



COMMENTARY

Current Advances in Vaccine Development for Severe Fever with Thrombocytopenia Syndrome Virus (SFTSV)

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Abstract

Severe fever with thrombocytopenia syndrome (SFTS), caused by the tick-borne severe fever with thrombocytopenia syndrome virus (SFTSV), is a disease that is endemic to East Asia and has mortality rates reaching 30%. Despite its substantial public health impact, no vaccines or antiviral treatments are currently available. The SFTSV genome encodes key structural proteins, including glycoproteins (Gn and Gc) and nucleocapsid protein (NP), which serve as critical vaccine targets. This Commentary reviews the current status of SFTSV-related vaccine platforms—such as viral vectors, inactivated viruses, DNA, mRNA, and protein-based approaches—and highlights the immune responses elicited by these platforms against key antigens, particularly glycoproteins and NP. Future research directions are additionally proposed to accelerate the development of effective SFTSV vaccines by leveraging insights from existing studies.

Key words: Tick, Vector, Viral diseases, Zoonoses, Arbovirus, Pathogen

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BACKGROUND

Severe fever with thrombocytopenia syndrome (SFTS) is an emerging tick-borne disease caused by the *Dabie bandavirus*, commonly known as the SFTS virus (SFTSV). Since the initial discovery of SFTSV in China in 2009, SFTS incidence has risen sharply, and case fatality rates have ranged from 10% to 30% [1–4]. Clinically, SFTS is characterized by high fever, thrombocytopenia, leukopenia, and multi-organ dysfunction. Severe cases can progress to hemorrhagic manifestations or death, particularly in older adults or immunocompromised individuals [5,6]. The virus is currently endemic in several East Asian countries/regions, including South Korea, Japan, China, and Vietnam, primarily because of the widespread distribution

of its vector, *Haemaphysalis longicornis* [7,8]. SFTS therefore poses a major public health threat in East Asia and potentially other regions [9]. Despite its extensive geographic spread and severe clinical outcomes, no vaccines or antiviral treatments are currently available, thus leaving substantial gaps in public health preparedness.

SFTSV is an enveloped virus with a negative-sense RNA genome comprising three segments: L, M, and S. The L segment encodes the RNA-dependent RNA polymerase (RdRp), which is essential for viral replication. The M segment encodes the glycoproteins Gn and Gc, which are synthesized as a single precursor protein and cleaved by cellular proteases. The Gn protein plays a critical role in receptor binding by mediating initial viral attachment to host cells [10], whereas the Gc protein is a

class II fusion protein that facilitates viral entry [11]. These glycoproteins are crucial for viral attachment and membrane fusion, and consequently are promising targets for vaccine development. The S segment encodes two proteins: the nucleocapsid protein (NP), which facilitates viral RNA encapsidation and ribonucleoprotein complex formation, and the non-structural protein (NS), a key virulence factor that suppresses host innate immune responses by interfering with interferon signaling [12–15]. The structural complexity of SFTSV, along with its ability to evade host immunity, poses substantial challenges in vaccine development.

Nonetheless, recent clinical evidence has indicated that SFTS survivors develop peak neutralizing antibody titers approximately 2 months after symptom onset. These titers decline rapidly between 6 months and 4 years, and subsequently show a slower rate of decline from 5 to 10 years post-infection [16]. Reinfection appears to be rare and, when it does occur, it is often asymptomatic or mildly symptomatic, thus suggesting the presence of partial or functional protective immunity [17]. These findings have provided a strong immunological rationale for developing vaccines that elicit sustained protection by mimicking natural infection. Promising candidates include viral vector-based platforms, recombinant protein vaccines targeting glycoproteins, and novel approaches such as mRNA or DNA vaccines. However, because most of these vaccines remain in preclinical stages, further research is required to uncover the underlying protective immune mechanisms, particularly the roles of T cells, antibody-mediated responses, and long-lasting memory immunity.

This Commentary provides a comprehensive overview of the current status of SFTSV vaccine development, with a particular focus on the immune responses elicited by various vaccination strategies. Furthermore, it examines the induction of B and T cell responses after vaccination and highlights survival rates as the definitive measure for evaluating vaccine efficacy in preclinical models. Finally, it outlines future research directions to address critical public health needs and advance vaccine development.

CURRENT STATUS OF VACCINE CANDIDATES

Various vaccine platforms, including viral vectors, inactivated viruses, DNA, mRNA, and protein-based vaccines, have been explored for the development of vaccines against SFTSV, and their efficacy has been validated primarily in animal models. These vaccine platforms target specific antigens, such as Gn, Gc, NP, or NS, and are aimed at eliciting robust humoral (B cell-mediated) and cellular (T cell-mediated) immune responses. Notably, most vaccine candidates have focused on glycoproteins as antigens to induce neutralizing antibodies (Table 1).

Live attenuated vaccines

Live attenuated vaccines contain a weakened form of the virus that can replicate but does not cause disease. For SFTSV, vaccine candidates engineered through NS gene

deletions or amino acid substitutions in the NS protein have been found to confer complete protection in aged ferret models [18]. Although T cell responses were not directly assessed in those studies, the vaccines achieved full protection despite eliciting relatively low neutralizing antibody titers. Therefore, live attenuated vaccines might induce broad and multifaceted immune responses, because of the use of replication-competent virus that can stimulate both innate and adaptive immunity.

Viral vector-based vaccines

Viral vector-based vaccine platforms have demonstrated promising outcomes. Recombinant vaccinia virus (rVACV) and recombinant vesicular stomatitis virus (rVSV), both expressing the Gn/Gc precursor or its mature form, have successfully prevented SFTSV lethal infection in animal models [19,20]. Notably, rVSV-Gn/Gc resulted in 100% survival when SFTSV infection was induced 60 days after primary vaccination, even in aged, type 1 interferon receptor knockout (IFNAR^{-/-}) mice. Unfortunately, that study did not evaluate T cell responses, and the cellular immune component remains unverified. Hicks et al. [21], using an rVSV-based strategy similar to that described by Dong et al. [20] have demonstrated cross-protection against Heartland bandavirus, a closely related phlebovirus. These findings further support the promise of rVSV-Gn/Gc as a vaccine candidate with a favorable safety profile for not only SFTSV but also related bandaviruses. Tian et al. have developed a rabies virus-based vector vaccine expressing the Gn antigen, but have not assessed its T cell responses or evaluated its protective efficacy against lethal SFTSV challenge [22]. Additionally, Zhao et al. have developed a recombinant adenovirus type 5 (rAd5) vaccine expressing Gn that induces neutralizing antibodies along with IFN- γ - and IL-4-producing T cells; however, its efficacy against lethal infection remains untested [23]. Qian et al. have similarly used a recombinant adenovirus-based vaccine expressing the Gn protein [24]. This vaccine enhanced the recruitment and activation of dendritic cells and B cells in the lymph nodes and peripheral blood. Moreover, passive transfer of immune sera conferred complete protection, thereby highlighting the potent humoral immunity induced by Gn-specific vaccination. Kim et al. have recently extended this approach by using a heterologous prime-boost strategy [25]. They administered rAd5-Gn as the priming dose, which was followed by a boost with purified Gn protein. Although survival data were not explicitly reported, weight loss was observed only in the control group, thus suggesting protective efficacy in the immunized group. However, the diminished efficacy of rVACV in the presence of pre-existing immunity to the vaccinia virus resulted in survival rates of 60–70% [19]. In contrast, the effects of pre-existing immunity on the rVSV-Gn/Gc platform have not yet been investigated and remain an important consideration in potential clinical applications.

TABLE 1 | Summary of studies of preclinical vaccines and their efficacy against SFTSV.

Type of vaccine	Vaccine antigen	B cells	T cells	Challenge dose/ strain	Challenge model	Protective ability	Reference
Live attenuated	SFTSV: NS 12aa/NS P102A	FRNT ₅₀ = ~10 ^{0.1}	-	10 ^{7.6} TCID ₅₀ CB1/2014	Aged ferrets	100% survive	Yu, Kwang-Min, et al. [18]
Viral vector	rVaccinia virus (LC16m8): NP/GnGc precursor	FRNT ₅₀ = ~10 ^{1.3} anti-Gn IgG = ~10 ^{3.6}	-	10 ⁵ TCID ₅₀ YG-1	C57BL/6 (IFNAR KO)	100% survive 60–70% survive (pre-existing immunity)	Yoshikawa, Tomoki, et al. [19]
	rVSV: GnGc	FRNT ₅₀ = ~10 ^{3.0} broad spectrum nAb	-	2 × 10 ⁴ FFU Wuhan	C57BL/6 (IFNAR KO)	100% survive	Dong, Fangfang, et al. [20]
Viral vector + protein	rVSV: GnGc	FRNT ₅₀ = ~10 ^{2.8}	-	10 FFU HB29	C57BL/6 (IFNAR KO)	100% survive (cross- protection against HRTV)	Hicks, Philip, et al. [21]
	Rabies virus: Gn	FRNT ₅₀ = ~10 ^{2.5}	-	2 × 10 ⁷ FFU JS2011-013-1	C57BL/6	Non-lethal model	Tian, Li, et al. [22]
	rAdenovirus type 5 (rAd5): Gn	FRNT ₅₀ = ~10 ^{2.0} anti-Gn IgG = ~10 ^{4.0}	Induced IFN-γ, IL-4 producing cells	10 ⁶ TCID ₅₀ JS2011-013-1	C57BL/6	Non-lethal model	Zhao, Zhongxin, et al. [23]
Inactivated virus	rAdenovirus type 5 (rAd5): Gn	FRNT ₅₀ = ~10 ^{2.6} anti-Gn IgG1 = ~10 ^{2.7} anti-Gn IgG2a = ~10 ^{2.7}	Induced activation of dendritic cells, B cells, IFN-γ producing cells	10 ^{5.25} TCID ₅₀ JS2011-013-1	BALB/c (+anti- IFNAR Ab)	100% survive	Qian, Hua, et al. [24]
	1 st rAd5-Gn + 2 nd Gn protein	FRNT ₅₀ = ~10 ^{3.5}	Induced IFN-γ producing T cells, activated T cells	10 ⁵ FFU JJ-01	C57BL/6 (+anti- IFNAR Ab, IL-10)	No weight loss	Kim, Jae-Yong, et al. [25]
DNA	BPL inactivated SFTSV	Anti-NP IgG, nAb	Induced IFN-γ producing cells	10 ⁵ TCID ₅₀ HB29	C57BL/6	Non-lethal model	Li, Aqian, et al. [26]
mRNA	NP, NS in microneedles	-	Induced IFN-γ, TNF-α producing T cells	-	BALB/c	-	Jung, Daeyoon, et al. [27]
	Gn, Gc, NP, NS, RdRp	Gn, Gc FRNT ₅₀ = ~10 ^{0.4}	Induced IFN-γ producing T cells, Ns specific T cells	10 ^{7.6} TCID ₅₀ CB1/2014	Aged ferrets	100% survive	Kwak, Jeong-Eun, et al. [28]
	Gn, Gc, NP, NS + IL12	Anti-NP IgG = ~10 ^{2.5}	Induced IFN-γ producing T cells	10 ⁵ FFU JJ-01	C57BL/6 (IFNAR KO)	100% survive	Kang, Jun-Gu, et al. [29]
	Gn head	FRNT ₅₀ = ~10 ^{4.0} anti-Gn IgG = ~10 ^{6.0}	-	2 × 10 ⁴ FFU CB1/2014	A129	100% survive	Kim, Dokyun, et al. [30]
	Gn	FRNT ₅₀ = ~10 ^{5.0} anti-Gn IgG = ~10 ^{7.0}	Induced IFN-γ producing and activated CD8 ⁺ T cells, follicular helper T cells	10 ⁵ FFU JJ-01	C57BL/6 (+anti- IFNAR Ab)	100% survive	Kim, Jae-Yong, et al. [31]
	Glycoprotein (Gn/ Gc)	FRNT ₅₀ = ~10 ^{3.0} anti-Gn IgG = ~10 ^{5.0}	Induced IFN-γ, IL-4 producing T cells, IFN-γ producing CD8 ⁺ effector memory T cells	100 TCID ₅₀ HB29	A129 or AG129	100% survive (cross- protection against HRTV, GTV)	Lu, Jia, et al. [32]

TABLE 1 | (continued)

Type of vaccine	Vaccine antigen	B cells	T cells	Challenge dose/ strain	Challenge model	Protective ability	Reference
Protein	NS	Anti-NS = $\sim 1/2560$	-	3×10^7 FFU WCH/97/HN/2011	C57BL/6J	Non-lethal model	Liu, Rong, et al. [33]
	Gn	FRNT ₅₀ = $\sim 10^{3.0}$ anti-Gn IgG = $\sim 10^{3.6}$	-	10^5 FFU JJ-01	C57BL/6 (IFNAR KO)	50% survive	Kang, Jun-Gu, et al. [29]
	Gn head	FRNT ₅₀ = $\sim 10^{4.0}$ anti-Gn IgG = $\sim 10^{6.0}$	Induced IFN- γ producing cells, TNF- α , IL-2 producing T cells	$10^{7.6}$ TCID ₅₀ CB1/2014	Aged ferrets	100% survive	Kim, Dokyun, et al. [30]
	NP	Anti-NP IgG = $\sim 10^{6.0}$	Not induced	10^3 FFU JJ-01	C57BL/6 (IFNAR KO)	66% survive 0% survive (after 12 months)	Kim, Sohee, et al. [34]

TCID₅₀, 50% tissue culture infectious dose; FFU, focus-forming units.

Inactivated vaccines

Li et al. have developed a whole inactivated virus vaccine eliciting balanced activation of B and T cells [26]. In that study, the SFTSV strain AH12 was inactivated with β -propiolactone, and the addition of an aluminum hydroxide adjuvant significantly enhanced antibody titers. The finding that inactivated SFTSV vaccine induced anti-NP IgG and neutralizing antibodies, alongside IFN- γ -producing T cells, underscores this vaccine's potential to elicit both humoral and cellular immune responses. Although a lethal challenge model was not used, immunization with the inactivated vaccine resulted in markedly greater viral clearance from the blood and spleen than observed in control groups, thereby suggesting potential protective efficacy.

DNA vaccines

DNA vaccines have advantages of incorporating multiple antigens simultaneously and enabling broader immune activation. In a study by Kwak et al., simultaneous immunization with DNA vaccines encoding Gn, Gc, NP, NS, and RdRp antigens in a ferret model elicited robust T cell responses and conferred 100% survival after a lethal infection dose [28]. Furthermore, immunization with either Gn/Gc or NP/NS/RdRp antigens yielded equivalent survival rates. Combining the IL-12 gene with DNA vaccines further enhanced T cell responses and achieved complete protection against SFTSV [29]. In that study, co-expression of IL-12 increased IFN- γ -producing T cells and increased survival from 40% to 100%, whereas vaccination without IL-12 achieved only 40% protection, and the unvaccinated control group showed 0% survival. These findings highlight the potent adjuvant effect of IL-12 in enhancing cellular immunity. Another study has demonstrated the effective enhancement of NP or NS DNA vaccination with nano-patterned microneedles [27]. However, because the article focused primarily on the development of the microneedles, the investigation of immune responses was limited. Although a greater T cell response was observed with nano-patterned microneedles than conventional microneedles, data on B cell responses and survival rates were not reported.

mRNA vaccines

All mRNA vaccine candidates have used the Gn protein as the target antigen and consistently induced high levels of binding and neutralizing antibodies, thereby resulting in 100% survival in challenge models. Remarkably, potent immune responses have been achieved with use of only the Gn head domain [30]. In a study by Kim et al., vaccination using the Gn sequence encompassing the signal peptide through the transmembrane region induced robust cellular immunity, including IFN- γ -secreting T cells, follicular helper T cells, and activated T cell subsets (CD25⁺, CD69⁺) [31]. Lu et al. have developed an mRNA vaccine encoding the full-length Gn/Gc glycoprotein, which conferred durable protection against SFTSV for at least 5 months post-immunization [32]. Notably, this vaccine also provided complete cross-protection against related bandaviruses,

including Heartland virus and Guertu virus. These findings highlight the potential of mRNA platforms to induce broad-spectrum and long-lasting immunity, and offer guidance for pan-bandavirus vaccine development.

Subunit vaccines

As with mRNA vaccines, subunit vaccines targeting the Gn head domain have also demonstrated protective efficacy. Both protein-based vaccines targeting the Gn head antigen have shown exceptional efficacy, achieving a 100% survival rate and inducing robust neutralizing antibody titers [35]. Notably, the Gn protein vaccine further elicited a diverse population of T cells capable of producing TNF- α or IL-2. Kim et al. have also conducted a comparative study of protein immunization with Gn, Gc, and NP antigens, among which only NP conferred partial protection, with a 66% survival rate, whereas Gn and Gc resulted in 18% and 0% survival, respectively [34]. Combination immunization

(Gn/NP, Gc/NP, or Gn/Gc/NP) increased the efficacy but did not achieve complete protection. Notably, the protective memory response to NP waned over time, and no protection was observed in a challenge 12 months post-immunization. In addition, the memory response to NP was notably diminished: no protective effect was observed during a challenge conducted 12 months post-immunization. Liu et al. immunized mice with the NS protein and analyzed viral copy numbers in mouse tissues after infection but were unable to confirm effective viral clearance [33].

Extensive research has been conducted to develop effective SFTSV vaccines by using diverse platforms, including viral vectors, inactivated viruses, DNA, mRNA, and protein-based approaches, each of which has distinct advantages and limitations. These platform-specific strategies and their associated antigenic targets are summarized in a schematic overview (Fig 1), which provides a visual foundation for the comparative analysis that follows. Viral

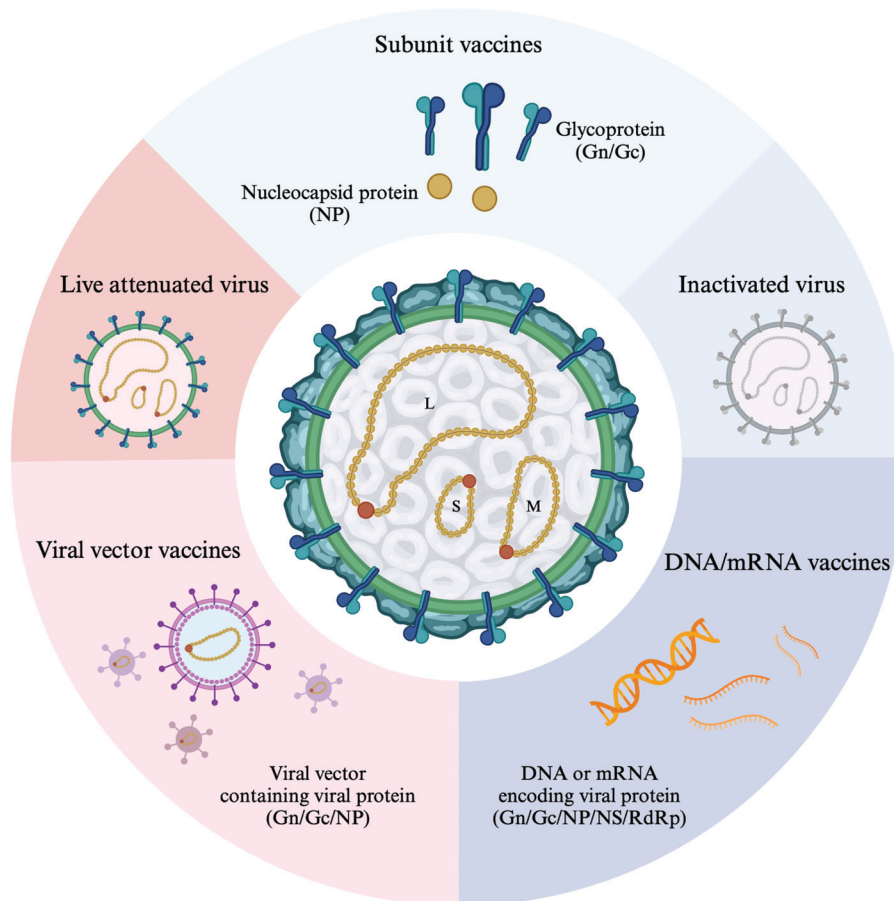


FIGURE 1 | Schematic representation of SFTSV structure and antigen targets used by various vaccine platforms. The central illustration shows the three-segmented genome (L, M, and S segments) of SFTSV, an enveloped RNA virus. The surrounding area depicts five major vaccine platforms: (1) subunit vaccines, using purified viral proteins such as Gn, Gc, or NP; (2) inactivated vaccines, consisting of whole virus particles rendered non-infectious; (3) DNA/mRNA vaccines, encoding viral antigens (e.g., Gn, Gc, NP, NS, and/or RdRp) for endogenous expression; (4) viral vector vaccines, delivering genes encoding viral proteins via modified live viruses; and (5) live attenuated vaccines, based on replication-competent but non-pathogenic SFTSV strains. Each platform is associated with specific antigenic components, thus reflecting the diverse strategies for inducing protective immunity. The color scheme indicates the relative safety profile: platforms in blue (e.g., subunit, inactivated, DNA/mRNA) are generally considered to have a high margin of safety, whereas those in red (e.g., viral vectors, live attenuated) may require more stringent safety evaluation, because of their replicative or viral vector-based nature.

vector vaccines are highly immunogenic but may be compromised by pre-existing immunity to the vector. DNA and mRNA vaccines enable rapid development and can elicit balanced humoral and cellular responses, although challenges such as delivery efficiency and thermal stability persist. Protein subunit vaccines are generally safe but often require strong adjuvants to induce robust cellular immunity. Inactivated vaccines offer safety through non-replicating platforms but may induce relatively short-lived immune responses. These differences underscore the importance of platform-specific optimization and strategic selection for clinical development. Despite these advances, the breadth and durability of vaccine-induced immunity, particularly in terms of long-term protection and immune correlates, remain to be fully characterized. In addition, translating preclinical findings to human application remains a major challenge requiring both mechanistic insight and rigorous immunological evaluation.

CONCLUSION

Most SFTSV vaccine studies have evaluated primarily neutralizing antibody titers. However, an effective vaccine should induce both robust antibody and antigen-specific T cell responses. Whereas neutralizing antibodies prevent viral entry and initial infection, T cells are essential for eliminating infected cells and limiting viral dissemination [36,37]. T cells are broadly categorized into cytotoxic (CD8⁺) and helper (CD4⁺) subsets. CD4⁺ T cells aid in B cell maturation and promote high-affinity antibody production, whereas CD8⁺ T cells directly eliminate virus-infected cells [36,38]. Neutralizing antibodies act through two mechanisms: binding viral glycoproteins to block entry or via Fc-mediated effector functions, such as ADCC and phagocytosis through Fcγ receptor interactions [39]. The synergy between B and T cell responses is critical for long-term immunity and effective vaccine-induced protection.

However, studies examining the specific roles of T cells in SFTSV vaccine efficacy remain limited. Few SFTSV vaccine studies have directly analyzed the contributions of B cells or T cells. Several studies have conducted serum transfer experiments to investigate how vaccine-induced antibodies affect protection. After adoptive transfer of immune serum from mice immunized with either rVSV-Gn/Gc or rVACV-GnGc, the survival rates in recipient mice decreased to 60% and 40% those observed at the time of immunization [19,20]. Therefore, antibodies induced by immunization can provide partial protection. However, after CD8⁺ T cell depletion, the survival rate after rVACV-GnGc immunization remained at 100%; therefore, CD8⁺ T cells play a minimal role in the vaccine's protective efficacy. Interestingly, the 100% survival rate achieved through glycoprotein (Gn/Gc)-based DNA vaccine immune serotransfer in a ferret model highlights the critical roles of specific and neutralizing antibodies generated by Gn/Gc immunization [28]. These findings

support the rationale for prioritizing glycoproteins, particularly Gn, as central antigens in SFTSV vaccine design, given that multiple studies have indicated consistently high survival rates with inclusion of Gn. Immunization with DNA encoding NP/NS/RdRp antigens, which did not elicit neutralizing antibodies, resulted in complete mortality after serum transfer. However, because the vaccines themselves provided full protection, T cell-mediated immunity might compensate for the lack of neutralizing antibodies in these cases. These findings underscore the complexity of vaccine-induced protection, which is likely to rely on a balanced induction of both humoral and cellular responses.

Vaccine platforms differ in their ability to induce immune responses. DNA and mRNA vaccines enable endogenous antigen expression and presentation through MHC class I and II pathways, and consequently promote both humoral and cellular immunity. These platforms are generally safe and flexible. Protein subunit vaccines, although safe and stable, rely on exogenous antigen presentation and often require strong adjuvants to induce cytotoxic T cell responses [40]. Live-attenuated and viral vector vaccines are highly immunogenic, because of intracellular replication, and elicit broad systemic immunity. However, their safety depends on optimal attenuation without loss of immunogenicity [38]. Among SFTSV vaccine candidates, live-attenuated, viral vector, DNA, and mRNA platforms have generally yielded higher survival rates than protein subunit vaccines, possibly because of their superior stimulation of multi-arm immune responses. Vaccine efficacy also varies according to antigen choice: Gn-based immunogens have more consistently induced neutralizing antibodies than Gc or NP antigens in preclinical studies.

Despite considerable progress in SFTSV vaccine development, most studies have focused on short-term outcomes, whereas the long-term durability of immunity remains insufficiently characterized. Future research should focus on optimizing vaccine formulations to enhance memory responses, as well as on assessing the persistence of antibody and memory B/T cell responses. Challenge infection models that evaluate long-term immunity over months or years would better approximate real-world vaccine performance. Comparative analyses across platforms—considering antigen selection, delivery methods, immune response profiles, and durability—are essential to identify the most promising candidates. Understanding how each platform modulates the quality and breadth of immunity will be valuable in informing rational vaccine design and development.

Translating preclinical findings to human vaccines also remains challenging, because of interspecies immune differences and regulatory complexities. Mestas and Hughes have highlighted differences in MHC haplotypes, cytokine networks, and T cell dynamics between mice and humans [41]. Estes et al. have emphasized that studies in murine models might not fully reflect the complexity of human immune responses; consequently, more predictive models

and the identification of reliable correlates of protection are necessary [42]. Although each animal model offers unique advantages, the aged ferret model, which displays disease symptoms and immune responses similar to those in human SFTS, might provide a complementary platform to bridge the translational gap in preclinical evaluation. Safety and ethical considerations are particularly critical for live-attenuated and viral vector-based platforms. These vaccines necessitate thorough preclinical safety evaluations and strict adherence to biosafety and regulatory standards. Ethical trial design, informed consent, and benefit-risk assessments must be integrated throughout clinical development, particularly in endemic regions.

The successful development of an effective SFTSV vaccine will require an integrated approach combining optimal antigen design, balanced immune activation, and rigorous translational strategies. Leveraging advances across diverse vaccine platforms—and addressing safety, durability, and ethical considerations—will be essential for enabling broad, long-lasting protection against this emerging viral threat. Continued research on the immunological correlates of protection and long-term efficacy is expected to not only facilitate clinical translation but also strengthen preparedness for future outbreaks.

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CONFLICTS OF INTEREST

The authors declare no conflict of interests.

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