***Review Article***

**Recent Advances in Tick Vaccine Development and Future Prospects**

**ABSTRACT**

Ticks are an obligate blood-feeding ectoparasite having significant economic challenges by infesting a range of domestic and wild animals. They rank just behind the mosquitoes as effective vectors for numerous bacterial, viral, protozoan, and rickettsial diseases. This leads to economic losses in the livestock sector. Current methods for controlling ticks primarily rely on acaricides; however, the emergence of acaricide resistance, along with environmental contamination and residues in food products, highlights the need for alternative strategies. Immunization presents a promising, cost-effective, and eco-friendly approach to tick control. A key challenge in development of vaccine is identifying tick’s antigens that play essential roles in survival and reproduction of tick. There have been many studies during the last few decades on finding potent candidate antigen (surface-exposed and hidden) using methods such as expression library immunization (EST), immune mapping, RNA interference, and bioinformatics. This review aims to provide an overview of the current development in tick vaccine. The future prospects include combining tick antigens with different protective mechanisms and pathogen-derived antigens.

**Keywords:** Antigen, vaccine development, tick control, Immunization.

**Introduction**

Ectoparasites, mainly ticks are significant contributors to transmission of various diseases affecting both humans and livestock. Ticks and its borne pathogens are increasingly recognized as important global challenges, raising both social and economic concerns. Ticks could lead to remarkable economic losses within the livestock industry globally. Nearly 899 tick species are known to infesting various hosts like amphibians, reptiles, birds, and mammals (Ghosh and Nagar, 2014). Their direct effects include anemia, tick-induced paralysis (a sudden flaccid motor paralysis that ascends), toxicosis, and skin damage. Controlling ticks is particularly challenging, with traditional methods relying heavily on chemical acaricides, which have shown limited effectiveness and come with drawbacks such as the rising of tick resistance in populations with a potential harm to animal’s health and environment (Mollong et al., 2025). Reports of multi-acaricide-resistant ticks appearing worldwide and growing environmental concerns about pesticide use complicate the continued reliance on conventional tick management strategies (Bishop et al., 2023).

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Indirectly, ticks function as carriers for bacterial infections, viral diseases, protozoan, and rickettsial pathogen. Ticks are recognized as most impactful and adaptable vectors of diseases, second only to mosquitoes; success in transmitting of various pathogens due to their ability to parasitizing a wide variety of hosts and their feeding behaviour on multiple individuals during their life cycle. In addition, ticks exhibited several biological benefits that enhance their survival and transmission potential, including high reproductive rates, the capacity to endure extreme environmental factors, and relatively long lifespans (Dehuri et al., 2022). These factors contributed significantly to their role in spreading numerous pathogens to animals and, in some cases, humans. The economic impact of tick infestations is also substantial; for instance, the cattle tick *Rhipicephalus microplus* is responsible for heavy financial losses, with estimated annual costs reaching approximately USD $2 billion in Brazil and around USD $170 million in the United States (Grisi et al., 2002; Playford, 2005). In India, a predominantly agricultural nation where 70% of the population relies on farming, the costs associated with tick-borne diseases are estimated at US $787.63 million annually. Consequently, ticks pose a significant economic burden on farmers and represent a global threat to both livestock and human health (Singh et al., 2022).

One Health and the United Nations Sustainable Development Cooperation Framework mentioned that vaccination has gained recognition as a highly promising, safe approach to controlling tick populations and minimizing the spread of tick-borne diseases. This strategy aligns with global efforts to reduce reliance on chemical acaricides, which often lead to environmental contamination and development of tick resistance. Vaccines provide a more targeted and environmentally friendly alternative by triggering host immune responses that interfere with tick feeding, survival, reproduction (Estrada-Peña et al., 2022).

Despite the promising outcomes observed in experimental trials, various formulations have shown significant efficacy in reducing tick infestations (Parizi et al., 2023), but only a few vaccines have advanced to commercialization. The only commercially available vaccines are based on Bm86 and Bm95 antigens—namely, TickGARD in Australia and Gavac in Cuba—designed specifically to control *Rhipicephalus microplus* populations (de la Fuente et al., 2007). Recently, TickGARD is not commercially available, only GAVAC is marketed in some countries of Latin America. This review examines the historical development of tick vaccinology. It also emphasizes recent innovations of antigen discovery, delivery systems, and vaccine formulation techniques aimed at creating next-generation advanced anti-tick vaccines. These advancements not only enhance efficacy and cross-species protection but also contribute to integrated tick management strategies that are sustainable, cost-effective, and globally applicable (Boulanger and Wikel, 2023).

**Immune Response in Ticks**

Ticks secrete saliva into the host’s while feeding blood, which contains various digestive enzymes that facilitate the feeding process help suppress immune response of the host. For example, kinases enzymes and histamine-associated proteins in the salivary secretion can break down the molecule bradykinin plays a key role in causing pain and itchiness. Certain tick species, such as *Ixodes scapularis*, produce specific proteins that bind to complement components and suppress C3 production., reducing the host's scratching and grooming behaviors. This immune suppression allows ticks to feed more effectively and can also assist any pathogens introduced via their saliva (Francischetti et al.,2009).

The host immune response to tick saliva can be classified into three types, low-molecular-weight salivary components that bind to skin proteins like collagen, and acting as haptens to trigger the Th1 immunity. Repeated exposure of haptens may trigger delayed-type hypersensitivity responses. Additionally, certain salivary antigens can engage with Langerhans cells, initiating a cutaneous basophil hypersensitivity reaction (Boulanger and Wikel, 2023). This response is marked by Th1 cell activity, IgG production, and the recruitment of basophils to the affected site. Lastly, there is a Th2 response involving IgE production, which leads to immediate hypersensitivity reactions. This can result in localized skin inflammation, causing pain or itching (Shahardar, 2021).

**Development of Tick Vaccines**

The idea of developing tick vaccines belongs to 1939, when Targer discovered that repeated exposure to tick larvae induced an adaptive immunity in guinea pigs and rabbits, offering protection against ixodid tick infestations. Comparable immune responses were observed when guinea pigs were immunized with native protein extracts derived from *Dermacentor variabilis* (Targer, 1939). These immune reactions were associated with a reduction in the number of ticks that successfully engorged, diminished blood intake, decreased tick weight, and lower fertility, reflected by fewer viable eggs (Ndawula and Tabor, 2020). Later studies further validated the concept of host immunization using tick-derived antigens (de la Fuente and Kocan, 2003).

To identify protective tick proteins and antigens, several strategies have been employed. These include: fractionating crude tick extracts and evaluating the immunogenicity of the fractions through challenge experiments; Identifying the tick antigens that elicit antibody responses in infected hosts by immunomapping. using monoclonal antibodies to identify and characterize protective antigens; employing Using expression library immunization, RNA interference techniques and bioinformatics for analysed data interpretation.

**Attributes for Selecting Candidate Antigens for Anti-Tick Vaccine Development**

When selecting candidate antigens for anti-tick vaccines, several key attributes should be considered. Firstly, the target antigens should be easily accessible to host immune system during the tick’s blood feeding procedure. Additionally, antigen should play a crucial role in tick biology; disruption of its function should lead to significant reductions in tick survival or reproductive capacity, thereby impacting tick populations. Lastly, the ideal antigens should contain conserved epitopes that are shared among multiple tick species, providing protection against various vector infestations (Diaz-Martin et al. 2015).

Candidate antigens for tick vaccines are primarily classified into two types:

1. **Exposed Antigens**: Secreted in saliva during the tick attachment and feeding, these peptides originate from salivary glands and include examples like P29, 64TRP, and Hl34.
2. **Concealed Antigens**: Located in the gut lining, these antigens are typically hidden from the host's immune system but react with antibodies during blood feeding. They offer protection across tick life stages and can help from pathogen transmission. Bm86 is a well-known example (de la Fuente and Kocan, 2003).

**Targets for Vaccine Development**

Several categories of antigens evaluated for their potential in tick vaccine development:

* **Crude Extracts**: These include whole tick homogenates, such as ground tick suspensions (GUTS), and extracts obtained from its salivary glands.
* **Salivary Gland-Specific Antigens**: This group features proteins like P29, Hl34, RIM36, 64P, various metalloproteases, cystatins, Salp15, and Salp25D, which are secreted during feeding (Parizi et al., 2011).
* **Gut-Derived Antigens**: Examples include Bm86 and its related proteins (homologs and orthologs), along with acid peptidases, ferritins, aquaporins, and serpins that are in the tick midgut (de la Fuente and Contreras, 2015).
* **Pathogen Transmission-Blocking Antigens**: Antigens likely 64P, Salp15 and TROSPA, have been shown to interfere with the transmission of tick-borne pathogens**.**
* **Multi-Species Antigen**: Like subolesin.
* **DNA-Based Vaccines**.
* **Miscellaneous Antigens**: Including voraxin, glutathione peroxidase.

**Vaccination Trials with Crude Antigens**

Several studies have assessed the efficacy of crude tick extracts for immunization. It was reported that rabbits vaccinated with whole extracts of *Hyalomma anatolicum anatolicum* showed alterations in tick biology and cross-protection against *H. marginatum isaaci*. These whole extracts outperformed salivary gland extracts, producing higher antibody levels and a lower lymphocyte stimulation index, though this did not directly correlate with protection. Thakur et al. (1992) demonstrated that mid-gut extracts of *H. anatolicum*, combined with saponin and Freund’s Complete Adjuvant, reduced tick fertility in rabbits. Similarly, Kumar and Kumar (1996) found that mid-gut antigens from *H. dromedarii* induced immunity and cross-protection against *H. anatolicum*. Allen and Humphery (1979) showed that guinea pigs immunized with mid-gut and reproductive organ extracts had reduced tick loads, egg production, larval hatching, and feeding success. In calves, Sran et al. (1996) observed strong immune responses when whole salivary gland extracts of *H. a. anatolicum* were combined with *Ascaris* extract. Sangwan et al. (1998) found that whole nymphal extracts offered superior protection in cattle compared to soluble or membrane antigens. Additionally, Ghosh and Khan (1996, 1997) used crude extracts from partially fed adult and unfed larval *Rhipicephalus microplus* to immunize calves, identifying protective proteins of 105.4 kDa and 92.2 kDa**.** Immunization trials with two purified fractions elicited humoral responses and significant protection against O. savignyi and H. dromedarii infestation, resulted in the reduced blood feeding, and reproductive index (Toaleb et al., 2019).

**Drawbacks**

Despite the potential, vaccination using the use of crude tick extracts and homogenates have yielded variable with inconsistent outcomes. Preliminary findings have not always been validated in field conditions, which underscores the need for the identification, purification, and rigorous testing of upcoming vaccines.

**Salivary Gland Antigens**

**Cement Cone Antigens:** Research using a cDNA expression library from female *Haemaphysalis longicornis* identified two collagen-like proteins, P29 and an uncharacterized protein Hl34, which are involved in the formation of cement cones (Tsuda et al. 2001). Immunizing rabbits with recombinant P29 led to a mortality rate of 40% in *H. longicornis* larvae and 56% in nymphs (Mulenga et al., 1999). Likewise, the vaccination with recHl34 reduced survival across immature and adult ticks, leading to a 17% decrease in feeding weight.

In the case of *Rhipicephalus appendiculatus*, the proteins RIM 36 and 64P function as key cement cone antigens that play an essential role in the tick’s ability to feed and attach to the host. RIM 36 is a glycine-rich protein known for its strong immunogenicity and is commonly used as a marker to identify cattle that have previously been exposed to tick infestations. The 64P protein, which has a molecular weight of 15 kDa and shows structural similarity to mammalian keratin and collagen, is secreted during feeding and has been shown to trigger a protective immune response in guinea pigs. This response led to a significant reduction in infestation rates, with decreases of up to 48% in nymphs and 70% in adult ticks. The 64TRP-based vaccine was found to stimulate both antibody-mediated (humoral) and delayed-type hypersensitivity responses. It also demonstrated cross-protective effects, offering immunity not only against *R. appendiculatus* but also against *R. sanguineus* and *Ixodes ricinus*, along with protection against tick-borne encephalitis (Nuttall et al., 2006).

**Metalloprotease:** Metis 1, a salivary gland metalloprotease from *Ixodes ricinus*: showed promise when expressed recombinantly. Testing in rabbits revealed reduced engorgement weights in female ticks and a decline in their reproductive capabilities (Decrem et al., 2008). However, this protein increased mortality in rabbits by 30% without affecting mice (Prevot et al., 2007).

**Aquaporins:** Ticks utilize aquaporins to effectively transport water, which is essential for digesting blood. These water channels, such as IrAQP1 from *Ixodes ricinus* caused 50% decrease in weight of semi-engorged female ticks after five days of feeding (Campbell et al., 2010). Meanwhile, aquaporin protein RmAQP1 from *Rhipicephalus microplus* showed 75% effectiveness in cattle, highlighting its potential as promising vaccine candidate (Guerrero et al., 2014).

**Acid Peptidases:** These enzymes are crucial for blood digestion in the tick gut. Various types of acid peptidases, including aspartic peptidases Aspartic proteases like cathepsin D, along with cysteine endo- and ecto-peptidases such as cathepsins B, C, and L, as well as asparaginyl endo-peptidases, represent a range of antigenic targets for tick control strategies (Sojka et al., 2013). Although immunization of rabbits with a combination of recombinant cathepsins produced strong antibody responses, it resulted in only limited mortality among female *Ixodes ricinus* ticks (Franta et al., 2011).

**Ferritins:** Ferritin proteins, which are essential for regulating iron balance during tick feeding, have emerged as promising targets for vaccine development (Kopáček et al., 2003). Suppression of ferritin 2 (rmFER2) through RNA interference, along with immunization of rabbits using the recombinant form of the protein, resulted in reduced feeding success, lower egg-laying, and diminished reproductive capacity in *Ixodes ricinus*, *Rhipicephalus microplus*, and *R. annulatus* (Hajdusek et al., 2010).

**Other Miscellaneous Antigens**

**Vitellogenesis and Fertility Enzymes:** Disrupting reproductive processes like vitellogenesis offers a viable strategy to manage tick infestations, especially in *Rhipicephalus microplus*. Three key enzymes involved in this pathway have been identified: aspartic peptidase, Boophilus yolk cathepsin (BYC), and a cathepsin L-like cysteine endopeptidase responsible for vitellogenin degradation (VTDCE), (Logullo et al., 1998; Sorgine et al., 2000). Immunizing cattle with BYC and VTDCE antigens resulted in a 50% decrease in the number of semi-engorged female ticks and an increase in body weight among vaccinated animals. However, the effectiveness of the individual antigens remained relatively modest (Seixas et al., 2008; Parizi et al., 2011).

**Glutathione S-Transferases (GSTs):** GSTs are important detoxification enzymes that help neutralize metabolic by-products and harmful substances (Zhan et al., 2005). When the GST from *Haemaphysalis longicornis* was tested in cattle to assess its protective effect against *Rhipicephalus microplus* infestations, it led to a 50% reduction in tick numbers (Parizi et al., 2011).

**Transmission Blocking Vaccines**

**TROSPA:** The tick receptor for outer surface protein A (TROSPA) is essential for the colonization of *Borrelia burgdorferi*. Blocking this receptor using anti-TROSPA sera or RNA interference decreases the adherence of spirochetes to the gut of *I. scapularis*, thereby reducing bacterial colonization and pathogen transmission. OspA has been considered a candidate for vaccines aimed at preventing pathogen transmission (Pal et al. 2004). Vaccination with OspA in mice inhibited the transmission of the pathogen to ticks. Combining OspA with TROSPA has been shown to enhance vaccine efficacy.

**64TRP and Salp 15:** The cement protein 64TRP, derived from *Rhipicephalus appendiculatus*, has shown potential in halting the transmission of tick-borne encephalitis, making it a strong candidate for transmission-blocking vaccine development. Similarly, Salp15, an immunosuppressive molecule secreted by *Ixodes scapularis*, interferes with the host's immune response by binding to OspA. Blocking this interaction supports its candidacy as a transmission-blocking antigen.

**Subolesin (Tick Protective Antigen):** Subolesin, also known as 4D8, is a highly conserved protein related to the akirin family found in both insects and vertebrates. It plays a crucial role in regulating feeding and reproductive processes in ticks. Initially identified in *Ixodes scapularis*, subolesin has been linked to the modulation of immune responses. Silencing this gene through RNA interference disrupts various cellular pathways and weakens innate immunity, resulting in increased susceptibility to infections. Early vaccine trials using recombinant subolesin from *I. scapularis* demonstrated promising results against species like *Dermacentor variabilis* and *Amblyomma americanum* (Almazan et al., 2003). Furthermore, vaccines based on subolesin epitopes have shown protective effects not only against multiple tick species but also against mosquitoes and sand flies, suggesting its potential as a universal anti-arthropod vaccine (Pulcini et al., 2013).

**DNA VACCINE**:

There has been growing interest in using DNA-based vaccines to combat tick infestations (Rodriguez-Vivas et al., 2007; Wikel, 2018). These vaccines introduce genetic material either complete genes or specific coding sequences into the host via bacterial plasmids. Once delivered, the plasmid DNA enters host cells, where it remains as episomal DNA, continuously expressing protective antigens for the duration of the cell's life (Myhr, 2017; Ghaffarifar, 2018). Since antibody-mediated (humoral) immunity plays a key role in resisting tick infestations, DNA vaccines need to be designed to stimulate a strong Th2-type immune response (Abbass et al., 2023). Despite the promise, the use of DNA vaccines in controlling tick-borne diseases in veterinary and medical contexts is still in its early stages (Ghosh et al., 2007).

One such approach involved immunizing Merino crossbred sheep against *Boophilus microplus* using a DNA vaccine containing the full-length Bm86 gene. This strategy led to only a minor decrease in the average weight of engorged female ticks. However, combining the Bm86 plasmid with one encoding GM-CSF resulted in a more noticeable reduction in tick fertility. Even so, the commercially available product Tick Guard Plus proved to be significantly more effective, approximately 25 times more than the DNA-based vaccine (De Rose et al., 1999).

Another notable candidate is paramyosin (Pmy), a structural protein with immunomodulatory properties found in invertebrates. Researchers developed a eukaryotic expression plasmid containing the *Pmy* gene and used it to vaccinate rabbits. The vaccine successfully triggered a specific immune response and offered partial protection against *Haemaphysalis longicornis*, with notable decreases in engorgement weight, egg-laying, and the overall size of adult female ticks (Zhang et al., 2017).

**Microbiota-Based Tick Vaccine:**

The microbial communities within ticks play an essential role in shaping their biological functions and capacity to spread pathogens. When larvae have altered microbiota, it affects the integrity of the gut peritrophic membrane, which can change how spirochetes adhere to the epithelial cells. For instance, inhibiting chitin-binding proteins in the peritrophic membrane of *I. scapularis* affected the colonization and spreading of *B. burgdorferi* to mice (Yang et al., 2021).

Additionally, female ticks often host endosymbionts such as *Coxiella* (*D.silvarum*), *Rickettsia* (*I. affinus*), and Francisella-like endosymbionts ( *Hyalomma lusitanicum*). These endosymbionts are thought to provide essential nutrients, including vitamin B cofactors, amino acids, and the de novo synthesis of folate (Duron et al. 2018). Manipulating these endosymbionts could be a strategy for controlling vector-borne diseases. Approaches might include using *Wolbachia* spp. for chemotherapeutic and immunological interventions or exploiting Wolbachia’s cytoplasmic incompatibility.

Immunization of animals with inactivated endosymbiotic bacteria or their purified and recombinant proteins antigens can confer immunity to tick vectors. Concealed antigens of ticks serve as promising target. Antibodies produced in immunized hosts can enter the ticks during a blood meal, potentially disrupting endosymbionts and impairing tick physiology, leading to their death (Gupta et al. 2012).

**Vaccine Compositions and Administration Methods**

The formulation and delivery of vaccines are critical for ensuring their success, particularly in the context of tick control. Advances in this area have highlighted the promise of targeting the gut microbiota of tick vectors. Experimental approaches using antibiotics and sterile-rearing methods have demonstrated that manipulating tick microbiota can lead to significant physiological changes (Mateos-Hernández et al., 2020, 2021). Vaccination strategies aimed at microbiota have shown effects such as increased weight gain during feeding and modifications in microbial composition and diversity in a taxon-specific manner.

Evidence also indicates that these vaccines may disrupt pathogen development. For instance, the interaction between *Plasmodium relictum* and *Culex quinquefasciatus* was altered by microbiota-targeted immunization (Aželytė et al., 2022). In ticks, shifts in microbial populations influenced the susceptibility of *Borrelia* species, imposing metabolic costs on the pathogen due to microbiota disruption by the spirochete itself (Wu-Chuang et al., 2021). Despite this, broad-spectrum microbiota changes pose challenges for selectively removing specific bacterial taxa. To overcome this, precision-designed microbiota-modifying vaccines are being developed (Wu-Chuang et al., 2021; Maitre et al., 2022).

Innovative approaches, including the use of probiotics and alpha-gal-enriched formulations, are being evaluated for their potential in tick control (Cabezas-Cruz and de la Fuente, 2017; Hodžić et al., 2020; Bamgbose et al., 2021). Heat-inactivated alpha-gal bacteria have been proposed as adjuvants for oral immunization (Kasaija et al., 2022). Notably, oral vaccines combining SUB antigens from *Rhipicephalus appendiculatus* with heat-inactivated mycobacteria achieved high protection rates—96% against *R. decoloratus* and 99% against *R. appendiculatus* (Kasaija et al., 2022).

Although recombinant proteins have been the conventional choice in tick vaccines, recent developments are shifting toward mRNA-based platforms (Sajid et al., 2021; Boulanger and Wikel, 2023; Matias et al., 2023). Emerging strategies include the delivery of chimeric antigens via microparticles and mRNA encapsulated in lipid nanoparticles to enhance immune response and vaccine stability (Sajid et al., 2021; Matias et al., 2023).

**Effectiveness of Vaccines Across Different Tick Species:**

Although Bm86/Bm95-based vaccines have shown promise in managing *Rhipicephalus microplus*, there is still a pressing need to discover conserved antigens capable of offering protection across multiple tick genera. Subolesin (SUB), formerly referred to as 4D8 and homologous to the protein Akirin, emerged as a promising candidate through expression library immunization studies conducted using *Ixodes scapularis* in a murine model (Almazán et al., 2003). The SUB vaccine induces a protective immune response primarily through anti-SUB antibodies, which, despite the unclear mechanisms of cellular entry, interfere with nuclear translocation of regulatory proteins within tick cells. This disruption impairs tick physiology and activates a range of host immune defense pathways (de la Fuente et al., 2011; Merino et al., 2011; Artigas-Jerónimo et al., 2020).

SUB-induced immunity interferes with several biological pathways across a range of hosts, including cattle, deer, sheep, dogs, rabbits, mice, and chickens, resulting in reduced fitness and reproductive success in various tick species, such as *Ornithodoros*, I*xodes*, *Haemaphysalis*, *Amblyomma*, *Dermacentor*, *Hyalomma*, and *Rhipicephalus*, as well as other arthropod vectors like mosquitoes and sand flies (Artigas-Jerónimo et al., 2018; Parizi et al., 2023). The efficacy of SUB-based vaccines has been assessed in both controlled pen studies (Shakya et al., 2014; Artigas-Jerónimo et al., 2018) and field trials (Torina et al., 2014; Mendoza-Martínez et al., 2021). In field conditions, vaccinated cattle & sheep revealed a 63% reduction in tick infestations in sheep, an eightfold decrease in infested cattle, and a tick weight declined by 32–55%, along with fewer application of acaricides alongside a reduction in *Anaplasma marginale* prevalence genotypes associated with tick transmission (Torina et al., 2014).

Recent studies report that the SUB vaccine achieved 67% efficacy in cattle challenged with *Rhipicephalus microplus* (Mendoza-Martínez et al., 2021), and showed between 83% and 90% protection in cattle immunized against *Rhipicephalus appendiculatus* when exposed to *R. appendiculatus*, *R. decoloratus*, and *Amblyomma variegatum* (Kasaija et al., 2020). These results underscore the broad-spectrum potential of SUB-based vaccines in controlling various tick genera and other arthropod vectors. In addition to SUB, several other antigens—such as P29, Aquaporin, Metalloprotease, potassium channels, protease inhibitors, Calreticulin, ribosomal protein P0, Ferritin 2, and Tropomyosin—have been shown to elicit protective immune responses against a range of tick species (de la Fuente and Kocan, 2003; Manjunathachar et al., 2019; Abbas et al., 2023; de la Fuente et al., 2023; Parizi et al., 2023; Nepveu-Traversy et al., 2024).

**Synergizing Immunization with Genetic and Microbial Modifications:**

Recent advancements in Genome modification technologies, such as CRISPR-Cas9-mediated editing, have been successfully applied to ticks using methods like microinjection into embryos and the use of the ReMOT Control technique (Sharma et al.,2022). CRISPR-Cas technology also facilitates paratransgenesis by allowing targeted alterations within the tick's microbial and viral communities (Ramachandran and Bikard, 2019). A ground breaking strategy termed Frankenbacteriosis has been introduced, which involves engineering the commensal bacterium *Sphingomonas* within ticks to reduce their fitness and lower the transmission rate of *Anaplasma phagocytophilum* (Mazuecos et al., 2003).

Combining anti-tick immunization, transgenic and para transgenic strategies holds the potential to improve their effectiveness. This could include innovative approaches like Suicidal bacteriosis, where genetically altered commensal bacteria in ticks are designed to produce and release antigens during blood feeding, thereby protecting against both ticks and tick-borne diseases (de la Fuente et al., 2023b). Modifying the microbiome and virome composition could enhance the susceptibility of ticks to immune responses induced by vaccines, potentially increasing the success rate of controlling tick infestations and reducing their role as disease vectors. Despite these promising developments, the use of gene-editing tools comes with inherent risks, such as unintended mutations. High frequencies off-target Impacts have observed in human cellular structures, emphasizing the need for rigorous evaluation and mitigation strategies to ensure the safe application of these technologies (de Jong et al.,2020)**.**

Gene editing technologies, though powerful, are not without risks, including the possibility of off-target mutations. While human cells have shown relatively high rates of such effects, studies have indicated that these occurrences tend to be less frequent in other organisms, such as mice and zebrafish (Hwang et al., 2013; Yang et al., 2013). The presence of similar DNA sequences in large genomes can lead to unintended deletions, potentially resulting in cell death otherwise transformation. Although effort is underway to minimize these risks, further advancements are necessary for safe and efficient gene delivery, particularly into hard-to-transfect cell types (Nuss et al.,2021).

There are also concerns about the unintentional transfer of modified genes to other species and the challenges of controlling the spread of gene-driven traits. The potential extinction of target populations through gene drive approaches could disrupt ecological balance. Therefore, thorough evaluations of each application and stringent regulatory frameworks are essential to address these risks (Chehelgerdi et al.,2024).

**Conclusion**

As the global community transitions toward a post-insecticidal and acaricidal era, there is a pressing imperative to develop innovative vaccines targeting ectoparasites, particularly ticks. This necessitates a comprehensive evaluation of novel vaccine formulations and candidate antigens across various tick species and host systems, with a focused effort on creating Multispecies tick vaccines. Rigorous animal trials should be designed to assess the efficacy of diverse adjuvants along with delivery systems, including the DNA vaccination methods. These trials must also involve a thorough investigation of biological processes, the control of their gene expression, and the analysis of immune responses triggered in the host by potential vaccine candidates. Moreover, it is essential to incorporate antigens that can effectively inhibit transfer of pathogens facilitated by tick vectors into vaccine formulations.

An integrated tick control strategy, wherein vaccination serves as a central component, represents a promising approach for achieving sustainable and environmentally sound control of tick populations in the future. Such a strategy is anticipated to enhance the efficacy and cost-effectiveness of tick management efforts while mitigating the ecological impacts associated with conventional chemical treatments.

Disclaimer (Artificial intelligence)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

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