves and abstaining from recommending it to their patients (93–96) may contribute to patient vaccine refusal and the observed low rates of vaccination acceptance, as also suggested in the discussion of one of the considered studies (76). A recent systematic review of the literature on vaccine hesitancy and vaccination coverage among healthcare workers in Europe has highlighted significant variability across countries and among vaccines (97). Vaccine hesitancy varies by country, with rates of 8% among all healthcare workers in Italy and up to 40% among physicians in France. Variations are also higher in respect to COVID-19 vaccines. Eventually, despite methodological differences across studies, physicians consistently exhibited lower levels of vaccine hesitancy compared to nurses, alongside higher vaccination rates for several vaccines, including COVID-19, influenza, diphtheria, tetanus, and pertussis (97). Contributing factors to vaccine hesitancy and vaccination refusal among healthcare professionals include concerns about adverse side effects, influence from individuals in personal networks who refuse vaccination, and diminished trust in vaccines,

paralleling trends observed in the general public (97). It is anyhow worth noting that not all healthcare practitioners are experts in vaccinology, and their vaccine hesitancy may stem from uncertainties or even doubts regarding potential risks, public controversies, misinformation, as well as interactions with hesitant patients (97, 98). Hence, the training and implementation of tailored educational interventions on vaccination also for healthcare professionals are deemed imperative because awareness and knowledge were also found to increase healthcare professionals' willingness to recommend vaccination (93).

Moreover, the execution of educational interventions facilitated by healthcare professionals specially trained may serve to alleviate misinformation concerning vaccines, which may stem from traditional (99) and social (100) mass media or word-of-mouth sources (101). Indeed, mass media have the potential to exert negative effects on vaccine-hesitant populations or instead, they could be used as a vital tool for disseminating vaccination culture (99, 102), despite assertions in existing literature indicating that women place greater trust in information provided by healthcare professionals compared to that disseminated through mass media or informal communication channels (89). For this reason, an effective strategy could be represented by educational intervention, carried out through social media but by healthcare professionals. Three studies (74, 75, 78), examined in the review, exemplify a commendable utilization of media for enhancing vaccination awareness among pregnant women, employing online platforms and the internet as vehicles for educational interventions and subsequent evaluation of outcomes, showing an effective approach toward addressing vaccination awareness. In one of the included studies (75), social media platforms were leveraged for participant recruitment, thus allowing the target population to be easily reached, as prospective parents demonstrate regular activity on social media and those uncertain about their decision about vaccination tend to look for information online.

Even if vaccination refusal is usually multifactorial (103), the deficiency of information regarding the safety and efficacy of vaccines commonly catalyzes vaccination refusal (104). The results of our review showed a notable deficiency in knowledge and awareness concerning the vaccination field, specifically recommended vaccines during pregnancy (72, 74, 76, 77), vaccine-preventable diseases, and their severity for both pregnant women and offspring (72–74, 76, 78) before any educational intervention, consistent with extant literature (29, 91, 105–107).

Conversely, following the implementation of educational interventions, there was a discernible increase in comprehension within these domains, leading to an escalation in the inclination to receive vaccinations during pregnancy (72), consequently resulting in a significant enhancement in adherence to recommended vaccination recommendations (73, 76, 77). Nevertheless, caution should be paid in the interpretation of these results because it is expected that pregnant women's knowledge about recommended vaccination increases with the increase in gestation week. Unfortunately, the specific week of pregnancy during which knowledge was assessed was not explicitly stated, except indirectly in the case of two Italian studies that reported that the most of participants were in the third trimester (73, 74).

Nevertheless, in this respect a standardized and validated curriculum should be developed to lead educational interventions and make them more comparable. This curriculum should be evidence-based and encompass vaccine-preventable diseases characteristics, recommendations for vaccination in pregnancy, and vaccines efficacy, effectiveness and safety. The curriculum could be adopted by trainers in the field as well as by all healthcare professionals engaged in prenatal care, including gynecologists, obstetricians, midwives, and nurses. A particular attention should be paid to adapt the curriculum to pregnant women's needs and capabilities. In fact, our data also showed a general lower likelihood of vaccination during pregnancy in individuals with a low degree of education (74, 76, 77), in accordance with existing literature (108, 109). Thus, it is advisable to customize educational interventions to align with the educational and socio-demographic context of the target population, given that these variables may exert influence on vaccination decisions.

The educational intervention ought to comprehensively address not only the potential adverse effects of vaccination, debunking associated misconceptions and contrasting negative affect, i.e., fear, discomfort, anticipated regret (75), and perception of complications and damage after administration (76), but also underscore the risks associated with vaccine refusal for both the pregnant woman and her offspring, which may lead to significant complications.

The multi-component approach, incorporating educational interventions and vaccination administered by trained personnel, alongside healthcare professional training and continuous education, has exhibited superior effectiveness in enhancing maternal attitudes toward recommended vaccines during pregnancy (94–96, 98). Moreover, it has proven efficacious in augmenting vaccination adherence rates among both prenatal and postnatal women (94–96, 98). Furthermore, new methodologies, including reminder and active call systems (94, 95), as well as the utilization of digital modalities such as text, video, or audio messages, and internet-based interventions (e.g., websites, mobile applications, or social media platforms), have underscored their effectiveness in a context significantly influenced by the recent COVID-19 pandemic. This context is also marked by heightened vaccine hesitancy, alongside an overall increase in the complexity of vaccination schedules, heightened expectations from caregivers, and lifestyle changes (100).

The findings of our work should be read considering some limitations. First of all, the search strategy adopted to look for both vaccination policies in European countries and the evidence on educational intervention might have failed in identifying all relevant information also considering that some recommendations could be issued in local languages thus being difficult to find and report. Another aspect to be considered is that vaccination policies could be implemented differently between and within countries. Regarding the evidence on the impact of educational interventions, it should be noted that, because all studies relied on questionnaires, whether validated or not, the potential for social desirability bias could not be ruled out. Notably, the studies included in our review did not employ tools designed to specifically measure social desirability bias. However, the use of anonymized questionnaires in these studies may have helped mitigating this bias. Additionally, in one instance (75), being a randomized experimental study, the process of randomization may have contributed to controlling for this bias. As a matter of fact, all studies included in our work were judged of fair quality and this calls for other research in the field to better disentangle the potential impact of educational interventions also considering different contexts.

5 Conclusion

In conclusion, there is considerable variability across European countries regarding vaccination policies during pregnancy. Tailored vaccination policies and recommendations, aligned with WHO guidelines, reflect the diverse epidemiological contexts and healthcare systems of individual countries.

Educational interventions carried out to promote pregnant vaccination by increasing knowledge and changing attitudes varied in approach and context so far. Nonetheless, they collectively demonstrated significant impacts on pregnant women's vaccination-related knowledge, attitudes, and behaviors in Europe. From antenatal classes to online platforms and informational leaflets, these interventions led to increased awareness of vaccination recommendations, reduced misinformation, and improved understanding of the severity of vaccine-preventable diseases. Indeed, pre-intervention assessments revealed gaps in knowledge and concerns about vaccine safety, but post-intervention, there was a notable improvement, leading to enhanced adherence to recommended vaccination protocols.

Healthcare professionals emerged as the most trusted source of vaccination information, highlighting their crucial role in addressing vaccine hesitancy.

Attitudes emerged as a significant predictor of intention to vaccinate, with positive attitudes associated with stronger intentions. Emotional regulation strategies also played a role in increasing vaccination acceptance.

Behaviorally, there was a significant increase in adherence to influenza and DTPa vaccination post-intervention, particularly among those with higher education levels. However, vaccine hesitancy persisted among some, driven by concerns about adverse events and a lack of recommendations from healthcare professionals.

Overall, the findings of this investigation underscore the importance of strengthening the process behind the development of evidence-based vaccination policies and the need for specific educational interventions to increase vaccination acceptance and optimize maternal and fetal health outcomes in the European context. Further research and collaborative efforts are warranted to address barriers and facilitators to vaccination uptake among pregnant women.

Author contributions

SP: Data curation, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. RC: Data curation, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. VB: Data curation, Investigation, Writing – review & editing. VC: Data curation, Investigation, Writing – review & editing. BM: Data curation, Investigation, Writing – review & editing. ES: Data curation, Investigation, Writing – review & editing. EB: Writing – review & editing. CW: Conceptualization, Supervision, Writing – review & editing.

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Policy brief: Improving national vaccination decision-making through data

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Life course immunisation looks at the broad value of vaccination across multiple generations, calling for more data power, collaboration, and multi-disciplinary work. Rapid strides in artificial intelligence, such as machine learning and natural language processing, can enhance data analysis, conceptual modelling, and real-time surveillance. The GRADE process is a valuable tool in informing public health decisions. It must be enhanced by real-world data which can span and capture immediate needs in diverse populations and vaccination administration scenarios. Analysis of data from multiple study designs is required to understand the nuances of health behaviors and interventions, address gaps, and mitigate the risk of bias or confounding presented by any single data collection methodology. Secure and responsible health data sharing across European countries can contribute to a deeper understanding of vaccines.

KEYWORDS

National Immunisation Technical Advisory Groups, National Immunisation Programs, life course immunisation, vaccine policy, vaccine-preventable diseases, big data analysis, AI technologies

Introduction

In the current climate, infectious disease prevention faces significant challenges that are multifaceted and increasingly global in scope:

- Climate change causes changes in weather patterns, expanding the geographical reach of vector-borne infectious diseases like malaria and dengue (1).
- Increasingly complex geopolitical tensions disperse vulnerable populations and disrupt local and global vaccination provision.
- An ageing population and low vaccine uptake mean more people are at risk of experiencing illness from vaccine-preventable diseases (VPDs) (2).
- Inequality, insufficient financing and public sentiment are some factors that disrupt access and hinder effective coverage targets.

Amidst these evolving global health challenges, this review critically assesses the landscape of national vaccination decision-making. It focuses on integrating robust data analysis to inform effective strategies and explores how data-driven approaches can significantly enhance policy recommendations and public health outcomes.

The Coalition for Life Course Immunisation (CLCI) – www.cl-ci.org – is a charity registered in Belgium and the United Kingdom that aims to Increase vaccine uptake in all ages to improve health and protect Europe from vaccine-preventable diseases. CLCI promotes the interpretation

of broad data sets to advocate for life-course immunisation strategies. These strategies aim to capture the total value of vaccination across generations, address future health risks and threats, prevent vertical transmission from parent to child, and mitigate long-term health consequences. As shown in Figure 1, the CLCI's manifesto emphasises adopting data-driven policies and a coordinated approach as essential for advancing life course immunisation. The CLCI recognises the importance of utilising extensive data to uncover valuable insights and identify strategic opportunities for preventive measures, including vaccination. Advances in artificial intelligence, such as machine learning and natural language processing, significantly enhance our ability to use data for shaping policies, tracking diseases, and developing vaccines (3–5).

This review, adopting the perspective of the CLCI, aims to underscore how leveraging data-driven insights can support vaccination policies and improve public health outcomes for all.

In Europe, establishing coordinated life course vaccination schedules aligns with the Treaty on the Functioning of the European Union. Vaccines safeguard the health of all EU citizens, allowing them to safely and freely move and reside across the EU (article 45), and play a critical role in ensuring a high level of human health protection, which should be in all EU policies and activities (article 168) (6).

Ensuring equitable access to vaccination in Europe for all citizens was emphasised in the December 2018 EU Council recommendation on strengthened cooperation against VPDs (7) and the December 2022 EU Council conclusion on vaccination (8).

FIGURE 1
CLCI's manifesto.

The case for expanding sources of data and evidence to inform vaccine policy

National Immunisation Technical Advisory Groups (NITAGs) make vaccination recommendations to the government, who then decide whether to implement them in the national immunisation programs (NIPs). NITAG vaccination recommendations only become available after a review of current scientific medical data (e.g., the burden of disease), sometimes including financial aspects (healthcare budget) by multiple stakeholders. Other factors, such as cultural or religious beliefs and expected public acceptance, are considered, too (9, 10).

As per World Health Organization guidance, almost all EU countries have standardised, clear-cut pathways for vaccine licensure and market authorisation. While most countries have a NITAG, which follows WHO guidance, group composition and practice vary significantly between countries (9, 11).

The GRADE methodology of assessing evidence quality

Most NITAGS use the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) method to evaluate the quality of evidence and make recommendations (12). Figure 2 illustrates the GRADE approach to rating the quality of evidence.

The quality of evidence is based on the research methodology's ability to remove or control for confounding and bias. For example, data from randomised controlled trials (RCTs) are of high quality, and observational studies are of low quality according to the GRADE ranking (12, 13).

In this approach, RCTs are the golden standard for evidence quality. However, RCT findings are often less generalisable to the real world due to the study's strict inclusion/exclusion criteria (lack of external study validity) (13). RCTs can also be misinterpreted; for example, if event-driven RCTs are analysed as if they were evaluating incidence rates, it could result in overestimating the vaccine's effectiveness (14).

Value of real-world data

Expert opinion is considered low-quality evidence, yet most emerging infectious diseases are discovered because clinicians notice abnormalities (15). The timeliness of decision-making can be hindered by waiting for sufficiently strong GRADE evidence.

Real-world data offers an essential complement to RCT data, spanning more diverse population profiles and vaccination administration scenarios. However, large-scale data is needed to compensate for its diversity and heterogeneous quality statistically.

Communication of contextual factors

Contextual factors influencing NITAG recommendations, as depicted in Figure 3, are often poorly communicated to the public, who may not understand why one country recommends a vaccine when another does not. Consistent and thoughtful collaboration across stakeholders supports more transparent communications to the public, which can build understanding and trust.

Abbreviations: AI, Artificial Intelligence; GRADE, Grading of Recommendations Assessment Development and Evaluation; NITAGs, National Immunisation Technical Advisory Groups; NIPs, National Immunisation Programs; LCI, Life Course Immunisation; EHDS, European Health Data Space; VPDs, Vaccine-Preventable Diseases; RCTs, Randomised Controlled Trials; TPP, Target Product Profile.

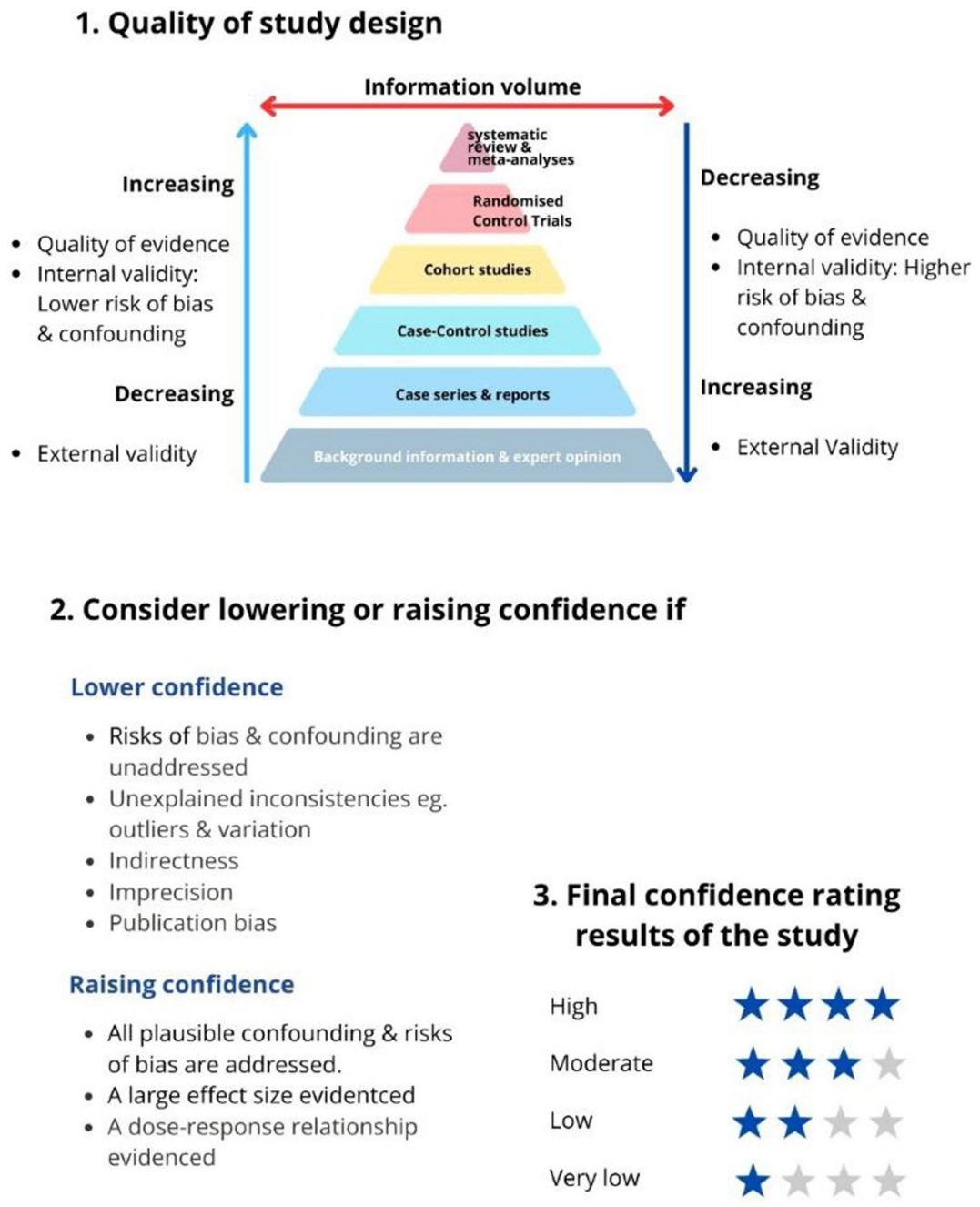

FIGURE 2
GRADE's approach to rating the quality of evidence (12).

Policy options and implications

A life course perspective

Life course immunisation looks at the broad value of vaccination for individuals, communities, and society across multiple generations. This wider lens requires more data power, collaboration, and multi-disciplinary work at various levels.

With this broader perspective, NITAG recommendations should be designed to achieve clear public health outcomes for all and implemented by governments with clear responsibilities and accountabilities. They should include regular evaluation and adjustments as appropriate based on factors, including vaccine uptake and emerging disease burden.

AI-driven "big-data" analysis in decision-making

Population health is an adaptive, dynamic, and unpredictable system with multiple interdependencies and various factors influencing outcomes (16). Analysing data from numerous study

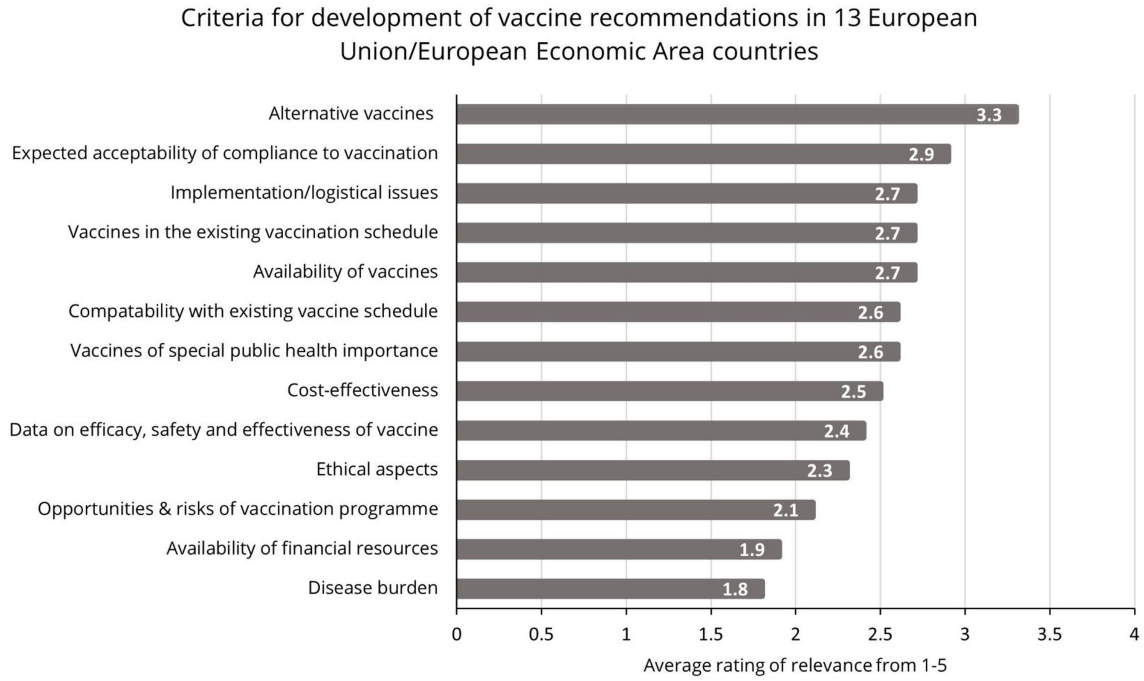

FIGURE 3
Criteria for the development of vaccine recommendations in Europe (23).

designs, RCTs, real-world data, and conceptual models, is required to understand the nuances of health behaviors and interventions and to mitigate the risk of bias or confounding presented by any single data collection methodology. 'Big data' analysis involves modern technologies which interpret large volumes of variable data and spot patterns, often in real time (3). This can facilitate effective rapid response and inform long-term planning, as seen during the pandemic when AI was integral to forecasting COVID-19 spread, contact tracing, pharmacovigilance, and fast testing and detection (4).

The applications of AI are vast in public health research and planning. For example, machine learning approaches such as "neural networks" can improve predictive modelling of complex, nonlinear relationships in data. This can support more accurate forecasting of future trends and predicting disease outbreaks based on historical data (17). Natural language processing has been used to analyse vaccine sentiment via social media (18).

Governments and institutions must look at upskilling NITAGs to effectively interpret insights from large volumes of multi-dimensional data, predictive analytics, and conceptual modelling to forecast vaccination needs and outcomes.

Availability of harmonised data sets

Combining multiple data sources presents challenges of standardisation and system interoperability. The European Commission launched the European Health Data Space (EHDS) in May 2022, which will be crucial in harmonising data from across Europe, ensuring data quality, compatibility and security. It is a vital pillar of a strong European Health Union and is the first specific data space to emerge from the European data strategy (19).

Gathering and utilising health data depends on overcoming technical, legal, and implementation challenges to ensure the effective transfer of AI models across different healthcare systems. Data privacy and security are significant hurdles to overcome in the context of public trust and vaccine acceptance, calling for a delicate balance between data access and privacy protection.

EHDS will provide a solid legal framework for using health data for research, innovation, public health, policy-making and regulatory purposes. Under strict conditions, researchers, innovators, public institutions, and industries will have access to high-quality health data crucial to developing vaccines. The availability of large-scale health data can support the generation of robust evidence on vaccine effectiveness and safety. Researchers can analyse data across different populations, age groups, and geographical regions to assess the real-world impact of vaccines, identify potential subgroups that may benefit most from vaccination, and detect rare adverse events. Also, EHDS will facilitate information exchange between Member States on vaccination plans and verification of vaccination certificates.

Multi-stakeholder collaborations

Collaboration and technology can support access to timely and accurate data during the early phase of an outbreak when the chance for containment is highest (20). Global.health is an open-source platform working towards this by facilitating access to

real-time, anonymised health data on infectious disease outbreaks. The platform has a 100-day Mission: to provide decision-makers, researchers, and the public with timely and accurate data during the early phase of an outbreak when the chance for containment is highest. With over 100 million verified case records from 130+ countries, it is a comprehensive repository of COVID-19 line-list data. Facilitating the secure and responsible sharing of health data across European countries can contribute to a deeper understanding of vaccine effectiveness, safety profiles, and real-world outcomes.

Bi-directional communication and collaboration on critical data are required for development, and monitoring and evaluation should be enhanced between governments, NITAGs, and Ministries of Health. There are foundations to build on; for example, the WHO sets research and development targets for funders and developers through target product profiles (TPP), which outline the desired 'profile' or characteristics of a target product aimed at a particular disease. TPPs state intended use, target populations and other desired attributes of products, including safety and efficacy-related characteristics (21). Such structures and frameworks with strict data ownership and security protocols support a more coordinated approach to improving vaccine impact through broader coverage and strategic use of certain vaccines.

Communicate nuances in decision-making to the public

The risk of communicating inaccurately is significant. When COVID emerged, reporting journalists unintendedly propagated misunderstanding, which fuelled distrust. For example, the media reported daily disease incidences. However, few countries calculated and communicated scientifically valid incidences with a denominator (persons-tested) that reflected the variation in people getting tested daily based on the ever-changing testing recommendations. Media coverage also focused on the COVID-19 vaccine reducing transmission, which to date is almost impossible for respiratory virus vaccines. These can only "control" respiratory tract infection, i.e., minimise morbidity and mortality (22). Understanding and educating the public and working with key stakeholders, including community leaders, to share trusted, accurate information can inform and empower the public.

Governments might look to their NITAGs, with their expertise and multi-disciplinary composition, to help bridge gaps between various stakeholders, promote transparency, and encourage open dialogue.

Actionable recommendations

At the national level, NITAGs and governments can work more strategically together and utilise modern tools and resources to build NIPs that span the life course and promote public trust.

- NITAG recommendations for NIPs should be driven by broader public health improvement goals and implemented with clear responsibilities and accountabilities.
- NIPs should include clear communications and regular evaluations of vaccine sentiment, uptake and emerging disease burden.
- A dialogue between multi-disciplinary stakeholders, including healthcare professionals and physicians, should complement the GRADE process to comprehensively address current and future threats alongside opportunities for health promotions of all ages.
- Invest in and upskill NITAGs to utilise data platforms and modern technologies to use large volumes of multi-dimensional data, predictive analytics and conceptual modelling to forecast vaccination needs and outcomes.
- Utilise the multidisciplinary nature of the NITAGs to develop communication channels with different stakeholders, including community leaders, to share data, knowledge, and context regarding vaccine recommendation and impact.

Although health is not a mandate of the European Union, EU institutions can support and guide member states via

- A toolkit or training resource on using AI and modern technologies in data collection and interpretation for policy development.
- Expanding data standardisation protocols that align with the European Health Data Space to ensure data compatibility and ease of analysis.
- Developing transparent and accountable knowledge-sharing channels between member states and private stakeholders to inform future-proofed prevention strategies.
- Support member states with EU-wide dialogue on public sentiment, communication, and raising awareness, including community leaders and reporters.

Conclusion

A future where everyone, regardless of age or life stage, can be protected from VPDs through comprehensive vaccination programs is underpinned by data-driven decisions. This must involve standardising data sets through platforms like the EHDS, enhancing surveillance systems with AI, and transparent communication between governments, NITAGs, industry, and the public. Future-proofed decision-making requires the upskilling of NITAGs to utilise modern technologies that analyse large volumes of data and generate reliable modelling data to develop recommendations. We must counteract information overload, confusion and misinformation with multidisciplinary stakeholder collaboration, transparency, open dialogue and clear accountability.

In line with the Treaty on the Functioning of the European Union, we urge stakeholders across the European vaccination landscape to champion a future where health protection is paramount. By harnessing the full potential of technology in vaccine distribution, planning and evaluation, we can secure the well-being of Europe, fortify communities, and safeguard our socio-economy. This commitment will contribute to a resilient Europe that flourishes within an ethical framework that prioritises innovation, health, and prosperity for all its citizens.

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COVID-19 vaccination: challenges in the pediatric population

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Vaccination is considered to be one of the most effective means of protecting individuals and populations from the risks associated with exposure to various pathogens. The COVID-19 pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), affected people of all ages worldwide. In response, several pharmaceutical companies rapidly leveraged their resources to develop vaccines within a very short period of time, leading to the introduction of new, improved, and combination vaccines for community-wide immunization. This review aims to provide a summary of the available literature on the efficacy and safety of COVID-19 vaccines in the pediatric population ranging from 0 to 18 years. An analysis of recent published studies reveals that the majority of clinical trials have reported a sustained immune response following COVID-19 vaccination in children across various age groups worldwide. The majority of the authors highlighted the effectiveness and safety of immunization schedules in children and adolescents. The population-level efficacy of this vaccination remains to be determined, provided that the benefits outweigh the potential risks. Long-term side effects must still be monitored to enable the development of safer and more effective vaccines for future pandemics.

KEYWORDS

vaccine, COVID-19, SARS-CoV-2, efficacy, safety, children

1 Introduction

The COVID-19 infection, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), emerged at the end of 2019 in Wuhan, China, and rapidly spread to all continents. This virus affects people of all ages worldwide and was declared a pandemic by the World Health Organization (WHO) on 11 March 2020 (1). The global impact of COVID-19, with hundreds of millions of confirmed cases and over 9 million fatalities, has spurred significant scientific interest. Researchers have focused on understanding the pathogenesis of the disease, its epidemiology, and how it varies with age or pre-existing clinical conditions. There is also a strong emphasis on exploring methods of prevention and treatment.

Vaccination is considered to be one of the most effective interventions for individual and collective protection of the population against the risks caused by exposure to various pathogens. Vaccination efforts at local, regional, national, and global levels have consistently demonstrated their benefits over time, eradicating life-threatening diseases, reducing

morbidity, and limiting the consequences of infections that determined suffering, disability, and death in the pre-vaccine era (such as diphtheria, tetanus, whooping cough, poliomyelitis, measles, rubella, and so on). The proof of these effects is also represented by the fact that the number of deaths caused by vaccine-preventable diseases decreased from 0.9 million in 2000 to 0.4 million cases reported in 2010 (2, 3).

A key benefit of vaccination programs is the induction of population-wide immunity, often referred to as "herd immunity." This immunity protects the community against disease through widespread vaccination, resulting in a decrease in pathogen circulation within that community (3). Among various medical interventions involving biologically active medications, the protection of an entire community is uniquely achievable through extensive vaccination efforts (4, 5). Unvaccinated individuals can benefit from "herd immunity," which creates a potential ethical issue of "free-riders." These are people who gain the advantages of vaccination programs without personally taking on any of the risks associated with receiving the vaccine directly (3, 4).

The lack of high-quality research hampers a comprehensive understanding of the post-acute and long-term consequences of COVID-19. By standardizing the definitions and harmonizing research, diagnosis, and treatment approaches for long-term COVID-19, we can improve the coherent collection of national and international data. This would enable better estimates of incidence, prevalence, and risk factors tailored to different age groups. There is a critical need for large, coordinated longitudinal studies to explore the various aftereffects of SARS-CoV-2 infection in children and adolescents. While relatively few studies have targeted this demographic, patient support groups have reported that many children suffer from the lingering effects of COVID-19. High-quality evidence is urgently needed, and this could be facilitated by conducting controlled trials that account for societal variables.

Additionally, robust case–control studies are essential for identifying sources and risk factors for various long-term COVID-19 conditions, which will aid in the development of targeted interventions and support mechanisms.

2 Methods

A substantial body of literature has emerged on surveillance advancements during the COVID-19 pandemic. While wastewater epidemiology has seen extensive research, topics such as health equity for racial and ethnic minorities are less studied. In areas with extensive research, conducting systematic reviews may be the logical next step. Conversely, in fields where knowledge is scarce, further research is essential to advance monitoring in the post-pandemic era.

Additionally, the widespread implementation of these surveillance techniques necessitates a comprehensive analysis of potential consequences, including ethical, legal, security, and equity implications, as highlighted by numerous studies (5). Our literature search was conducted using Medline and Medscape, focusing on articles published from 2019 to 2024 with keywords including "pandemic," "SARS-COV2 infection," "vaccine," "children," "safety," and "efficacy."

Researchers' findings support the development of multidisciplinary collaborative rehabilitation programs for younger populations impacted by COVID-19 and the deployment of monitoring systems to monitor the health effects of the virus. There are meta-analyzes, cross-sectional studies, reviews, and prospective studies to prove that vaccination in early age groups can reduce the burden of COVID-19 infection. To close the gap between research results and clinical application in this discipline, it is critical that non-physical outcomes be given top priority in future attempts (6).

Our objective is to offer suggestions for filling in the knowledge gaps on the long-term effects of COVID-19 on children. Priorities for studying the effects of COVID-19 on children's bodies, minds, emotions, and social interactions must be determined within a systems framework and coordinated on a national and worldwide scale. We call on national and international funding organizations to promote coordination efforts between families impacted by long-term COVID-19 and experts such as pediatricians, epidemiologists, rehabilitation clinicians, psychologists, psychiatrists, researchers, and public health experts. A dynamic assessment of the effects of prolonged COVID and the care required for children with this illness may be made easier by longitudinal repeated examinations of representative samples of children and adolescents with a diagnosis of SARS-CoV-2 infection and matched control individuals. This type of research design could also help clinicians to discriminate between short- and longer-term outcomes of the condition and the impact, as well as provide evidence-based profiles of individuals who are affected by long-term COVID-19, identify those at higher risk, and inform targeted interventions to improve long-term outcomes.

Children may serve as a reservoir for the virus and spread it, even if the majority of them are asymptomatic or just mildly afflicted by COVID-19 infections. The financial burden and vaccine accessibility are crucial factors in requiring the COVID-19 vaccine. Before vaccinations are required, a number of ethical issues also need to be considered. Unknown are the vaccine's efficacy and safety for kids, their vulnerability to infection, their part in the disease's spread, and the anticipated advantages. Moreover, religious beliefs, parental hesitancy, media involvement, and anti-vaccination campaigns might also be considered real challenges in children's COVID-19 vaccination.

3 COVID-19 vaccines

This infection is characterized by clinical and evolutionary polymorphism, which is influenced by the viral variants that emerge over time (such as the alpha, delta, and omicron strains) and the age at which the infection occurs. This variability contributes to skepticism regarding the vaccination of children (1). This situation is principally based on the limited knowledge about advancements in developing more effective and less harmful vaccines, and this is again a reason for which authors should focus on proving the efficacy of vaccines and the lack of side effects. Then, there is the deep-rooted idea that the best immunization is provided by the disease. Therefore, the human body should be allowed to face the disease (7), a principle that has still not been proved in the case of COVID-19 infection.

For example, the pediatric population evaluated in studies and meta-analyzes is inferior to cohorts of adult subjects, which implies a greater degree of extrapolation of the obtained data but also necessitates continuous efforts. The lack of studies focusing on the efficacy and safety of COVID-19 vaccines for children and infants complicates efforts to vaccinate these population groups. While

COVID-19 vaccination in adults was reported to decrease in percentage, children and young people (CYP) registered higher rates of vaccination in the past 4 years (8).

The main benefits of COVID-19 vaccination for children include overcoming potential side effects and achieving immunity. Nevertheless, even minor vaccination risks need to be considered, as the likelihood of serious illness in otherwise healthy children is very low. The majority of the potential benefit of vaccination in preventing serious illness and/or PIMS-TS/MIS-C has been diminished because of pre-existing immunity to infection and decreased incidence of hyper-inflammatory response as a result of both viral evolution and pre-existing immunity. Any possible advantage in stopping the spread of viruses is negligible and transient. If there is already a high level of community immunity due to infection, then any benefits from temporarily boosted immunity for otherwise healthy children may be outweighed by the high financial and opportunity costs associated with starting new vaccination programs. For children with significant comorbidities, there is a much larger absolute reduction in risk provided by periodic vaccination, which is the basis of the majority of current national public health recommendations (9).

Possible (or probable) post-vaccination reactions, in the context of the use of biologically active vaccines, are currently reduced as a result of the evolution of knowledge in the field of modern vaccinology. The security measures adopted in the case of the production and use of vaccines, as in fact of any procedure or medicinal product that is applied to an individual or a large population, provided safety for the recipient. Developing vaccines with high immunogenicity and low reactogenicity characteristics has determined an extremely limited possibility of installing such reactions under the condition of compliance with specific regulations and protocols, which are necessary in the case of application of preventive or therapeutic action (10, 11).

The increasingly advanced knowledge of the mechanisms of the vaccines, as well as the circumstances that allow the minimization of risks, is a priority for the medical world that has the duty to make known these scientific truths in order to regain the trust of the population in a measure that has demonstrated, over time, to be beneficial to the individual and the human community (8, 12). There has to be higher compliance from the caregivers (parents, family doctors, specialists) in order to protect young patients against COVID-19 infection, which proved to be life-threatening in children's pathology (13).

The majority of the studies initially stated that there is a low susceptibility to SARS-CoV-2 infection in children. The disease also has a generally milder course than in adults, with a low percentage of severe cases and usually burdened by an underlying chronic pathology (chronic pulmonary conditions such as cystic fibrosis, tuberculosis, pulmonary malformations, ciliary dyskinesia, cardiovascular malformations, genetic syndromes, oncological, and renal diseases) (13, 14). The phenomenon could be explained by several mechanisms. One would be the action of the innate immune response, the first line of defense against pathogens, which tends to be more active in children. Paradoxically, another explanation could be the immaturity of the children's immune system, which is probably not able to sustain the cytokine storm similar to that observed in the adult population. Also, the different distribution of membrane ACE2 receptors in adults and children with a lower receptor binding capacity could be responsible for the attenuated symptoms in their case, as well as a higher plasma concentration of soluble ACE2 receptors, the particular interaction with these receptors, thus being able to limit their replication in tissues (15, 16).

Multiple trials have evaluated the efficacy and safety of COVID-19 vaccines in both healthy adults and patients with comorbidities (14–19). Similarly, vaccination against coronavirus can prevent serious outcomes or hospitalization following the natural infection (20). Of note, children and adolescents had their education, safety, and mental and physical wellness negatively affected during the pandemic, making vaccination crucial for them to avoid further isolation (21). All children and adolescents should be considered for COVID-19 vaccination for their own protection against the infection and its different outcomes, and more importantly, because they are part of the COVID transmission cycle, thus being carriers and serving as a reservoir of disease for elders (parents, grandparents) (8–12, 22–24).

Several clinical trials supported the favorable immune response, effectiveness, and safety profiles of COVID-19 vaccines in healthy children and adolescents and even in those with underlying medical conditions (25–28). In almost all studies, authors aimed to collect data regarding the immunogenicity, efficacy, and safety of COVID-19 vaccines to guide healthcare workers and families in vaccinating the younger population.

Patients with autoimmune diseases or immunodeficiencies have a higher risk of COVID-19 infections, hospitalization, and death than the general population and are a priority for vaccination (29). Due to a lack of information, medication side effects, and the possibility of triggering severe side effects in those special categories of patients, both doctors and caregivers are often reserved in recommending and/or accepting COVID-19 immunization.

Juvenile idiopathic arthritis (JIA) is the most common pediatric rheumatic disease, the burden within young children and adolescents being related to infectious risk factors and autoimmunity as a trigger. This is the reason that makes preventing viral infections the most effective tool in controlling the disease. Authors have been challenged in proving the efficacy and the real need for COVID-19 vaccination for those specific population categories. An observational study that compares the immunogenicity and the safety of the Pfizer COVID-19 vaccine in patients with JIA in the age group between 12 and 16 years and a group of healthy controls shows no statistically significant differences in the average levels of antibodies in the patients and controls, in line with other studies of Pfizer immunogenicity in adolescents with JIA. An important matter is that of immunosuppressive therapy, and this is why methotrexate was discontinued during the weeks of the first and second vaccine inoculations. Non-steroidal anti-inflammatory drugs (NSAIDs) and biological drugs were not discontinued while treating the patients for COVID-19 (30). The authors also observed that patients with systemic JIA produced lower antibody titers than patients with other types of JIA (31). It's been underlined in those findings the fact that COVID-19 vaccination does not interfere with the JIA treatment and does not exacerbate symptoms of the disease. Authors have proven, in fact, that vaccination protects against developing COVID-19 in children with JIA (32).

Since the beginning of the pandemic, children with primary immune deficiency (PID) have been the main category of concern (33). Before the worldwide extension of the viral strains of COVID-19, children with primary immune deficiencies were also at very high risk of acquiring and manifesting infections, making them a special category of eligible candidates for the majority of the vaccines. Transplantation, substitutive therapy, specific medication, young age, and comorbidities were the main concerns in having the PID children vaccinated against COVID-19. Questions were raised regarding the

benefits or the risks for those special patients. Although PID is among the main preexisting conditions associated with COVID-19 infection in children, patients with phagocytic or antibody defects or children with combined PID who have already been transplanted can develop mostly asymptomatic or mild COVID-19 (34, 35). The authors agreed on the need for pediatric patients with primary immune deficiency to be vaccinated, thus reducing the risks of severe COVID-19 illness and death. This most vulnerable population must be sheltered from infection, taking into consideration that the immune response to SARS-CoV-2 vaccines may differ in people with primary immune deficiency. This is why an individual approach is required, and specific organizations, such as the Centers for Disease Control and Prevention (CDC), have developed specific guidance, COVID-19 vaccination being the primary prevention strategy (36), along with specific and reliable therapies that have been approved in the case of those patients.

PID pediatric patients may also develop prolonged or severe forms of COVID-19 infection, and it is mandatory to define their immune response to the disease. Thus, the Committee of Experts on Primary Immunodeficiency has included vaccination both as a diagnostic tool (to assess the specific antibody response to protein and polysaccharide antigens) and as a means of prevention (37). The response to COVID-19 infection by developing antibodies was assessed later on, and the efficacy of vaccination relied on the detection of specific antibodies against SARS-CoV-2 antigens. In the general population, the level of neutralizing antibodies is correlated to protection, and mRNA vaccination generated robust humoral and cellular immune memory to SARS-CoV-2 for at least 6 months following mRNA vaccination (32). In particular, patients with PID may not be able to maintain this immunogenicity over time. However, even in healthy individuals, the antibody response may wane over time or may not be detectable in patients with antibody deficiency (37).

For children and adolescents with allergic conditions such as wheezing and asthma, there were concerns regarding the safety of vaccination, given the risk of having an anaphylactic reaction to a COVID-19 vaccine, even though severe allergic conditions were not noted in a pediatric population. A systematic review of the literature noted that the incidence of an allergic reaction to an mRNA-based COVID-19 vaccine is 7.91 cases per million doses (95% CI 4·02–15·59) (40), a very low risk if we take into consideration the benefit of protection. There were no reported anaphylactic fatalities related to COVID-19 vaccination, and the local allergic reactions resolved rapidly without long-term sequelae. Furthermore, revaccination after an initial allergic reaction was well tolerated within those patients (41).

Anaphylaxis is unpredictable, so a prudent approach is advisable, such as allergic evaluation in case of previous systemic reactions to vaccines or drugs. Risk assessment of allergic reactions to COVID-19 vaccines is useful in limiting contraindications to vaccination and obtaining medical recommendations and parental consent. All vaccine centers should follow international and national guidelines, and doctors should be trained in preventing, recognizing, and managing post-vaccinal anaphylaxis (42).

4 Immunogenicity of COVID-19 vaccines in children

Immunogenicity concerns regarding children, including those with chronic illnesses as well as for healthy individuals, have been in focus since the beginning of the pandemic. The primary concern was whether the immunogenicity achieved with one or multiple vaccine doses varies significantly based on age, medical history, or immune response in children. Specialists must consider factors such as age group, immune status, comorbidities, chronic illnesses, and/or immunosuppressive conditions. It can be stated that there still is an urgent need for continuous surveillance and extensive studies to assess the real status of immunogenicity achieved with vaccination versus naturally acquired antibodies (43). The differences between the population groups that were observed in extensive studies can explain the lack of protection against further infection in some categories of individuals with one or multiple vaccine protections (such as in the case of immune-deficient children).

Authors reported approximately 99% serologic response to the mRNA-1273 Moderna vaccine in people aged 12–17 years old, compared to a 98.6% response in younger adults—according to Ali et al. (44). Furthermore, the findings stated that the neutralizing antibody titers in younger ages (children) showed no inferiority when compared to those in older patients.

Frenck et al. (45) conducted a randomized clinical trial to assess the effects of the BNT162b2 (Pfizer) vaccine in children and adolescents aged 12–15 years. The authors found these subjects developed higher post-vaccination antibody titers compared to vaccinated younger adults and the control group. Other authors (46, 47) revealed that nearly all (99.2%) of Pfizer-vaccinated children aged 5–11 years achieved a satisfactory serologic response 1 month after receiving the second dose.

These findings support the notion that immunization should be considered for early age groups, as many studies suggest that younger children tend to produce higher rates of antibody production. This may be due to the innate immune system, which is more active in infants and young children, enabling them to develop higher titers of antibodies and maintain these at protective levels for extended periods. However, the paucity of extensive studies confirming the safety of vaccinations in these age groups remains a concern, often due to parental hesitancy to provide consent.

5 Efficacy of COVID-19 vaccines in children and adolescents

The benefit of immunization was demonstrated in the adult population, as the levels of morbidity and mortality due to COVID-19 infection dramatically decreased worldwide. Regarding passive immunization in young children, there is still controversy among authors who conducted studies centered on the real need for vaccinating children. The majority of the studies initially stated that there is a low susceptibility to SARS-CoV-2 infection in children, the disease also having a generally milder course than in adults, with a low percentage of severe cases and usually burdened by an underlying chronic pathology (48).

On the other hand, several studies showed the need for children and adolescents' COVID-19 vaccination—first for the protection against the infection and second because they are part of the COVID-19 transmission cycle. Children represent important carriers of the disease, regardless of the fact that they express the symptoms more or less prominently, thus serving as a reservoir of disease for elders, in which the outcome may be fatal. Isolation, lack of

socialization methods, and mental and behavioral changes within the pandemic were issues that conducted authors in providing the population with "pro" and "con "arguments regarding the efficacy of vaccination in children and adolescents and the long-term protection against the infection.

The efficacy of the COVID-19 vaccine in children aged 5–11 years was reported to be nearly 91% after the second dose, according to Frenck et al. (45), using the Pfizer vaccine. Moreover, the authors noted a remarkable efficacy rate of 100% in individuals aged 12–15 years (45). In another study assessing the efficacy of the Pfizer vaccine in adolescents aged 12–18 years, only two patients out of 57 participants contracted COVID-19 after being immunized: one patient tested positive before receiving the second dose, and the other 46 days post-second dose (46).

A particular group of potential vaccine recipients—those with underlying medical conditions, chronic illnesses, or immunodeficiency due to chemotherapy regimens, as well as children with innate immunodeficiencies—requires careful evaluation of vaccine efficacy. The beneficial effects on these children and adolescents have been assessed in studies encompassing multiple vaccine types and considering various age groups.

Adolescent patients with solid tumor malignancies who completed the full Pfizer vaccine immunization schedule were not found to be at risk of developing COVID-19 infection (41). In studies involving other vaccine types eligible for the population under 21 years of age, such as Moderna, CoronaVac, and ZyCov-D, efficacy rates of 93.3, 65.5, and 100% protection against COVID-19 infection were reported among participants aged 12–19 years, respectively (46). Further extensive studies on additional vaccine types, including Sinopharm and COVAXIN (NCT04918797), also suggested high protection efficacy against COVID-19 in the 2–18-year-old age group (46).

There is also the question of whether efficacy should be discussed in terms of age group, as long as innate immunity may be an advantage in obtaining higher levels of protective antibodies in young children.

Recently, a group of Italian authors conducted a retrospective population study, assessing vaccine efficacy against SARS-CoV-2 infection and the severe COVID-19 infection rates (defined as an infection leading to hospitalization or lethal outcome) by linking the national COVID-19 surveillance system and the national vaccination registry. All Italian children aged 5–11 years without a previous diagnosis of infection were eligible for inclusion. The authors followed up with the patients over a 4-month period of time, relying on unvaccinated children as the reference group. Furthermore, the authors estimated the vaccine efficacy in those participants who were partly vaccinated (one dose) and in those who were fully vaccinated (two doses) (47).

The results showed that 35.8% of children aged 5–11 years included in the study had received two doses of the vaccine, and only 4.5% had received only one dose; 59.6% of all age groups represented the children who were unvaccinated. The results were not promising, with multiple cases of severe COVID-19 (627 hospitalizations, 15 admissions to intensive care units, and two deaths), as well as many mild infections. Overall, authors assessed the vaccine efficacy in the fully vaccinated group as being only 29.4% against SARS-CoV-2 infection and not higher than 411% against severe COVID-19, whereas vaccine efficacy in the partly vaccinated group was rather similar, with 27.4% efficacy against SARS-CoV-2 infection and 38.1% against severe COVID-19 (47). To sum up, the results demonstrated that vaccination against COVID-19 in children aged 5–11 years in Italy had, in fact, lower effectiveness in preventing SARS-CoV-2 infection and severe COVID-19 than in individuals aged 12 years and older. Effectiveness against infection appears to increase up to 14 days following immunization, with a decrease after completion of the current primary vaccination cycle of 43–84 days (47).

6 Safety of COVID-19 vaccines in children and adolescents

Regarding the safety and security of all vaccines, there is a comprehensive and lengthy chain of surveillance measures and regulations established in each region or country. Initially, it is determined whether the new vaccine can undergo evaluations to receive the license. The special accredited committees for the supervision and licensing of a vaccine, in collaboration with the manufacturers, monitor the safety and efficacy of the vaccine through a strategy based on national or international laws and regulations.

European regulation on the authorization and population use of medicinal devices for human use includes vaccines among immunological biological products. The evaluation of a vaccine is carried out identically to that of any medicine. The stages are laborious and take a long time to be carried out. They are completed by drawing up documentation that includes the results of clinical and pharmaceutical studies, particularly those related to the product's safety.

Improved vaccine safety monitoring and the timely, accurate, and transparent disclosure of safety findings were crucial aspects of the COVID-19 response during the US COVID-19 pandemic immunization program. This comprehensive approach included clinical consultations, long-term follow-up on individual cases of myocarditis after immunization, both active and passive surveillance, and monitoring of pregnancy and infant outcomes. The most efficient methods for disseminating the latest information to stakeholders and the public involved updating agency websites, engaging through social media, presenting findings to federal advisory bodies, and publishing safety results in scientific journals (48, 49).

Safety studies have been conducted for vaccines that have been approved for years and decades, thus guaranteeing the possibility of long-term surveillance of subjects. The COVID-19 pandemic was the turning point in drawing a new era for "fast-forward" developing and testing vaccines. A key point considered to be crucial for controlling the virus transmission and pandemic annihilation was the possibility of initializing vaccine development studies. This was the reason for observing and assessing early side effects even at the same time as actual immunization and not waiting longer for outcomes *in vitro* studies. Several pharmaceutical companies had the opportunity and the industrial means to develop a vaccine quickly, releasing new, improved, and combined vaccines for community immunization (50, 51).

Reported adverse reactions were mild to moderate and self-limiting, as long as the current studies have shown a significant percentage of parents willing to vaccinate their children and adolescents against the new coronavirus. The most common adverse reactions following immunization comprised injection site pain and erythema, headache, fatigue, fever, and chills (52–54), nothing more than in the case of other studied vaccines.

The authors had the opportunity to assess the side effects in a specific and distinct group within the community. In the case of adolescents and young adults (aged 16–25 years) residing in a long-term care facility who received the Pfizer vaccine, 84% experienced mild adverse reactions after the first dose, and 74.2% reported similar effects following the second dose. These reactions included discomfort, nausea/emesis, diarrhea, fever, chills, headache, and skin erythema at the inoculation site (54).

The Pfizer vaccine was administered to pediatric patients and young adults with juvenile inflammatory arthritis (JIA) aged 16–21 years, with no reported exacerbation of the chronic disease, indicating a good safety profile for this particular group (54). However, transient increases in agitation and changes in seizure patterns, specifically cluster seizures, were observed in recipients aged 12–15 years old with underlying neurologic and mental conditions. These observations highlight the need for further monitoring of post-immunization side effects in these vulnerable groups (53, 54).

Recent extensive studies have reported an increased incidence of myocarditis and pericarditis after COVID-19 vaccination, particularly among male adolescents and young adults, raising major global concerns. For instance, in Israel, five male patients with a median age of 23 developed myocarditis after receiving the BNT162b2 vaccine (55). Additionally, in the United States, eight male adolescents presented with myocarditis within 4 days of receiving a dose of the BNT162b2 vaccine, as noted by the authors (56). Another report highlighted a series of 25 children aged 12–18 years diagnosed with probable myocarditis after COVID-19 mRNA vaccination at eight US centers between May and June 2021. These cases did not show any clinical or functional impact post-treatment. Treatment approaches varied: three cases were managed with non-steroidal anti-inflammatory drugs, while four patients received a combination of intravenous immunoglobulin and cortisone therapy to control the condition (57).

Recent reports have demonstrated that multisystem inflammatory syndrome (MIS) can occur after SARS-CoV-2 vaccination, now identified as "MIS-V" rather than "MIS-V." An instance of such symptoms was documented in an 18-year-old adolescent following the administration of the Pfizer-BioNTech BNT162b2 vaccine (58). The primary clinical features mirrored those observed during the acute phase of infection, including fever lasting for 3 consecutive days, mild to moderate pericardial effusion, elevated levels of CRP, NT-BNP, troponin T, and D-dimers, which is evidence of cardiac involvement, and positive IgG SARS-CoV-2 antibodies, which helps to establish a link between the vaccination and the observed symptoms (58).

7 COVID-19 vaccination in MIS-C patients

Multisystem inflammatory syndrome developed after COVID-19 infection represents a milestone for developing further medication and prophylactic therapy, both for adults and especially for children, in which the outcome was severe (even lethal in some cases). Study data regarding adverse reactions after COVID-19 vaccination in adult pediatric patients with a history of multisystem inflammatory syndrome (MIS-C) are limited. This lack of safety and efficacy data in this specific population may cause limited approval for vaccination from healthcare professionals and hesitancy and concern for caregivers and parents. There is an interest in applying most of the study designs to a wide population of children when the analysis design and the reported data's applicability can be extended. Therefore, assessing the results and conclusions would appear to be more trustworthy.

MUSIC is a multicenter, cross-sectional study including 22 North American centers participating in a National Heart, Lung, and Blood Institute, National Institutes of Health-sponsored study, Long-Term Outcomes After the Multisystem Inflammatory Syndrome in Children. The pediatric population with a prior diagnosis of MIS-C that appeared to be eligible for COVID-19 vaccination at the time of enrolling (age $\geq$ 5 years; $\geq$90 days after MIS-C diagnosis) were surveyed over a period of 3 months regarding COVID-19 vaccination status and reported adverse reactions (59). The authors were trying to assess whether MIS-C would be a condition to take into consideration when establishing the need, the benefit, or the actual risk for vaccination. Patients were also randomized based on age group, ethnicity, and medication intake.

Almost half of all the 385 vaccine-eligible patients surveyed, 185 (48.1%), received at least one vaccine dose; the majority of vaccinated patients (73.5%) were male, at a median age of immunization of 12 years. Among vaccinated patients, there were mostly white children, as well as a significant percentage of Asian, Hispanic, and Black ethnicity. The median time lapse from the initial moment of MIS-C diagnosis to the first vaccine dose inoculation was almost 9 months. Out of them, 31 patients (16.8%) received one vaccine dose, 142 (76.8%) received two doses, and 12 (6.5%) received all three doses of the vaccine. It is important to observe that almost all patients received the BNT162b2 vaccine—98.9% (59).

Minor adverse reactions were observed in almost half of the study group—48.6%. The complaints most often included arm soreness and/or fatigue, which did not require medical attention. However, in 32 patients (17.3%), adverse reactions were treated with medications, most commonly for the fever and the pain, using either acetaminophen or ibuprofen. Only four patients were addressed for medical evaluation, but none required testing or hospitalization. Moreover, neither of the patients included in the study developed an MIS-C symptomatology after vaccination nor cardiovascular events, which are a key point in assessing the safety of immunization in young children (59).

The authors did not report any patients with serious adverse events, such as myocarditis or recurrence of MIS-C (59), proving that there were no severe adverse events after COVID-19 vaccination. Findings suggest that the safety profile of COVID-19 vaccination administered at a time-lapse of at least 90 days following MIS-C appears to be similar to that assumed in the general population.

Zambrano et al. (60) compared the odds of being fully vaccinated with two doses of the BNT162b2 vaccine ($\geq$28 days before hospital admission) between MIS-C case patients and hospital-based controls who tested negative for SARS-CoV-2. Authors examined those associations by age group, timing of vaccination, and periods of Delta and Omicron variant predominance (60). This study was conducted across 29 hospitals in 22 US states in the Centers for Disease Control and Prevention (CDC)–funded Overcoming COVID-19 (OC-19) pediatric vaccine effectiveness network. Clinical outcomes among MIS-C patients for those requiring ICU admission, vasopressor support, and noninvasive or invasive mechanical ventilation were clearly in favor of those who received a complete vaccination schedule. Those findings are also supported by a comparison of MIS-C cases resulting in life support or death between vaccinated and unvaccinated patients.

In comparison, Cortese et al.., out of a cohort of 77 patients, 58 children were identified who developed MIS-C within 90 days after receiving a COVID-19 vaccine and had evidence of past or recent SARS-CoV-2 infection. Additionally, four children met the MIS-C criteria but had no evidence of SARS-CoV-2 infection. The authors were unable to conclusively determine whether the COVID-19 vaccination contributed to the MIS-C cases identified in the study group. This uncertainty was partly due to the expectation of an increase in MIS-C cases associated with the Omicron variant of SARS-CoV-2, which coincided with the availability of the COVID-19 vaccine for this age group approximately 5–6 weeks prior to the enrollment of cases in the study (61).

Table 1 summarizes the studies regarding the efficacy and safety of vaccination in children.

Regarding the reason for conducting studies in pediatric age, the majority of the authors state that children's vaccination against COVID-19 is a moral obligation, as well as a practical need in reducing the burden of the infection, as long as the safety of the vaccines is to be assessed (62). Parental consent is sometimes impaired by the lack of studies in this field. According to the majority of the current literature, our manuscript highlights the crucial importance of children's vaccination against COVID-19 and the immunogenicity and safety of the vaccines at pediatric age (63).

According to the major topic of this literature review (COVID-19 vaccines, immunogenicity of COVID-19 vaccinations in children, efficacy of COVID-19 vaccines in children and adolescents, safety of COVID-19 vaccines in children and adolescents), the authors created a conceptual table (Table 2) that can be used in the future to produce better, safer, and more effective vaccines for children and adolescents to mitigate the impact of a potential new pandemic (45, 64, 65).

8 Conclusion

Rapid advancements in research on SARS-CoV-2 infection and COVID-19 immunization have led to recommendations from professional societies affirming the safety and efficacy of vaccinating children and adolescents. The emergence of new variants of SARS-CoV-2 (alpha, delta, omicron) had increased transmissibility and made it clear that acquiring herd immunity would be required to control the pandemic. Coinfection or superinfection comorbidities (viral, bacterial, fungal) equate to a poor prognosis for the pediatric patient. Additionally, younger age groups often exhibit more complex immunological backgrounds, including primary and secondary immunodeficiencies. When vaccinating younger patients, it is crucial to consider the epidemiological context in which acute COVID-19 infection may occur, especially during the seasonal circulation periods of other viral agents such as influenza, parainfluenza viruses, and respiratory syncytial viruses.

The costs associated with pediatric primary care, emergency services, and possible hospital admissions due to severe clinical manifestations, as well as direct or indirect costs for long-term care of children who experience recurrent COVID-19 infections or develop MIS-C, pose a significant economic burden. This burden is substantially higher than the cost of maintaining consistent and comprehensive immunization efforts. Community-wide epidemiological surveillance of COVID-19 infections and immunization in the pediatric population, along with the implementation of specific monitoring protocols, tracking of recurrent hospitalizations due to COVID-19-related respiratory infections, and conducting medium- and long-term follow-up in patients with MIS-C symptoms, will provide crucial data for the implementation of extended prophylaxis.

However, ethical and legal considerations regarding the vaccination of minors cannot be overlooked, particularly in light of ongoing debates in the scientific community about the inclusion of children and young people in COVID-19 vaccine trials. Moreover, it is essential that children, adolescents, and infants are included in comprehensive studies that monitor, describe, and document any adverse reactions following COVID-19 vaccination, especially in patients with a history of MIS-C. These measures are critical to ensuring the safety and efficacy of vaccines for this vulnerable population.

This review highlights that while the population-level effectiveness of this specific vaccination remains to be fully established, the global beneficial response generally outweighs the potential risks. Authors have emphasized the importance of monitoring long-term side effects, as this provides the opportunity to develop newer, safer, and more effective vaccines, potentially including combined formulations, to mitigate the impact of a future pandemic.

Author contributions

AA: Conceptualization, Investigation, Writing – original draft. IM: Methodology, Supervision, Writing – review & editing. AL: Investigation, Methodology, Writing – original draft. MMA: Investigation, Software, Writing – original draft. IS: Investigation, Visualization, Writing – original draft. MA: Investigation, Software, Writing – original draft. VL: Conceptualization, Project administration, Writing – review & editing. CD: Validation, Writing – review & editing. AN: Validation, Writing – review & editing. DS: Validation, Writing – review & editing. FD: Funding acquisition, Validation, Writing – review & editing. II: Investigation, Methodology, Writing – original 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.

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TABLE 1 Current studies recommendations and evidence regarding the safety and efficacy of mRNA COVID-19 vaccines.

Authors	Outline	No. patients	Efficacy/safety	Age range	Country/region
Opoka-Winiarska et al. (32)	Children and adolescents with JIA with remission without treatment or on long-term treatment—cDMARDs or even bDMARDs, can be safely vaccinated for COVID-19	43 with JIA	++/++	0–18 years	Poland
Quinti et al. (37)	Despite the antibody deficiency, T-cell immunity is thought to be largely intact in many patients with CVID, as immunologists recommend routine administration of multiple vaccines, including COVID-19 immunization	9 with PID	+/+	6–18 years and adult patients	Italy
Krantz et al. (42)	The majority of patients with allergic reactions to mRNA COVID-19 vaccines can safely tolerate a second dose of immunization	159	++/++	0–18 years	Australia
Sacco et al. (47)	Vaccine efficacy was 31% (95% CI 9–48) at 14–82 days after completion of the primary cycle in a sample of 1,364 children aged 5–11 years, very similar to our estimate of 29.4% after a similar interval of 0–84 days after full vaccination	1,364	+/+	5–11 years	Italy
Myers et al. (49)	V-safe contributed to the CDC's vaccine safety assessments for FDA-authorized COVID-19 vaccines by enabling near real-time reporting of the reactogenicity of the vaccines	9,342,582	++/++	0–18 years	United States
Zambrano et al. (60)	Vaccination with two doses of vaccine is associated with reduced risk of MISC C in children	304	++/++	5–18 years	United States
Cortese et al. (61)	MISC C illness in children after COVID-19 vaccination was below 1/million vaccinated children	58	++/++	0–18 years	
Tartof et al. (66)	BNT162b2 BA.4/5 bivalent mRNA vaccine against a range of COVID-19 outcomes in a large health system in the United States proved effective in a test-negative case–control study	24,246	++/++	0–18 years	United States

(Continued)

TABLE 1 (Continued)

Authors	Outline	No. patients	Efficacy/safety	Age range	Country/region
Feldstein et al. (67)	Bivalent mRNA COVID-19 vaccines are effective in preventing SARS-CoV-2 infection in children and adolescents aged 5–17 years	2,959	++/++	5–17 years	United States
Aldridge et al. (8)	Uptake of COVID-19 vaccinations among 3,433,483 children and young people showed safety and efficacy in a meta-analysis of UK prospective cohorts	3,433,483	++/++	0–18 years and adult patients	UK
Hu et al. (68)	Ancestral monovalent BNT162b2, mRNA-1273, and NVX-CoV2373 COVID-19 vaccines in US children aged 6 months to 17 years are safe and immunostimulant	410,2016	+/+	6 months-18 years	United States
Buoninfante et al. (69)	Myocarditis associated with COVID-19 vaccination is not as frequent as the first studies outlined at the beginning of the immunization	393	++/++	0–18 years	Italy

TABLE 2 Vaccine types, efficacy, and side effects in COVID-19 immunization in children.

Vaccine type	Pfizer/BioNTech	Moderna	Novavax
Recommendation	6 m–4 y: 3-dose series ≥5 y: 1-dose	6 m–5 y: 2-dose series ≥6 y: 1-dose	≥12 y: 2-dose series
Efficacy and immunogenicity	75% (6 m–28 m) 71% (2–5 years) 90% (6–11 years) 95% (12–17 years)	51% (6 m–28 m) 36% (2–5 years) 88% (6–11 years) 92% (12–17 years)	No data available No data available No data available 79.5%
Side effects	↑↑ (6 m–28 m) ↑↑ (2–5 years) ↑ (6–11 years) ↑ (12–17 years)	↑ (6 m–28 m) ↑↑ (2–5 years) ↑ (6–11 years) ↑ (12–17 years)	No data available No data available No data available ↑ (12–17 years)
Immunization in MIS-C pediatric patients	No data available	No data available	No data available

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Gender-neutral vs. gender-specific strategies in school-based HPV vaccination programs: a systematic review and meta-analysis

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Introduction: This systematic review and meta-analysis evaluated whether gender-neutral (GN) or gender-specific (GS) strategies more effectively enhanced knowledge, intention, and uptake of HPV vaccination among students in educational settings.

Methods: A comprehensive literature search of PubMed, Scopus, Web of Science, and Cochrane Library identified 17 randomized controlled trials encompassing 22,435 participants (14,665 females, 7,770 males). Random-effects models were used to calculate standardized mean differences (SMDs) for knowledge and intention, and risk differences for vaccination uptake.

Results: GN strategies achieved higher improvements in knowledge (SMD = 0.95) and intention (SMD = 0.59) compared with GS (SMD = 0.68 for knowledge, SMD = 0.14 for intention), and displayed a greater increase in uptake (5.7% versus 2.5% in GS), although this uptake difference was not statistically significant. Heterogeneity was more pronounced for knowledge outcomes and moderate for GS uptake results.

Discussion: Despite GN approaches seemingly offering more robust enhancements in HPV-related knowledge and vaccination intention, additional research with robust designs and longer follow-up is required to determine whether GN interventions definitively outperform GS strategies in achieving statistically significant increases in actual vaccination uptake.

KEYWORDS

HPV vaccination, gender-neutral strategies, gender-specific strategies, school-based interventions, vaccination uptake

1 Introduction

Human papillomavirus (HPV) is a significant global health concern, responsible for a substantial burden of disease worldwide (1–3). HPV is the primary cause of several cancers, including cervical, oropharyngeal, anal, and genital cancers (4). The introduction of HPV vaccines has shown substantial promise in reducing the incidence of these malignancies, particularly cervical cancer (5, 6). The World Health Organization (WHO) has set an ambitious goal to eliminate cervical cancer as a public health problem by achieving 90% HPV vaccination coverage among girls by the age of 15, coupled with high screening and treatment rates (7, 8).

In low- and middle-income countries (LMICs), the introduction and scale-up of HPV vaccination have been particularly challenging due to limited healthcare resources, cultural stigma, and logistical constraints in delivering multi-dose vaccines. From a meta-analysis of HPV vaccine coverage during the period 2006–2020, the pooled estimate of vaccination uptake in 24 LMICs was 61.69%, although this varied considerably across countries (9). Despite WHO's efforts, many regions have not achieved the desired vaccination coverage, primarily due to barriers such as vaccine hesitancy, lack of awareness, and limited access to healthcare services (8–10). Despite these variations, coverage rates in many LMICs still lag behind those in high-income countries. Addressing these obstacles is essential to fully realize the potential of HPV vaccines and to make significant strides toward the elimination of cervical cancer (10, 11).

Various interventions have been developed to improve HPV vaccination rates, with school-based programs emerging as particularly effective (12). Schools, colleges, and universities provide unique opportunities to reach adolescents and young adults in a structured environment conducive to health education and vaccination campaigns. School-based interventions have the advantage of integrating vaccination programs into existing health curricula, ensuring wider reach and accessibility. These interventions can leverage the trust and influence that educational institutions have over students, facilitating higher vaccination uptake (13–16).

Gender-specific (GS) strategies primarily target females, emphasizing the prevention of cervical cancer through focused educational sessions and health promotion activities (17). These interventions have demonstrated success in raising awareness and increasing vaccination rates among females, contributing significantly to the prevention of cervical cancer (18, 19). However, this approach has a notable limitation: it does not address the significant risk of HPV-related cancers in males, such as oropharyngeal and anal cancers. By focusing solely on females, GS strategies miss the opportunity to educate and protect the entire population at risk, thereby potentially underutilizing the full potential of HPV vaccination programs (20, 21).

In our review, we define GS strategies as those primarily or exclusively targeting females for HPV-related education, motivation, or vaccination campaigns. Although some GS programs may employ principles that could be considered 'gender-responsive' or 'gender-transformative,' our focus was on the overarching approach of directing HPV vaccination interventions specifically at female students rather than undertaking broader structural or systemic gender transformations. Conversely, GN strategies were those aiming to inform and involve all genders, often emphasizing male and female vaccination equally (22, 23).

The underlying hypothesis of GN strategies is that by targeting a wider demographic, these interventions can foster a more inclusive and widespread understanding of HPV prevention. This inclusivity is expected to lead to higher vaccination rates across all genders, thus maximizing public health benefits. Additionally, we hypothesize that the effect of GN strategies on females, even though not specifically focused on them, may be better than that of GS strategies (24, 25). This is because GN strategies place less emphasis on sexual activity and leverage the behavioral economic nudge of the "default" that all children should be vaccinated, which can reduce stigma and encourage vaccination uptake (26, 27). Emerging evidence supports the effectiveness of GN strategies in promoting vaccine equity and inclusivity, suggesting they may be more effective in reducing the overall burden of HPV-related cancers (28). By engaging all genders, GN strategies hold the potential to create a more holistic and effective public health response to HPV (29).

While one might initially assume that GN or GS strategies focus solely on providing vaccines to all genders or only females (30), it is intriguing to shift the focus toward strategies that go beyond merely offering vaccination. Instead, these strategies aim to improve vaccination uptake through educational and promotional efforts. This shift highlights the importance of interventions designed to enhance understanding and acceptance of HPV vaccination, thereby increasing actual vaccination rates. The objectives of this systematic review and meta-analysis are twofold: first, to assess the effectiveness of GN versus GS strategies in enhancing knowledge and attitudes toward HPV-related cancer prevention in educational settings; and second, to evaluate whether GN or GS strategies result in higher HPV vaccination rates among students in schools, colleges, and universities. To provide a comprehensive understanding, we will separate the analysis of outcomes into three categories: outcomes for all genders comparing GN versus GS strategies, outcomes for females comparing GN versus GS strategies, and outcomes for males comparing GN versus GS strategies. Through a comprehensive analysis of randomized controlled trials (RCTs) conducted in these settings, this study seeks to provide robust evidence to inform future HPV vaccination policies and programs, with the ultimate goal of optimizing vaccination uptake and reducing HPV-related cancer incidence globally.

2 Materials and methods

2.1 Study design

This systematic review and meta-analysis were conducted to rigorously evaluate the effectiveness of GS and GN strategies implemented in educational settings for improving knowledge, attitudes, and vaccination uptake related to HPV prevention. The research protocol was proactively registered with PROSPERO, the International Prospective Register of Systematic Reviews (ID: CRD42024566215), and the Open Science Framework (OSF), accessible at https://osf.io/qjbmu/ (accessed on 2 Jan 2025), to underscore our commitment to methodological rigor and transparency. Our methods and the reporting of results were strictly in line with the detailed recommendations provided in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines (31). We also adhered to the methodological standards set forth in the Cochrane Handbook for Systematic Reviews of Interventions (32).

2.2 Eligibility criteria

Eligibility for inclusion in this study was limited to peer-reviewed articles written in English that conformed to the PICOS (Population, Intervention, Comparator, Outcome, Study Design) framework as follows (33, 34).

2.2.1 Population (P)

We included studies involving adolescents and young adults in educational settings, such as schools, colleges, and universities. This

ensured the target demographic was relevant to the interventions aimed at increasing HPV vaccination uptake in these specific environments. Studies focusing on non-educational settings or involving populations outside of the specified age groups were excluded.

2.2.2 Intervention (I)

This review focused on both GS HPV prevention strategies targeted exclusively at females and GN HPV prevention strategies that were not targeted at a specific gender. The interventions encompassed a variety of strategies, including educational programs, web-based education, and motivational interviewing, all designed to enhance knowledge, attitudes, and vaccination rates. We included both onsite interventions and those delivered via web platforms or other digital means. Excluded were interventions that did not involve an active educational component, such as the passive distribution of materials like brochures or posters.

2.2.3 Comparator (C)

Included studies had to compare the effectiveness of school-based strategies against standard practices or control conditions that did not employ the targeted HPV prevention strategies. This could include usual care, waiting list controls, or different types of interventions. Studies using comparators that involved non-educational or non-behavioral strategies, such as pharmacological interventions or structural changes within healthcare settings, were excluded.

2.2.4 Outcomes (O)

The primary outcomes of interest were the effectiveness of GS and GN strategies in improving knowledge, attitudes toward HPV-related cancer prevention, and HPV vaccination uptake. This included specific measures of knowledge improvement, changes in attitudes, and actual vaccination rates. Studies that did not directly report on these outcomes, or focused on indirect measures such as general health outcomes or non-specific educational metrics, were excluded from this review. This focus ensured that our analysis directly assessed the impact of the interventions on tangible vaccination-related outcomes.

2.2.5 Study design (S)

We included only RCTs in this review, as they provide the highest level of evidence for assessing the efficacy of interventions. This choice was made to maintain the rigor and specificity of the evidence evaluated in this meta-analysis. Excluded were non-randomized studies, observational studies, case reports, review articles, and qualitative studies.

2.3 Search strategy

We conducted a comprehensive literature search using PubMed, Scopus, Web of Science, and the Cochrane Library on 3 June 2024. The search strategy was designed to include terms related to 'HPV vaccination', 'communication', and 'educational settings'. Keywords and MeSH terms were used in various combinations: (HPV OR 'human papillomavirus') AND (vaccin* OR immuni* OR 'vaccine uptake') AND (gender OR sex) AND (education OR 'school-based' OR 'college-based' OR 'university-based'). The complete search strategies are provided in the Supplementary material. Filters were initially applied to restrict the search to studies published in English from January 2000 to December 2023. However, since the first HPV vaccine became available in 2006, we focused on studies published from January 2006 to December 2023. Additional sources included reference lists of relevant articles and consultations with organizations. The last search was conducted on 3 June 2024.

2.4 Study selection

The reference lists of relevant systematic reviews and primary studies were reviewed to identify additional studies. NC and TT independently conducted an initial screening of titles and abstracts using Rayyan,[1] a systematic review software, to identify studies potentially meeting the eligibility criteria. Full-text articles of these potentially eligible studies were then thoroughly evaluated for final inclusion by a research assistant along with NC and TT. Discrepancies were resolved through discussion or by consulting a third reviewer to ensure the accuracy and reliability of the selection process. No automation tools were used beyond the initial screening in Rayyan (35).

2.5 Data extraction

Data extraction was performed independently by two reviewers using a standardized form to ensure a comprehensive and consistent approach. Extracted data included general study characteristics such as study design, duration, specific details about the interventions (e.g., type of intervention and delivery method), characteristics of the study sample (including demographic information and setting), and relevant outcome data necessary for calculating effect sizes.

For studies that reported both intention-to-treat and per-protocol analyses, intention-to-treat data were prioritized to maintain consistency and robustness in our analysis (36). In studies employing cluster sampling, the sample sizes were adjusted based on the reported design effect and intracluster correlation coefficients to accurately reflect the impact of this study (37). All extracted data were systematically organized and recorded in Microsoft Excel. Data extraction and coding were performed by a research assistant, overseen by NC and TT, to ensure the accuracy and reliability of the data handling process. When necessary, authors of the studies were contacted to clarify or obtain additional data that were not available from the publications. Discrepancies in data extraction were resolved through discussion or consultation with a third reviewer, ensuring the integrity of the data collected. No automation tools were used.

2.6 Quality assessment

To ascertain the credibility of the cluster randomized trials included in our systematic review, we employed the revised Cochrane risk-of-bias tool for randomized trials (RoB 2),

1 https://www.rayyan.ai/, accessed on 7 June 2024

specifically tailored for cluster-randomized trials (38). This comprehensive tool enabled us to assess bias across several domains: the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Each domain was meticulously examined to determine the level of bias present, with judgments categorized as 'low risk', 'some concerns', or 'high risk'. The evaluation of each domain was conducted independently by NC and TT to enhance objectivity, with any discrepancies resolved through discussion or consultation with a third reviewer. Additionally, to explore potential publication bias, we utilized funnel plots, which provided a visual assessment of the symmetry in the distribution of effect sizes, further validating the robustness of our meta-analytical findings (39).

2.7 Data synthesis and analysis

Data were synthesized quantitatively using meta-analysis methods where appropriate, employing the Comprehensive Meta-Analysis software version 4 (Biostat, Englewood, NJ, USA) to facilitate statistical analysis. Effect sizes were calculated using random-effects models to account for variability between studies. We used the risk difference of vaccination uptake as the main effect measure, represented as the mean percentage increase in vaccination uptake. For knowledge and intention outcomes, standardized mean differences (SMDs) were used to summarize the effect sizes. To accommodate potential variability across the included studies, we utilized a random-effects model, which is better suited for handling the expected heterogeneity. Subgroup analyses were conducted to compare GN versus GS strategies for knowledge, intention, and HPV vaccination uptake.

The extent of this heterogeneity was quantitatively assessed using the I^2 statistic, with cut-off values interpreted as follows: 0–40% may indicate low heterogeneity, 30–60% may indicate moderate heterogeneity, 50–90% may indicate substantial heterogeneity, and 75–100% may indicate considerable heterogeneity, as recommended by the Cochrane Handbook for Systematic Reviews of Interventions. Statistical significance was indicated by a p-value of less than 0.05. Uncertainty was expressed using 95% confidence intervals. Results are graphically presented using forest plots to visually represent the effect sizes and their confidence intervals (32).

3 Results

Figure 1 presents the flow diagram of the study selection process. Initially, searches across various electronic databases yielded 6,587 studies. After removing duplicates, 3,624 studies remained for further examination. Screening of titles and abstracts led to the exclusion of 3,489 studies, resulting in 135 full-text articles retrieved for detailed evaluation. Following a thorough review, studies that did not meet the inclusion criteria were excluded. Additionally, a study identified through alternative methods, such as website searches, Google Scholar searches, citation chasing, and references lists of existing systematic reviews, was added. Ultimately, a total of 17 studies were included in the final analysis.

All 17 studies included in this meta-analysis are randomized controlled trials (RCTs). The total sample size across these studies is

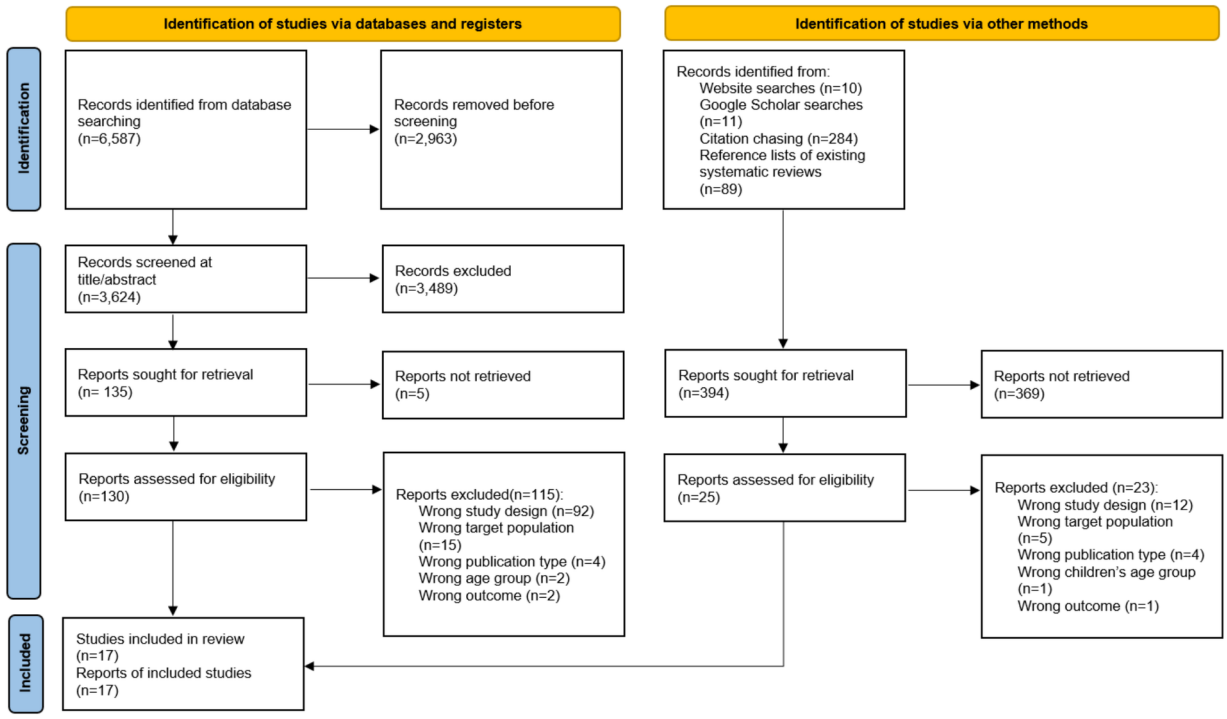

FIGURE 1
PRISMA 2020 flow diagram.

22,435 participants. Of these, 14,665 are females and 7,770 are males. The studies employed either gender-neutral (GN) or gender-specific (GS) strategies. Specifically, 10 studies used GN strategies, involving 13,678 participants (40–46), and 7 studies used GS strategies, encompassing 8,757 participants (31–40, 47–50).

3.1 Intervention strategies across studies

The studies were conducted in various educational settings, including schools, colleges, and universities (Table 1). Several studies targeted high school and secondary school students (35, 50, 51). Most of the studies focused on college and university students, utilizing the structured environment to deliver educational interventions (40, 44–46, 48–50, 52, 53). The age of participants varied across the studies, typically reflecting the educational setting. For high school students, participants were generally adolescents aged 12–17 years (35, 50, 51). For college and university students, participants were typically young adults aged 18–24 years (40, 44–46, 48–50, 52, 53).

The interventions varied in their approach and delivery methods. Some studies implemented tailored educational interventions that addressed specific knowledge gaps about HPV and its vaccines (40, 44–46, 49, 50, 52, 54). Others used narrative and storytelling methods to make the information more relatable and engaging for the participants (44–46, 48). Interventions also included components such as motivational interviewing, decisional support, and logistical strategies to facilitate vaccination (40, 50, 51, 55). The duration of interventions ranged from single sessions to daily sessions over a week, with follow-up periods varying from immediate post-intervention to several months. The use of technology was a common feature in the interventions, enhancing the delivery and engagement of educational content. Many studies used web-based platforms to deliver educational content and interventions (43, 44, 46, 48, 49, 52, 54). Some interventions utilized mobile applications for delivering content, reminders, and tracking vaccination status (40, 44, 46). Additionally, SMS reminders were used to prompt parents and students about vaccination appointments and educational content (50, 51, 55).

The studies employing GN strategies targeted both males and females, aiming to provide a comprehensive understanding of HPV and its associated risks across genders. These studies often used inclusive educational materials and interventions that addressed the full spectrum of HPV-related health risks, thus ensuring a broader reach and impact. For instance, GN strategies included web-based education and mobile applications that provided interactive and engaging content for all students (40–46). Additionally, GN interventions frequently involved peer education and storytelling methods to make the information relatable and engaging for both genders (44–46, 48). In contrast, GS strategies focused primarily on female participants, emphasizing the prevention of cervical cancer through targeted educational sessions and health promotion activities. These studies often highlighted the importance of HPV vaccination for preventing cervical cancer, with interventions designed to address specific knowledge gaps and misconceptions among women (40, 44, 46, 48–50, 52, 54). GS strategies also utilized tailored educational interventions and motivational interviewing techniques to increase vaccination intentions and uptake among female students (40, 44, 46, 49, 50, 52, 54).

The comparison groups in these studies typically received either standard or minimal educational interventions about HPV and its vaccination. In some studies, the control groups received standard health education materials, such as CDC factsheets or regular health class content (40, 44, 46, 48–52, 54). Other control groups received no additional information beyond what was typically provided in their educational settings (43, 44, 46, 48, 55). The aim of these comparisons was to evaluate the added benefit of the tailored, technologically enhanced, and nudge-based interventions over the standard or minimal educational approaches.

The outcomes assessed in the studies varied but focused on three primary areas: knowledge, intention to vaccinate, and actual vaccination uptake. Most studies evaluated the participants' knowledge about HPV, its related diseases, and the benefits of vaccination. The interventions generally led to significant improvements in HPV-related knowledge compared to controls (40–44, 46, 48, 50, 53–56). Several studies measured the intention to get vaccinated as an intermediate outcome. Interventions that included motivational and educational components were effective in increasing participants' intention to receive the HPV vaccine (40, 44, 46, 49, 50, 52, 54). Actual vaccination uptake was assessed in studies that had longer follow-up periods. Both GN and GS strategies showed effectiveness in increasing vaccination rates, but GN strategies demonstrated a broader impact by also addressing male vaccination, thereby contributing to higher overall uptake rates (44, 46, 48–50, 52–55).

3.2 Meta-analysis

3.2.1 HPV-related knowledge

The impact of interventions on HPV-related knowledge was assessed across multiple studies, with a total of 13 studies included in the analysis. The results from the fixed-effect analysis for both GN and gender-specific GS strategies are as follows:

For GN strategies, the pooled effect size from 5 studies was 0.954 (95% CI, 0.537–1.371) with a standard error of 0.213 and a variance of 0.045. The Z-value for the test of null was 4.482, with a p-value of <0.001, indicating a statistically significant improvement in knowledge. The heterogeneity among the studies was significant, with a Q-value of 88.16 (df = 4, $p < 0.001$) and an I^2 value of 95.46%, indicating substantial heterogeneity.

For GS strategies, the pooled effect size from 8 studies was 0.226 (95% CI, −0.185–0.638) with a standard error of 0.210 and a variance of 0.044. The Z-value for the test of null was 1.078, with a p-value of 0.281, indicating no statistically significant improvement in knowledge. The heterogeneity among these studies was also significant, with a Q-value of 202.07 (df = 7, $p < 0.001$) and an I^2 value of 96.54%, indicating considerable heterogeneity.

The subgroup analysis comparing the GN and GS strategies revealed a significant difference between the two groups. The Q-value for the subgroup difference was 5.914 (df = 1, $p = 0.015$). This indicates that GN strategies had a significantly greater impact on improving HPV-related knowledge compared to GS strategies (Figure 2).

TABLE 1 Summary of included studies.

Study	Location	Population	Sample size	Intervention	Comparison	Duration/Follow-up	Outcomes
Baxter et al. (40)	Canada	Female university students (GS)	Total = 193, *I* = 98, *C* = 95	Tailored HPV message for sexually inexperienced women	Detailed HPV message, Control	Immediate	Intention
Bennett et al. (48)	USA	Female university students (GS)	Total = 661, *I* = 330, *C* = 331	MeFirst tailored online educational intervention	Standard CDC factsheet	3 months	Knowledge, Uptake
Davies et al. (49)	Australia	Secondary school students (GN)	Total = 6,965, *I* = 3,485, *C* = 3,480	Complex intervention (education and distraction, decisional support, logistical strategies)	Usual practice	End of school year	Knowledge
Doherty et al. (41)	USA	College students (GN)	Total = 119, *I* = 60, *C* = 59	Web-based HPV educational intervention	Control	1 month	Knowledge, Intention
Grandahl et al. (52)	Sweden	Upper secondary school students (GN)	Total = 751, *I* = 376, *C* = 375	Face-to-face structured information about HPV by school nurses	Regular health interview	3 months	Intention
Hopfer et al. (42)	USA	Female college students (GS)	Total = 404, *I* = 202, *C* = 202	Narrative intervention (peer-only, medical expert-only, combined peer-expert)	Informational video, campus website, no message	2 months	Uptake
Kim et al. (50)	USA	Korean American college women (GS)	Total = 104, *I* = 52, *C* = 52	Storytelling video intervention using mobile, web-based technology	Information-based written material	2 months	Uptake
McKeever et al. (43)	USA	College-age women (GS)	Total = 73, *I* = 42, *C* = 31	Educational program about cervical cancer, HPV infection, and HPV vaccine	Educational program offered after 1 month	1 month	Knowledge, Intention
Merzouk et al. (53)	USA	High school students (GN)	Total = 626, *I* = 313, *C* = 313	HPV educational DVD plus health class	Health class only	Immediate	Knowledge
Nadarzynski et al. (44)	UK	Female university students (GS)	Total = 606, *I* = 303, *C* = 303	Information about cervical cancer and HPV (control, control + HPV, control + risk factors, control + both)	Control	1 week	Knowledge
Perez et al. (45)	USA	College-aged women (GS)	Total = 62, *I* = 31, *C* = 31	Information–motivation–behavioral skills (IMB) intervention	Attention control	1 month	Knowledge, Intention
Si et al. (46)	China	Female university students (GS)	Total = 3,739, *I* = 1936, *C* = 1803	10-min online IMB model-based education daily for 7 days	Health tips unrelated to HPV	Immediate	Knowledge, Intention
Steckelberg et al. (56)	Germany	Vocational school girls (GS)	Total = 105, *I* = 53, *C* = 52	Standard leaflet supplemented with numerical information on cancer risk and HPV vaccination benefits	Standard leaflet without numerical data	Immediate	Knowledge
Stock et al. (51)	USA	College students (GN)	Total = 238, *I* = 125, *C* = 113	Information on HPV, oral sex, and oral cancer	No information	Immediate	Knowledge, Intention
Tull et al. (62)	Australia	Parents of year 7 students (GN)	Total = 4,386, *I* = 2,834, *C* = 1,552	SMS reminder to parents (motivational vs. self-regulatory)	No SMS	End of school year	Uptake
Wang et al. (55)	China	Female first-year college students (GS)	Total = 449, *I* = 235, *C* = 214	7 days of HPV-related web-based education	Popular science education (not HPV-related)	3 months	Knowledge, Intention
Zhang et al. (54)	China	Female freshmen (GS)	Total = 946, *I* = 532, *C* = 414	7-day web-based health education on HPV and HPV vaccines	Non-HPV related materials	1 month	Knowledge, Intention

GN, Gender neutral; GS, Gender specific; I, Intervention; C, Control.

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3.2.2 HPV vaccination intention

The impact of interventions on the intention to receive the HPV vaccine was assessed in several studies. The results from the fixed-effect analysis for both gender-neutral (GN) and gender-specific (GS) strategies are summarized below:

For GN strategies, the pooled effect size from 1 study was 0.593 (95% CI, 0.242–0.944) with a standard error of 0.179 and a variance of 0.032. The *Z*-value for the test of null was 3.313, with a *p*-value of 0.0009, indicating a statistically significant improvement in vaccination intention. There was no heterogeneity among the GN studies, as the *Q*-value was 0 (df = 0, $p = 1$) and the I^2 value was 0%.

For GS strategies, the pooled effect size from 5 studies was 0.141 (95% CI, 0.006–0.282) with a standard error of 0.072 and a variance of 0.005. The *Z*-value for the test of null was 1.969, with a *p*-value of 0.049, indicating a marginally significant improvement in vaccination intention. The heterogeneity among these studies was minimal, with a *Q*-value of 0.923 (df = 4, $p = 0.921$) and an I^2 value of 0%.

The subgroup analysis comparing the GN and GS strategies revealed a significant difference between the two groups. The *Q*-value for the subgroup difference was 5.494 (df = 1, $p = 0.019$). This indicates that GN strategies had a significantly greater impact on improving HPV vaccination intention compared to GS strategies (Figure 3).

3.2.3 HPV vaccination uptake

The impact of interventions on HPV vaccination uptake was assessed using risk difference as the effect measure. The results from the fixed-effect analysis for both gender-neutral (GN) and gender-specific (GS) strategies are summarized below:

For GN strategies, the pooled risk difference from 2 studies was 0.057 (95% CI, 0.028–0.087), indicating a 5.7% increase in vaccination uptake (standard error = 0.015, variance = 0.00022). The *Z*-value for the test of null was 3.841, with a *p*-value of 0.00012, indicating a statistically significant improvement in vaccination uptake. There was no significant heterogeneity among the GN studies (*Q*-value = 0.559, df = 1, $p = 0.455$, $I^2 = 0\%$).

For GS strategies, the pooled risk difference from 5 studies was 0.025 (95% CI, −0.009–0.059), indicating a 2.5% increase in vaccination uptake (standard error = 0.017, variance = 0.00030). The *Z*-value for the test of null was 1.444, with a *p*-value of 0.149, suggesting a non-significant improvement in vaccination uptake. The heterogeneity among these studies was substantial (*Q*-value = 19.855, df = 4, $p = 0.00053$, $I^2 = 79.85\%$).

The subgroup analysis comparing the GN and GS strategies revealed no significant difference between the two groups (*Q*-value = 2.046, df = 1, $p = 0.153$). This indicates that while GN strategies showed a more substantial and statistically significant improvement in HPV vaccination uptake, the difference between GN and GS strategies was not statistically significant in this analysis (Figure 4).

3.3 Publication bias

Visual inspection of the funnel plot (Figure 5) did not reveal significant signs of publication bias, which supports the credibility of the meta-analysis findings. The effect sizes were distributed relatively symmetrically across the studies, suggesting that there was no systematic bias skewing the results. Most effect sizes fell within the funnel, indicating a uniform distribution. A few effect sizes that fell outside the funnel did so symmetrically on both sides of the mean, further reducing concerns about potential bias. This symmetry implies that both smaller and larger studies contributed evenly to the overall analysis, indicating that the meta-analytical conclusions are robust and reliable across different study sizes and conditions.

3.4 Risk of bias analysis

The risk of bias was assessed across all 17 studies using the Cochrane Collaboration's tool for randomized controlled trials (RoB 2). The assessment covered five domains: bias arising from the

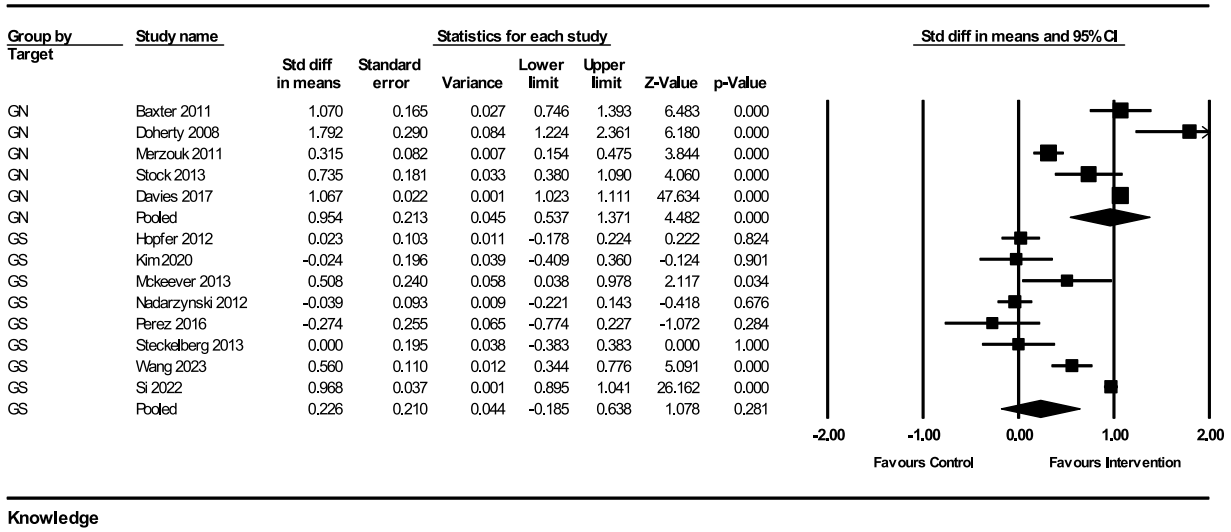

FIGURE 2
Forest plot of the effects on HPV-related knowledge of GN vs. GS.

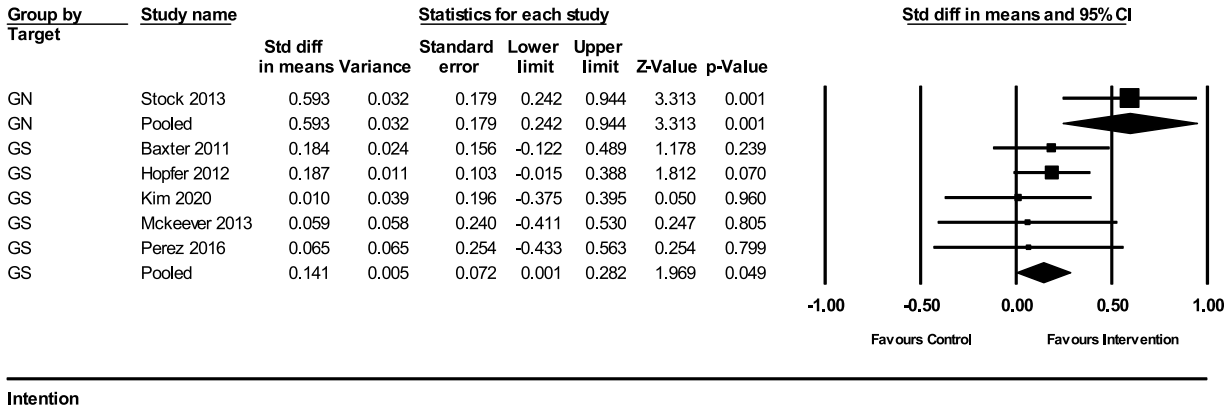

FIGURE 3
Forest plot of the effects on HPV vaccination intention of GN vs. GS.

randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result. Overall, the risk of bias assessment revealed that most studies had low risk in several domains, with some concerns primarily arising from randomization and deviations from intended interventions. This assessment underscores the robustness and reliability of the meta-analytic findings, although the identified risks highlight areas for potential improvement in future research designs (Figure 6).

4 Discussion

This systematic review and meta-analysis evaluated the effectiveness of GN versus GS strategies in enhancing knowledge, intention, and uptake of HPV vaccination among students in educational settings. Our analysis, which included 17 RCTs with a total sample size of 22,435 participants, revealed that both GN and GS strategies effectively improve HPV-related knowledge and vaccination intention. However, GN strategies demonstrated a more significant impact on vaccination uptake, suggesting a broader reach in public health interventions.

The analysis revealed that GN strategies significantly improve HPV-related knowledge compared to GS strategies. The SMD for GN strategies was 0.95, indicating a substantial increase in knowledge levels. This finding is consistent with previous research suggesting that inclusive educational interventions can enhance understanding across diverse populations (57, 58). However, the high heterogeneity observed in knowledge outcomes (I^2 = 95.46% for GN and 96.54% for GS) suggests variability in intervention delivery and educational settings, which may influence the effectiveness of knowledge dissemination. Both GN and GS strategies were effective in increasing vaccination intention, with GN strategies showing a more pronounced effect (SMD = 0.59) compared to GS strategies (SMD = 0.14). This aligns with earlier studies indicating the critical role of motivational and educational components in shaping vaccination intentions (58). The minimal heterogeneity observed in the GS group (I^2 = 0) suggests a consistent effect of these interventions on vaccination intentions, while the GN group exhibited no heterogeneity, reflecting a uniform impact across the included studies.

It is important to note that in this review, we defined GS strategies as those primarily or exclusively targeting female populations for HPV vaccination and education. Although some GS interventions may contain elements of gender responsiveness—by acknowledging and accommodating distinct needs of women—this does not necessarily mean they are fully gender-transformative, which would involve actively challenging gender norms and power imbalances. Similarly, GN strategies, while often involving both male and female participants, may still require further refinements to align with gender-transformative frameworks in certain cultural or educational contexts.

The findings from our study suggest that school-based HPV vaccination programs can improve knowledge about HPV infection and HPV vaccination among female students. This aligns with previous systematic reviews and meta-analyses, which have highlighted the effectiveness of educational interventions in increasing knowledge and altering perceptions about HPV and cervical cancer (57–59). Ampofo et al. (58) conducted a meta-analysis focusing on the effectiveness of school-based education for improving knowledge and perceptions of cervical cancer and HPV among female students. Their study found that while knowledge about cervical cancer and HPV infection improved significantly, there was no significant improvement in attitudes toward HPV vaccination. This finding is consistent with our results, where attitudes toward HPV vaccination did not show a significant change post-intervention in the gender-specific group, even though knowledge increased. Flood et al. (59) also emphasized the potential of school-based interventions in improving HPV knowledge and vaccination intentions among middle adolescents (15–17 years). Their review highlighted that although educational interventions significantly improved knowledge and intentions, only a few studies actually measured changes in HPV vaccination uptake. This suggests that while knowledge and intentions are critical steps, they may not directly translate to higher vaccination rates without additional behavioral or systemic interventions. Our study similarly found improvements in knowledge and intentions, but also showed an actual increase in vaccination uptake, especially in GN interventions, reinforcing the importance of comprehensive strategies.

Despite GN strategies demonstrating a higher point estimate (5.7% vs. 2.5%) in increasing actual HPV vaccination uptake, the

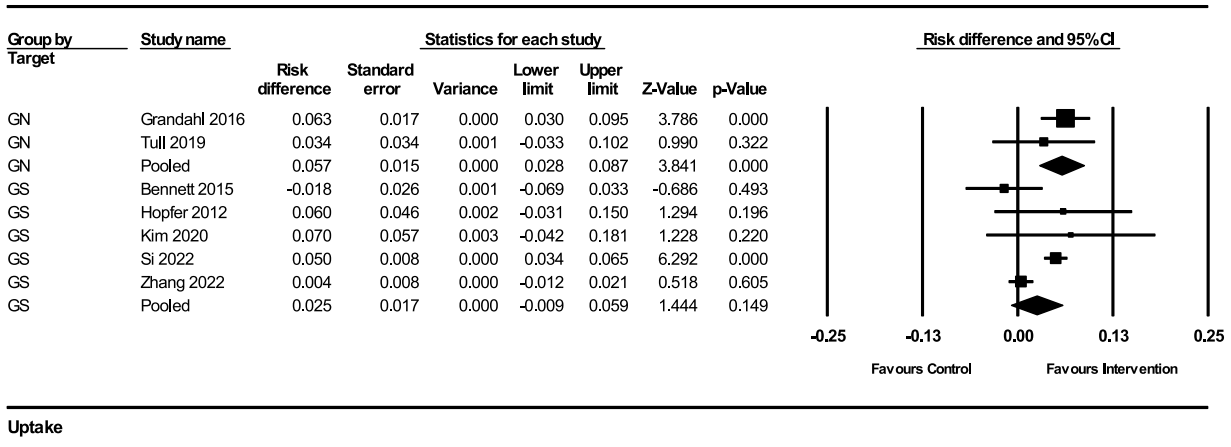

FIGURE 4
Forest plot of the effects on HPV vaccination uptake of GN vs. GS.

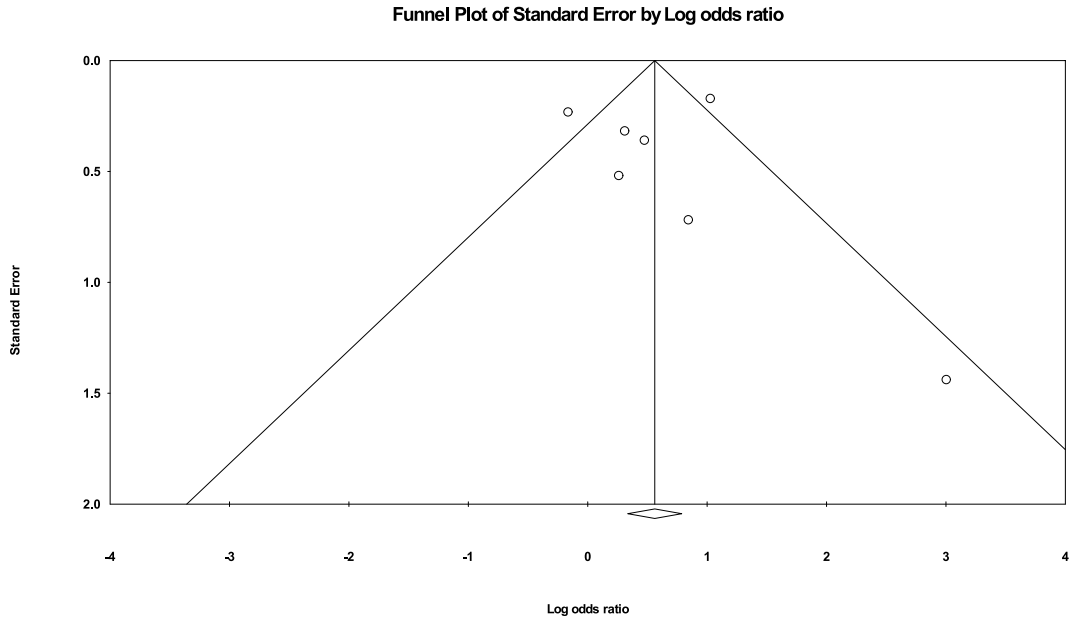

FIGURE 5
Funnel plot with symmetrical spread of effect sizes around the mean effect size.

subgroup analysis did not yield a statistically significant difference between GN and GS strategies ($p = 0.153$). This non-significant finding suggests that although GN approaches may have greater potential to reach a broader audience (58, 59) and foster inclusivity, further high-powered studies are required to determine whether GN interventions consistently outperform GS interventions in boosting vaccination rates. Notably, GN interventions are comparable to provider-based interventions, which have been shown to improve uptake by 5–10% (60, 61). In contrast, GS interventions achieve only about half of this improvement. This highlights the importance of tailoring school-based interventions to be inclusive and gender-neutral to maximize their impact on vaccination uptake. In practice, educators and policymakers may weigh the broader coverage benefits of GN interventions against the potentially more tailored messaging in GS approaches. Ultimately, conclusive recommendations on implementing GN or GS strategies will depend on context-specific factors, such as available resources, cultural perceptions, and baseline vaccination rates.

It is important to note that some studies have reported more modest improvements or even null effects of GN strategies, particularly in settings where vaccine misinformation or cultural stigma surrounding HPV vaccination is prevalent (53, 62). These nuances highlight that while GN approaches may have a broad appeal, their success is heavily context-dependent and may require further adaptation to local cultural norms and acceptance of sexual health education.

The limitations of this study include potential publication bias, heterogeneity in study designs and interventions, and reliance on self-reported data for some outcomes. The high heterogeneity in knowledge outcomes suggests variability in educational methods

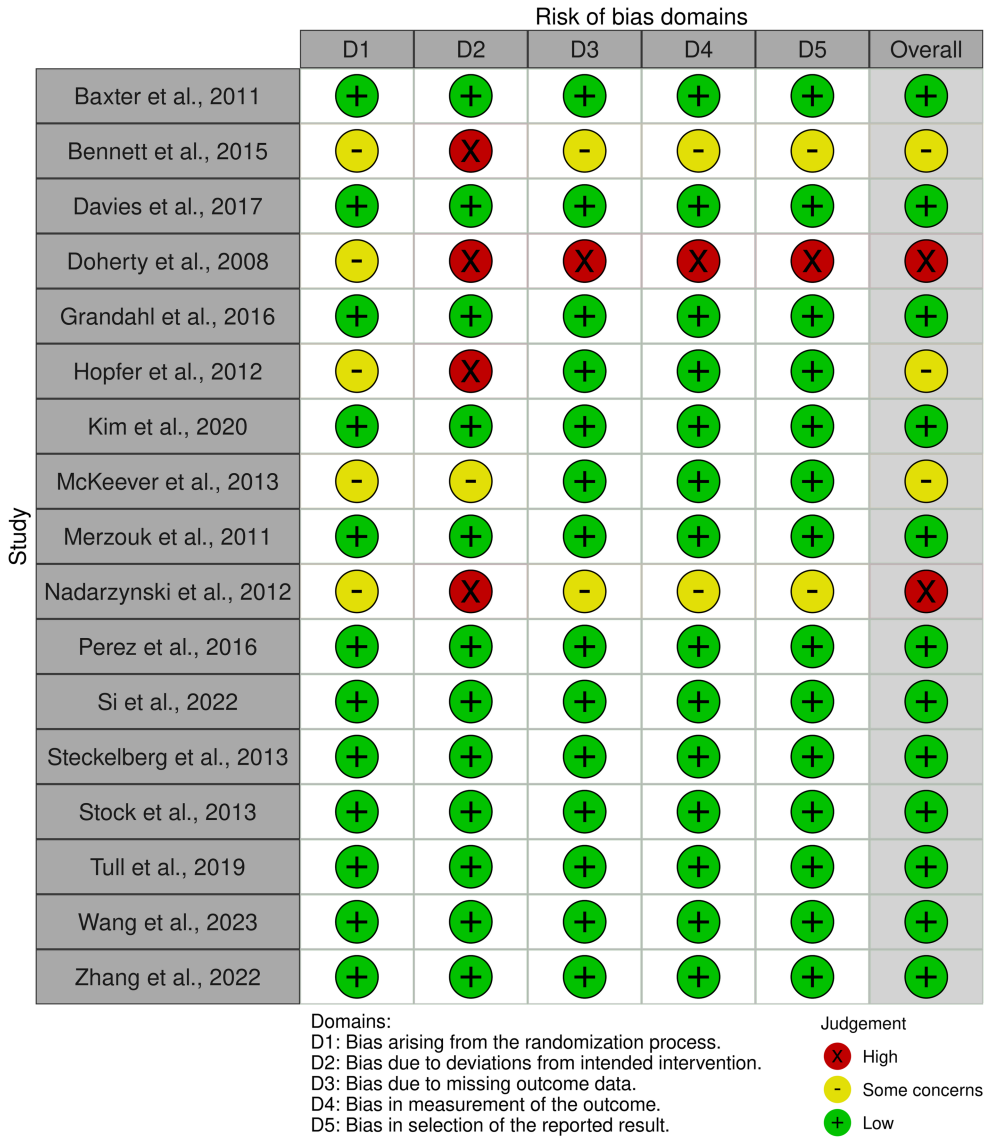

FIGURE 6
Risk of bias plots.

and settings. Although we hypothesized that educational settings (secondary schools vs. colleges/universities) could explain some of the observed heterogeneity, a formal subgroup analysis was not feasible given the limited number of eligible school-based studies in both the GN and GS groups (fewer than four studies per subgroup). This limitation underscores the need for more research in diverse educational contexts to better elucidate setting-specific effects on HPV vaccination knowledge and outcomes. Furthermore, the lack of long-term follow-up in some studies limits the understanding of the sustained impact of these interventions on vaccination uptake and intentions. This underscores the need for more standardized and methodologically rigorous studies to ensure the reliability and applicability of the findings. Additionally, the limited number of RCTs and the lack of outcome separation by gender restrict our ability to analyze the specific impacts of GN interventions on male and female participants separately, which is crucial for tailoring public health strategies effectively.

The findings underscore the importance of implementing GN strategies in educational settings to improve HPV vaccination uptake. These strategies, by addressing a broader audience, can potentially lead to higher overall vaccination rates. Future research should focus on methodologically rigorous studies with long-term follow-up to better understand the sustained impact of these interventions. Additionally, exploring innovative educational methods, such as game-based learning, could further enhance the effectiveness of school-based health education programs. Understanding the context-specific factors that influence the success of these interventions, particularly in low- and middle-income countries, remains a critical area for future investigation. The implementation and success of HPV vaccination strategies, whether GN or GS, are influenced by broader contextual factors. Cultural attitudes toward vaccination and sexual health, socioeconomic disparities that limit healthcare access, and variable healthcare infrastructures can all mediate the impact of interventions. In LMICs, for instance, a lack of consistent cold-chain systems,

inadequate health education frameworks, and sociocultural barriers may diminish the effectiveness of even the most robust school-based HPV programs. Future research should adapt interventions to these local contexts, ensuring that gender-neutral approaches are culturally sensitive and feasible within different economic and healthcare settings.

5 Conclusion

Our findings suggest that GN strategies, while demonstrating a potentially broader impact on HPV vaccination knowledge and intention, did not significantly outperform GS strategies in terms of actual vaccination uptake. Future studies should replicate these findings in larger, more diverse populations and with longer-term follow-up to definitively determine the comparative effectiveness of GN versus GS strategies.

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.

Author contributions

NC: Conceptualization, Data curation, Formal analysis, Investigation, Project administration, Resources, Writing – original draft, Writing – review & editing. PK: Data curation, Investigation, Methodology, Project administration, Resources, Writing – review & editing. SP: Conceptualization, Formal analysis, Methodology, Visualization, Writing – original draft. TT: Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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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.2025.1460511/full#supplementary-material

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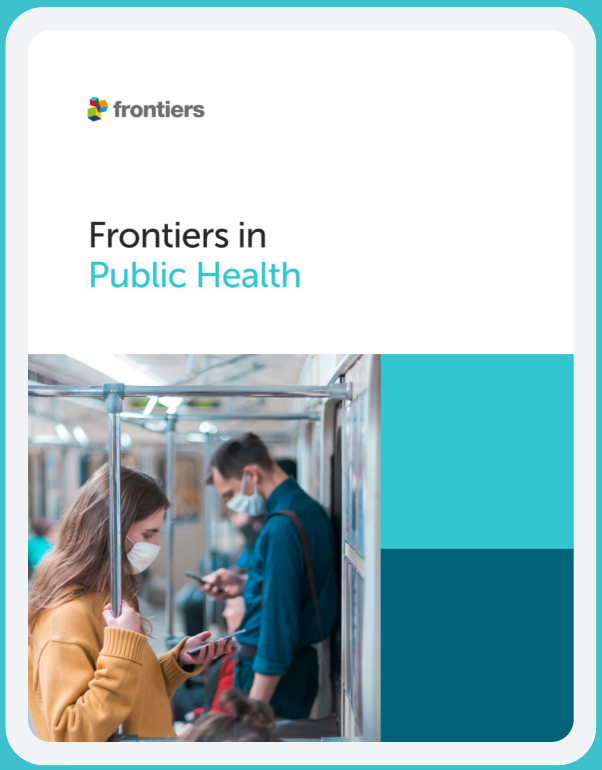

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