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EDITED BY
Joana Tavares,
University of Porto, Portugal

REVIEWED BY
Sunil Joshi,
QuantumImmunogenix-A Third Eye Network Inc., United States
Ugonna Henry Uzoka,
Michael Okpara University of Agriculture, Nigeria

*CORRESPONDENCE
Miray Tonk-Rügen
miray.ruegen@agrar.uni-giessen.de
Ludwig E. Hoelzle
ludwig.hoelzle@uni-hohenheim.de

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Microbiota-immune crosstalk in livestock: implications for tick-borne disease control

Miray Tonk-Rügen[1]*, Thorben Schilling[2,3], Alejandro Cabezas-Cruz[4] and Ludwig E. Hoelzle[2,3]*

[1]Institute for Insect Biotechnology, Justus Liebig University of Giessen, Giessen, Germany, [2]Institute of Animal Science, Department of Livestock Infectiology and Environmental Hygiene, University of Hohenheim, Stuttgart, Germany, [3]HoLMiR-Hohenheim Center for Livestock Microbiome Research, University of Hohenheim, Stuttgart, Germany, [4]ANSES, INRAE, Ecole Nationale Vétérinaire d'Alfort, UMR BIPAR, Laboratoire de Santé Animale, Maisons-Alfort, France

Globally, livestock health, which impacts animal welfare and agricultural productivity, is continuously threatened by tick-borne diseases (TBDs). The growing issues of acaricide overuse in livestock, emerging resistance, and vector adaptation to climate change require novel and sustainable intervention strategies. Recent advances in microbiome research reveal how host and vector microbiota influence immune responses, particularly through natural antibodies (nAbs) that modulate vector competence and pathogen transmission. In livestock, nAbs targeting microbial glycans are heritable, measurable, and linked to health outcomes. In cattle, nAb titers to bacterial antigens are associated with mastitis risk and longevity, while in pigs, early-life nAb levels are proposed as resilience markers. Studies in poultry further demonstrate the importance of high nAb phenotypes for health and production. These findings highlight nAbs as both immunological markers and potential targets for genetic selection to improve disease resistance. Emerging interventions, such as anti-microbiota vaccines and immunobiotics, aim to modulate nAb repertoires, disrupt pathogen colonization, and enhance disease resilience. Additionally, microbial glycans serve as key targets for inducing cross-reactive immunity against TBDs. Manipulation of the livestock microbiota through diet, probiotics, and prebiotics shows promise in diversifying nAb profiles and improving robustness against infection. Despite these advances, research gaps remain, particularly in establishing causality and practical feasibility in livestock systems. This review emphasizes the need for integrative research across immunology, microbiology, and veterinary sciences to leverage microbiota–immune interactions in enhancing livestock resilience against TBDs, exploring how nAbs shaped by the gut microbiota can modulate tick microbiomes and impact pathogen transmission.

KEYWORDS
livestock, microbiome, natural antibody, ticks, tick-borne diseases

1 Introduction

Livestock health and productivity are essential for global food security and economic stability, yet infectious diseases, especially those transmitted by ticks—remain a major challenge. Tick-borne diseases (TBDs) are a growing threat worldwide, with incidence increasing due to climate change, expanding tick distribution, and the overuse and resulting resistance to acaricides (1–7). Ticks transmit a diverse range of protozoan, bacterial, and viral pathogens to livestock (8–12). For example, the protozoa *Babesia bovis* and *Theileria parva* cause bovine babesiosis and East Coast fever, respectively, both of which lead to high mortality in cattle (13–15). These pathogens often manipulate host immune responses and evade detection, complicating treatment and prevention efforts (16–20). The burden of TBDs is substantial, with economic losses from reduced productivity, increased mortality, and disease management costs (21–25). Although live vaccines containing attenuated parasites are available, TBDs remain inadequately controlled, highlighting the urgent need for new preventive strategies to combat acute diseases and the spread of parasites into non-endemic regions (18, 26–28). Conventional tick control measures such as chemical acaricides, rotational grazing, and habitat modification face challenges such as resistance, environmental toxicity, and limited long-term efficacy (29–34). This creates a pressing need for novel, biology-based alternatives.

The microbiota — comprising diverse communities of bacteria, viruses, and fungi that reside in both hosts and vectors—has emerged as a crucial factor shaping host–pathogen–vector interactions (35–38). These microbial communities play essential roles in immune system development, metabolism, and susceptibility to infection (39, 40). In livestock, gut and other site-specific microbiota interact dynamically with the immune system to modulate defenses against vector-borne infections (41–43). In contrast, tick microbiota affects the ability of ticks to acquire and transmit pathogens, further influencing disease transmission (37, 37, 44–46).

Natural antibodies (nAbs), key components of innate immunity, are produced early in life without prior exposure to pathogens, playing crucial roles in pathogen neutralization, microbiota recognition, and cross-reactive defense in all vertebrates, including humans (47–51). They are produced by B-1 cells and provide a first-line defense by binding a broad range of exogenous and self-antigens (52–54).

nAbs recognize conserved microbial glycans, such as —such as lipopolysaccharides (LPS), lipoteichoic acids (LTA), peptidoglycans (PGN)), as well as Keyhole Limpet Hemocyanin (KLH) and β-glucans, which are especially relevant in livestock (48, 55–57). While α-Gal is a known model epitope, livestock naturally express this glycan, making other microbial glycans more significant for nAb targeting, modulated by microbial colonization and probiotics (48, 58, 59). For examples, probiotic supplementation has been linked to increased nAb levels in chickens, enhancing both mucosal and systemic immunity (58, 60). This presents opportunities for microbiota-based interventions in livestock, with potential effects on TBD transmission by (i) neutralizing pathogens via pre-existing nAbs and (ii) altering the tick gut microbiome (56, 59). These relationships are summarized in Figure 1, which outlines the conceptual framework linking microbiota, nAbs, and TBP transmission.

In this review, we explore microbiota-driven immune crosstalk as a novel avenue to enhance livestock resistance against TBDs. We focus on how gut microbiota can shapes nAb production in livestock and, how these antibodies can modulate tick gut microbiome and interfere with TBPs. We also emphasize the translational potential of specific microbial epitopes and interventions. This approach will facilitate the identification of robust findings versus knowledge gaps and support the design of next-generation probiotic or vaccine strategies to reduce the burden of TBDs in livestock.

2 Importance of gut microbiota

The gut is a complex ecosystem of host cells, microbiota, and available nutrients (61). The microbiota constitutes a diverse ecological community encompassing commensal, symbiotic, and pathogenic microorganisms, which include bacteria, viruses, archaea, fungi, and protozoa (62–64). The gut microbiota composition is likely to affect many organ systems, including the cardiovascular, neural, immune, and metabolic systems (61, 65–70). Importantly, it plays a pivotal role in gut immune homeostasis and response (71, 72). The gut microbiota can influence the scope and quality of the immune system response; in turn, the immune system participates in regulating the localization and composition of the gut microbiota (71, 73). It has been shown that diet and nutrients significantly affect gut microbiota composition and its connection to immunological pathways (74).

2.1 Livestock gut microbiota and host immunity

Advances in shotgun metagenomics have revolutionized our understanding of microbial communities and their functionality (75, 76). The gut microbiota of livestock comprises diverse communities of bacteria, fungi, archaea, protozoa, plasmids, and viruses (76, 77).

The importance of the gut microbiome in livestock extends beyond digestion and nutrient absorption to maintaining immune homeostasis and pathogen defense. Extensive research in cattle, sheep, goats, and pigs demonstrates its critical roles in animal health and productivity by supporting gut development, digestion, and immune function (76, 78–87). Compared to other ruminants, studies on the cattle gut microbiome are especially comprehensive, mapping microbial communities across various regions of the gastrointestinal tract (88). Particularly in the rumen, studies have uncovered numerous novel bacterial taxa and revealed complex interactions between the microbiome, its metabolome, and the host, further highlighting the microbiota's impact on digestion and overall health (75, 76, 83, 89).

Microbiota composition and stability in livestock are profoundly influenced by factors such as diet, environment, and antimicrobial use (90, 91). Feeding practices influence microbial diversity along the

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Abbreviations: TBDs, Tick-borne diseases; TBPs, Tick-borne pathogen; nAbs, Natural antibodies; LPS, Lipopolysaccharides; LTA, Lipoteichoic acids; PGN, Peptidoglycans; KLH, Keyhole Limpet Hemocyanin; MAMPs, Microbial-associated molecular patterns; PRRs, Pattern recognition receptors; PAMPs, Pathogen-associated molecular patterns; SCFAs, Short-chain fatty acids; FMT, fecal microbiota transplantation.

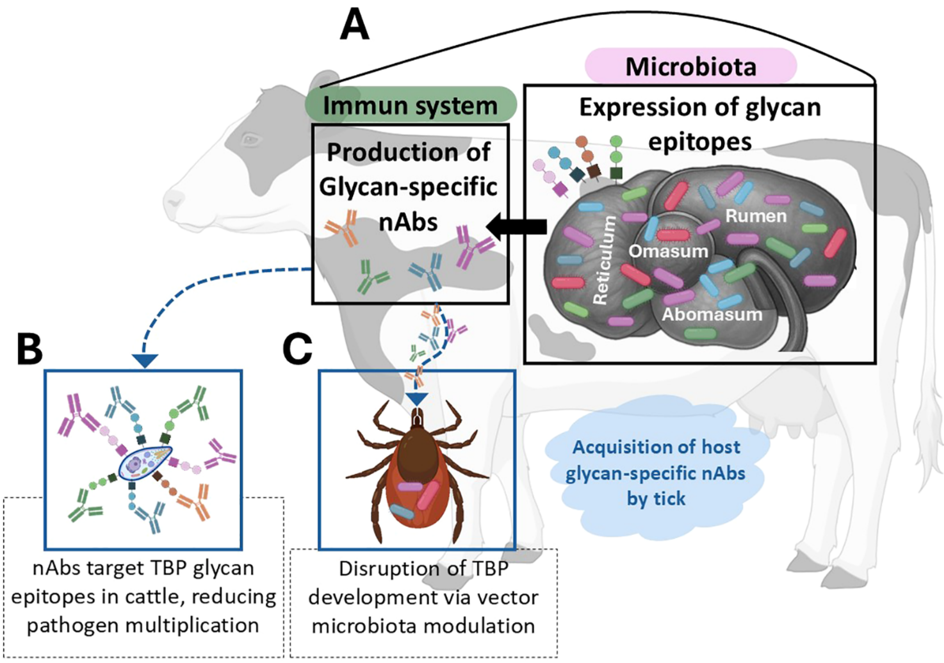

FIGURE 1
Natural Antibodies (nAbs): a dual-function immune component: **(A)** Cattle gut microbiota harbors bacteria that express glycan epitopes, thereby inducing the production of glycan-specific nAbs. **(B)** Cattle acquire tick-borne pathogen particles containing glycan epitopes through tick bites, triggering recognition by glycan-specific nAbs. These antibodies may facilitate the control or neutralization of the pathogen, reducing its capacity to multiply. Alternatively, **(C)** Ticks obtain these nAbs during the bloodmeal. These antibodies can access the tick gut lumen and target bacteria expressing glycan epitopes within the tick microbiota, resulting in alterations to the bacterial community composition and structure. nAbs-driven modulation of the tick microbiota may reduce the development of tick-borne pathogens (TBPs), thereby lowering pathogen transmission rates.

gastrointestinal tract, and parasite infections have been linked to alterations in microbiome composition (79, 92–94). A balanced microbiota maintains a symbiotic relationship with the host, modulating immune responses, preserving homeostasis, and preventing harmful inflammatory reactions against commensals, while simultaneously protecting the host from pathogenic invasion and the overgrowth of indigenous pathobionts (95, 96). Disruptions in this balance, or dysbiosis, have been associated with increased susceptibility to infections and inflammatory diseases (87). Furthermore, antibiotic-induced dysbiosis may exacerbate disease by promoting inflammatory immune responses (97, 98). Strategies to modulate the microbiota—including probiotic and prebiotic supplementation, dietary adjustments, and microbiota transplantation—have been explored to improve feed efficiency and disease resistance (76). However, the effectiveness of probiotics such as *Lactobacillus* and *Bifidobacterium*, and prebiotics such as inulin and oligosaccharides, varies across species and diets (76).

3 Microbiota-immune system interactions: mechanisms of natural antibody modulation

Microbiota–immune system interactions influence both innate and adaptive immunity, shaping pathogen clearance and immune memory (95, 99–102). While the detailed mechanisms by which microbiota alterations affect infection susceptibility in livestock remain under-explored, existing studies highlight their significant impact. For instance, it was highlighted the critical role of gut microbiota in modulating immune responses and influencing disease susceptibility (102).

Gut bacteria, through characteristic epitopes such as glycans, trigger the production of nAbs, which target conserved microbial glycans—ubiquitous pathogen-associated molecular patterns (PAMPs) central to host–microbe interactions (57). In dairy cattle, nAb titers are genetically associated with mastitis risk, longevity, and immune competence (103). Genome-wide association studies have identified SNPs linked to variation in nAb responses, supporting their potential as indicator traits (104). In pigs, early-life nAb levels are heritable and have been proposed as markers of resilience under polymicrobial challenge (105). High nAb levels correlate with increased fitness and pathogen resistance in multiple species: wild boar with high nAbs showed resilience to classical swine fever (106), In poultry, selection lines bred for high anti-KLH nAbs exhibited improved resistance to *E. coli* and show consistent production and health benefits (107), validating the robustness of the trait across species. These findings highlight that livestock nAbs are not only immunological features but also promising targets for genetic selection, potentially integrated into breeding programs, genomic selection, or microbiota-based strategies to enhance heritable immune traits and boost livestock resilience.

nAbs act systemically in livestock, including at skin and blood sites where ticks interact with their hosts. While the role of nAbs in shaping host–ectoparasite microbiome interactions remains underexplored, glycan-specific nAbs, including those targeting epitopes like α-Gal, can influence vector microbiomes and affect tick fitness (36, 55, 108–111). Notably, nAbs provide the first line of protection against vector-borne pathogens such as Dengue virus and *Plasmodium* spp., while also potentially targeting epitopes like α-Gal in experimental models (48, 95, 112–116). Microbial-associated molecular patterns (MAMPs)—including lipopolysaccharides, peptidoglycans, and flagellins—activate pattern recognition receptors (PRRs) on immune cells, triggering B-cell activation and differentiation into antibody-producing plasma cells (117, 118). This immune response is essential for defending against vector-borne pathogens.

Evidence also points to nAbs shaping vector microbiomes. Glycan-specific nAbs can modulate tick gut microbiota and reduce vector fitness (36, 49). Microbiota-targeted vaccination in canaries and mice reduces pathogen prevalence in mosquitoes (110) and ticks (36). For example, *Borrelia afzelii* colonization in *Ixodes ricinus* was reduced following anti-microbiota vaccination, and avian malaria transmission by mosquitoes was suppressed by immunization with microbial antigens (110). Zebrafish fed probiotics expressing α-Gal antigens developed strong nAb responses and improved resistance to mycobacterial infection (119). These findings suggest that immunobiotics—beneficial microbes or their derivatives that modulate immune responses (119)—could be used to strategically enhance nAb production in livestock.

4 Tick microbiota: shaping vector competence and pathogen transmission

Ticks harbor diverse microbial communities that influence their physiology, immunity, and ability to transmit pathogens (36, 120). The composition of the tick microbiota varies with species, developmental stage, environment, and host blood meal (45, 121). Core taxa include genera such as *Rickettsia*, *Coxiella*-like endosymbionts, and *Francisella*-like endosymbionts, which may contribute to tick nutrition and reproduction (45, 122). Disruption of these symbionts can impair tick development and survival, underscoring their biological relevance (122).

The role of tick microbiota in shaping vector competence is increasingly recognized. Recent studies have highlighted the potential of microbiota manipulation as a strategy to reduce pathogen prevalence in ticks (36, 37, 123). Perturbations of the tick microbiome through antibiotics or environmental factors can alter pathogen acquisition and transmission (37, 123). Dysbiosis in *Ixodes scapularis* has been associated with enhanced *Borrelia burgdorferi* colonization (37). Similarly, vaccination against specific symbionts can reduce tick fitness and pathogen prevalence (36). These findings highlight the potential of microbiota modulation as a strategy to disrupt pathogen transmission.

Host-derived antibodies can also indirectly alter tick microbiota. Glycan-specific nAbs raised by microbiota-targeted vaccines have been shown to shift the composition of the tick gut microbiome and reduce vector fitness (36). Glyco-immunogenic bacteria within the gut microbiome can stimulate the production of glycan-specific nAbs, which may directly target vector-borne pathogens, shape the vector microbiota, and trigger immune signaling pathways that influence pathogen development (109, 116).

Microbiota-targeted vaccination in canaries and mice has been shown to lower pathogen prevalence in mosquitoes and ticks (124, 125), highlighting the potential of nAbs to modulate vector microbiomes and impair vector fitness and competence. Altering the vector microbiome may also impact the vector's immune system through the activation of key signaling pathways (126, 127).

Host–vector microbiota interactions are reciprocal. Blood meals deliver host-derived immune molecules and metabolites that shape the microbial balance inside the tick gut (45). Conversely, tick saliva introduces microbial and immunomodulatory components back into the host, influencing host immunity and microbiota composition (128–130). These bidirectional influences suggest that interventions targeting either host or vector microbiota could have cascading effects on pathogen transmission cycles.

We hypothesize that nAbs produced by livestock in response to microbiota may directly influence the tick microbiome, potentially by altering microbial communities within the tick gut. This, in turn, could impact the tick's vector competence by either enhancing or inhibiting the colonization of tick-borne pathogens. Experimental models could test this hypothesis by examining shifts in tick microbiota composition following nAb modulation in livestock.

Although compelling results have been obtained in mosquitoes, poultry, and rodent models, extrapolation to livestock–tick systems for modulation nAb require caution. The complexity of ruminant microbiota, variation among tick species, and environmental heterogeneity mean that outcomes observed in experimental models may not directly translate to agricultural settings. More integrative and livestock-focused studies are required to test whether microbiota-based interventions can reliably disrupt TBP transmission in real-world systems. While studies in mosquitoes and zebrafish have shown microbiota–immune interactions impacting pathogen transmission, evidence in livestock–tick systems is sparse. For instance, in cattle, microbiota modulation could influence tick gut microbiomes and reduce pathogen acquisition, though this remains largely untested in real-world agricultural settings.

5 Strategies and practical implementation of microbiota modulation for enhanced disease resistance in livestock

The limitations of chemical acaricides and conventional vaccines have driven interest in microbiota-based approaches to control TBPs. These strategies focus on exploiting the host–microbiota–immune axis to improve livestock resilience and reduce tick vector competence. Various avenues are being explored, including probiotics, prebiotics, postbiotics, anti-microbiota vaccines, selective breeding, management and nutrition (36, 125, 131, 132) (Figure 2).

Translating microbiota-based strategies into practical applications for livestock requires consideration of production environments, economic feasibility, and compatibility with existing management practices. While experimental studies demonstrate proof-of-concept, scaling to real-world systems involves several challenges and opportunities. Pilot studies in cattle, pigs, and poultry are essential to evaluate the effectiveness and scalability of these interventions.

5.1 Probiotics and prebiotics supplementation

As discussed earlier, probiotic supplementation can modulate host microbiota composition, enhance gut barrier function, and stimulate immune responses relevant to pathogen resistance (61, 133–135).

In poultry, probiotic administration has improved antibody responses to vaccination and reduced colonization by pathogenic bacteria such as *Salmonella* and *E. coli* while also improving growth performance (59, 136, 137). For example, multi-strain *Lactobacillus* probiotics have been shown to enhance growth and gut health, with *L. salivarius* reducing *E. coli* colonization, and Lavipan, containing *Lactococcus*, *Lactobacillus*, and *Saccharomyces*, lowering coliform levels and boosting weight gain in chicken (138–140). Prebiotic fibers, such as inulin and oligosaccharides, promote the growth of beneficial microbial taxa and their metabolites, including short-chain fatty acids, which influence B-cell metabolism and nAb production (141–145). In dairy cattle, for instance, supplementation with yeast-derived products has improved rumen function and immune responses, with some evidence linking dietary modulation to altered antibody profiles (146–149). However, the effects of probiotic and prebiotics can be strain- and species-specific, and may vary depending on host's physiological state, highlighting the need for tailored microbiota modulation strategies in livestock health and production (150).

Although direct evidence from livestock–tick systems is lacking, these findings suggest that diet-based microbiota modulation could enhance nAb diversity and support livestock resilience against polymicrobial infections and reduce TBP transmission. These approaches could potentially enhance resilience Nonetheless, results can be inconsistent across species and production systems due to factors such as diet, host genetics, and management practices, highlighting the importance of customizing microbiota modulation strategies to specific livestock needs.

5.2 Immunobiotics

Immunobiotics are beneficial microorganisms or microbial products that specifically modulate the immune system to

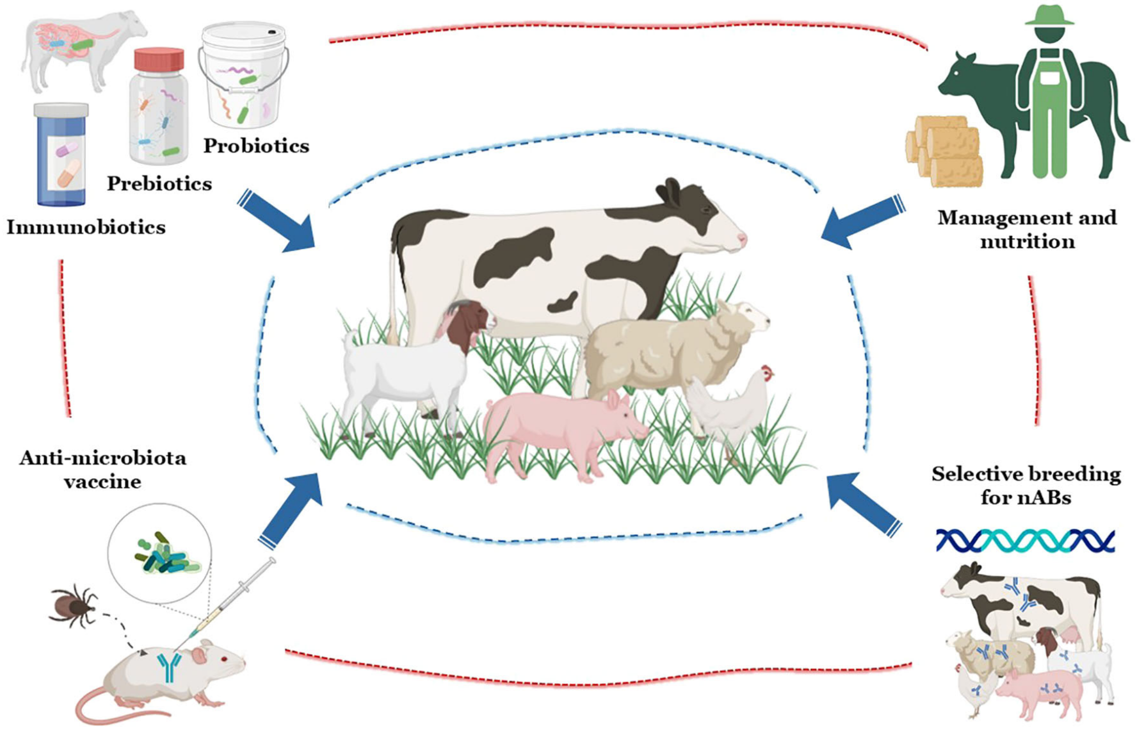

FIGURE 2
Integrated microbiota-based strategies to enhance livestock resistance to tick-borne diseases: The figure illustrates complementary approaches linking microbiota modulation and immune enhancement to reduce tick-borne pathogen transmission in livestock. Key interventions include probiotics, prebiotics, and immunobiotics to strengthen gut health and natural antibody (nAb) responses; anti-tick vaccines targeting vector microbiota; selective breeding for higher nAb titers; and improved management and nutrition to sustain immune resilience. Together, these strategies promote a sustainable, One Health-oriented framework for tick-borne disease control.

enhance disease resistance (119, 151, 152), and target immune function by stimulating natural defenses, promoting antibody production, and modulating inflammatory responses (153). Therefore, they may enhance cross-reactive immunity against TBPs by shaping the nAb repertoire, with microbial glycans in livestock (154, 155).

5.3 Anti-microbiota vaccines

Vaccination targeting vector microbiota or symbionts is an emerging strategy to disrupt pathogen transmission (36). In ticks, vaccination against specific gut bacteria has been shown to alter microbial composition and reduce *B. afzelii* colonization, with proof-of-concept studies demonstrating promising results (36). However, translating these findings to livestock systems will require careful validation, including the development of stable, affordable vaccine formulations compatible with existing vaccination schedules. Field trials are necessary to assess efficacy across diverse tick species and ecological conditions, as well as to evaluate the ecological impacts and long-term feasibility. Integration with existing herd vaccination programs may facilitate adoption in the future, contingent upon the demonstration of safety and cost-effectiveness.

5.4 Selective breeding for nAbs

nAbs could serve as valuable biomarkers for selective breeding programs aimed at enhancing immune competence and disease resistance. Integration of nAb profiling into genomic selection pipelines may offer a sustainable approach to improving livestock resilience against TBPs.

In species like pigs, chicken and cattle nAb levels have been linked to increased disease resilience (103, 105, 107), suggesting their potential for inclusion in genomic selection indices to enhance livestock robustness and reduce reliance on chemical treatments, thereby providing a sustainable, cumulative strategy.

5.5 Integrated approaches

Integrated approaches offer the most promising avenue for reducing the burden of TBPs. A combination of diet-based microbiota modulation, targeted immunobiotics, and selective breeding, complemented by vector-focused interventions such as anti-microbiota vaccines, may provide the most effective means of reducing the burden of TBPs (36, 125, 156, 157). These approaches align with the One Health principles, connecting livestock productivity, environmental sustainability, and reduced antimicrobial use. By modulating both host and vector microbiomes, such interventions could enhance innate immunity, decrease dependence on antibiotics and acaricides, and limit TBP transmission.

5.6 Management and nutrition

Diet, housing, and antimicrobial exposure influence livestock microbiota composition and thereby the nAb repertoire (158–160). For example, antimicrobial use—such as intramammary ceftiofur treatment in dairy cattle—has been shown to cause persistent changes in the gut microbiome and increased antibiotic resistance, which may constrain nAb development (161). In pigs, antibiotic administration significantly altered microbial composition and reduced production of short-chain fatty acids, including decreases in *Bifidobacterium*, *Lactobacillus*, and *Ruminococcus*—likely impacting immune-metabolite interactions relevant to nAb induction (162). In contrast, diet diversification—such as transitioning cattle from grain-fed to grass-fed systems—has been associated with distinct microbiome and resistome profiles, suggesting enriched microbiota–immune interactions (163). Practical implementation will therefore need to integrate microbiota-based strategies with broader herd management practices that promote microbial diversity.

5.7 Systems-level considerations

Adoption of microbiota-driven interventions must account for economic and logistical realities. Interventions must be affordable for producers, compatible with existing feeding or vaccination programs, and demonstrate measurable improvements in health and productivity. Pilot field trials in cattle, pigs, and poultry will be essential to establish feasibility. These approaches should complement, rather than replace, other control measures such as acaricide use, rotational grazing, and tick vaccines to ensure long-term sustainability.

6 Challenges and knowledge gaps in microbiota-immune research

Although advances in microbiota and nAb research offer promising directions, several challenges currently limit translation into livestock–tick systems. Much of the mechanistic evidence is derived from model organisms and from laboratory-maintained mosquitoes and ticks. Major microbial targets, intervention strategies, and associated immune and disease outcomes across livestock, poultry, rodent, zebrafish, and tick models are outlined (Table 1). While these studies have provided critical insights, their application to ruminants offers a valuable basis for species-specific research, considering differences in microbiota composition, immune ontogeny, and host–vector interactions. This highlights the urgent need for cattle- and pig-specific research that reflects the complexities of livestock production systems.

Elucidating causal mechanisms represents a key priority for future investigations. Many existing studies are correlative in nature, providing associations between microbiota modulation, nAb diversification, and pathogen outcomes without demonstrating direct mechanisms. Carefully designed experiments—including longitudinal studies, microbiota transplantation, targeted microbial depletion, and defined probiotic supplementation in livestock—will be essential to determine whether microbiota-based interventions can reliably reduce TBP transmission.

A key challenge in advancing the field is the measurement and standardization of nAbs. Although assays for glycan-specific nAbs have been developed in cattle and pigs, their application remains inconsistent across laboratories, production systems, and

TABLE 1 Comparative summary of livestock and experimental models investigating microbiota–natural antibody (nAb) interactions.

Model	Microbial targets	Types of intervention	Observed immune & disease outcomes	References
Cattle	Glycan antigens (LPS, LTA, PGN, mannan, β-glucans); rumen taxa (*Firmicutes*, *Bacteroidetes*)	Yeast-derived supplements, mannan oligosaccharide, diet shifts, selective breeding for nAb phenotypes	Improved rumen function and milk yield; systemic Ig changes; nAb titers linked to mastitis resistance, longevity; diet/antibiotics alter microbiota & resistome	(103, 146, 147, 154)
Pigs	Glycan antigens; core gut taxa (*Bifidobacterium*, *Lactobacillus*, *Ruminococcus*)	Management/nutrition changes; reduced antibiotics; probiotic/prebiotic supplementation; selection for nAb traits	Heritable early-life nAb levels; antibiotics reduce SCFA & beneficial taxa; nAbs proposed as resilience markers	(105, 163)
Poultry (chickens, layers)	Gut bacteria expressing glycan epitopes; *Salmonella*, *E. coli*	Commercial probiotics (*Lactobacillus* spp., mixes), *in-ovo*/oral probiotics, prebiotics	Probiotics boost natural antibodies, improve vaccine responses, reduce pathogens, enhance performance; high anti-KLH nAb lines resist disease	(58, 60, 107, 138)
Rodents & other model mammals	Glycan epitopes; commensal taxa	Antibiotics, FMT, defined probiotics, anti-microbiota vaccinations	SCFAs modulate B-cell metabolism and antibody responses; antibiotics reduce diversity and immune responses; microbiota→nAb→reduced pathogens	(142, 164)
Zebrafish	α-Gal–containing microbes; probiotic strains with glycan epitopes	Probiotics/immunobiotics expressing α-Gal or glycan epitopes	α-Gal probiotics induced nAbs; zebrafish gained resistance to mycobacterial infection	(55, 119)
Ticks (vector models)	Tick gut symbionts (*Coxiella*-like, *Rickettsia*, *Francisella*-like)	Anti-microbiota vaccines, antibiotic perturbation of tick microbiome	Altering tick microbiota reduces pathogen colonization, affects tick fitness & vector competence	(36, 45, 109)

Listed are microbial targets, intervention strategies, observed immune outcomes, and supporting references.

environmental conditions due to the lack of standardized protocols. Addressing this challenge through harmonized protocols and validating nAb assays under diverse field conditions will be crucial for enabling reliable cross-study comparisons and the development of validated biomarkers. Standardizing these methods will not only accelerate progress in microbiota-based immune interventions but also ensure their accuracy and relevance in real-world agricultural settings, ultimately unlocking the full potential of these interventions.

The ecological complexity of livestock production presents a stimulating challenge for advancing microbiota-based strategies. Factors such as diet, housing, antimicrobial exposure, and vector ecology interact to shape both microbiota and immune responses, creating an opportunity to investigate these dynamics in real-world system. Conducting large-scale field studies that account for such heterogeneity will be essential to evaluate the feasibility, effectiveness, and robustness of targeted interventions, ultimately guiding the development of practical, resilient solutions.

At the same time, understanding and managing potential unintended consequences presents an important research opportunity. Manipulating microbiota to enhance nAbs may alter beneficial symbionts or influence opportunistic pathogens, and anti-microbiota vaccines targeting vector competence could affect tick symbioses with broader ecological impacts. These considerations highlight the value of integrating ecological evaluations with technological development, ensuring that interventions are both effective and sustainable. Finally, any new microbiota-based approaches will need to be integrated into existing livestock management frameworks. Interventions will not be applied in isolation but alongside acaricides, grazing strategies, and vaccination programs. Understanding whether microbiota-targeted tools act synergistically or antagonistically with current measures remains an unresolved challenge, yet one that will determine their practical adoption and long-term sustainability.

7 Future perspectives: towards innovative microbiota-based therapies against tick-borne diseases

Modulating microbiota–immune interactions to enhance livestock health and reduce the burden of TBPs is a promising approach, which requires considerable refinement before it can be translated into practice. Future progress will depend on clarifying causal mechanisms, validating interventions in real production systems, and ensuring that any new tools complement rather than replace existing control measures. A key priority is to establish mechanistic pathways linking specific microbial taxa, glycan epitopes, and nAb responses to measurable outcomes in livestock. Controlled work in species like cattle and pigs, supported by functional genomics and metabolomics, will be essential to identify microbial drivers of protective antibody repertoires.

Another area where progress is needed is the development of reliable biomarkers. Glycan-specific nAbs have shown promise as indicators of immune competence. However, standardization of assays and validation across diverse breeds and environments are critical before they can be adopted in breeding programs or herd health monitoring.

Probiotics, prebiotics, and immunobiotics hold promises for shaping the nAb repertoire, but their design should prioritize microbial epitopes relevant to livestock. Similarly, anti-microbiota vaccines need to be tailored to the ecology of livestock-associated ticks and evaluated for long-term stability and safety. One of the most urgent priorities is the field validation of microbiota-based interventions. Large-scale, longitudinal trials under farm conditions are needed to test whether microbiota-based interventions genuinely improve health, reduce pathogen prevalence, and maintain productivity. Such studies must also address economic feasibility, farmer adoption, and regulatory frameworks, since these factors will ultimately determine whether interventions reach practice.

Furthermore, One Health approach, highlights the importance of livestock microbiota in influencing not only animal health and welfare but also human health. For instance, the modulation of livestock microbiota can help reduce zoonotic disease transmission and lower the reliance on antibiotics, which in turn supports the global fight against antimicrobial resistance. Understanding these interactions provides critical insights into improving public health outcomes, as strategies designed for livestock may be adaptable to human health solutions.

Taken together, future progress will depend on integrating microbiota-based approaches into broader livestock health strategies. Rather than serving as stand-alone solutions, microbiota interventions are likely to be most effective when combined with genetic selection, nutritional management, vaccination, and conventional tick control. By situating microbiota-immune interactions within this integrated framework, the field can move towards practical, sustainable, and One Health-aligned solutions for managing TBDs in livestock.

8 Conclusions

TBPs remain a major threat to livestock health and productivity worldwide, and their control is becoming increasingly difficult as acaricide resistance spreads and climate change expands tick distributions. Conventional approaches, while still important, are unlikely to provide durable solutions on their own. This review highlights how the microbiota and the nAbs it elicits represent an underexplored dimension of host–vector–pathogen interactions, one that could be leveraged to improve livestock resilience.

Microbiota-targeted interventions, including probiotics, prebiotics, immunobiotics, and anti-microbiota vaccines, provide novel opportunities to shape these antibody repertoires and disrupt pathogen transmission cycles. Much of the current evidence comes from non-livestock models, and causal links between microbiota modulation, antibody diversification, and disease outcomes are not yet firmly established. Standardized methods for measuring nAbs, together with large-scale field studies in livestock systems, will be necessary to move from concept to application.

Prospectively, microbiota-based strategies should not be seen as replacements for existing practices but as components of an integrated approach to tick control and animal health. By aligning microbiota research with breeding, nutrition, management, and vaccination, the field can contribute to more sustainable livestock production. Integrating these insights into practical interventions offers a path towards reducing the burden of TBDs, improving animal welfare, and advancing One Health objectives that link agriculture, the environment, and human well-being.

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MT: Conceptualization, Investigation, Visualization, Writing – original draft, Writing – review & editing. TS: Writing – review & editing. AC: Conceptualization, Writing – review & editing. LH: Resources, Writing – review & editing.

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