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UDC 578.7 **Review article**

Advances and challenges in the development of Crimean-Congo Hemorrhagic Fever vaccines: from traditional approaches to modern technologies

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Abstract

Crimean-Congo Hemorrhagic Fever (CCHF) is a high-mortality, tick-borne viral illness endemic to Africa, Asia, the Middle East, and certain regions of Europe. Notwithstanding its peril to public health, there is presently no licensed vaccination available. This study highlights important progress and challenges in developing CCHF vaccines, including traditional methods (inactivated and live-attenuated vaccines) and new approaches (subunit, DNA, mRNA, and viral vectors). We also investigate the functions of adjuvants and delivery technologies – such as nanoparticles and viral vectors – in enhancing immunogenicity and safety. Insights from historical endeavors and recent advancements underscore the pressing necessity for safe, effective, and scalable vaccinations, especially in endemic areas. Future initiatives must emphasize cross-protective formulations, thermal stability, and international cooperation.

Keywords: Crimean-Congo Hemorrhagic Fever Virus; Live-Attenuated Vaccines; mRNA Vaccines; Vaccine Development.

Introduction

Crimean-Congo Hemorrhagic Fever (CCHF) is a serious zoonotic illness caused by a *Nairovirus* of the *Bunyaviridae* family. CCHF, largely transmitted by *Hyalomma* ticks and through contact with infected animal or human blood, has a case fatality rate of 10% to 40%, contingent upon healthcare accessibility. The virus sustains a natural cycle between ticks and vertebrates, primarily livestock, with humans acting as inadvertent hosts [1, 2, 3].

CCHF is endemic in regions of Africa, Asia, the Middle East, and Eastern Europe, with recorded instances in more than 30 countries Europe [4, 5, 6, 7]. Figure 1 illustrates that the geographic distribution of endemic regions encompasses Kazakhstan, specifically the southern provinces of Turkestan and Zhambyl, where environmental circumstances promote tick circulation and human exposure. The extensive dispersion highlights the critical necessity for region-specific vaccination measures and global cooperation [8, 9].

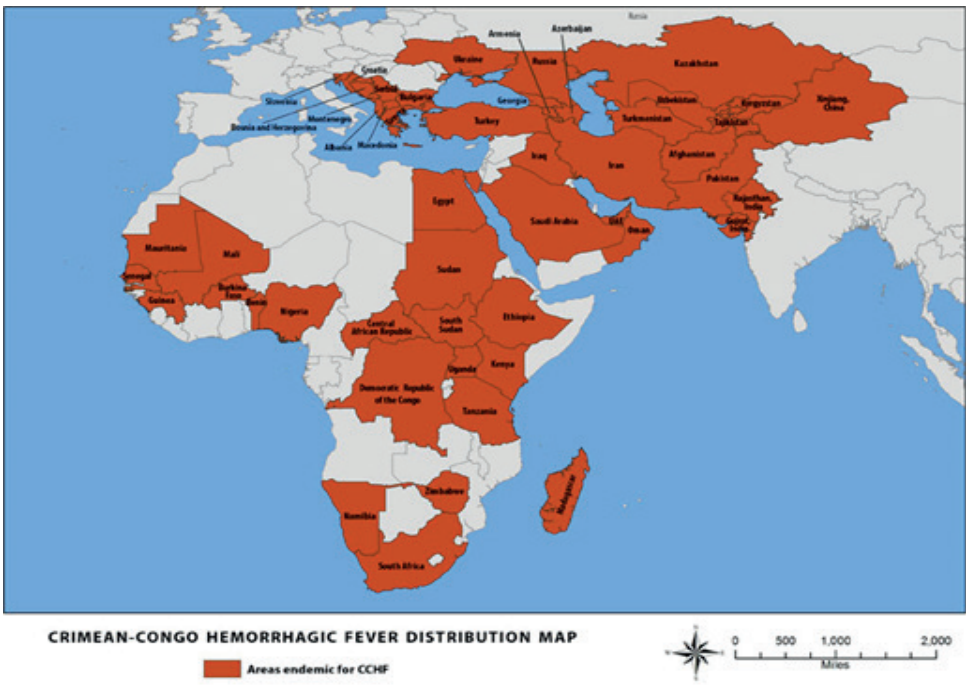

Figure 1 – Global distribution of Crimean-Congo Hemorrhagic Fever Virus (CCHFV) endemic regions. Countries marked in red have reported CCHFV presence or outbreaks. Data reflect surveillance records compiled by international health organizations [10]

The disease presents a significant concern owing to its epidemic potential and multiple modes of transmission (vector-borne and person-to-person). This disease is designated as a Risk Group 4 agent and a possible bioterrorism threat, highlighting the critical necessity for a viable vaccination [11, 12].

The development of vaccines has been impeded by the virus's genetic variability, segmented RNA genome, and biosafety concerns. Traditional vaccine methods, like inactivated and live-attenuated vaccines, have safety problems and limited effectiveness, while modern approaches face technical and immune system challenges [13].

This study outlines the current status of CCHF vaccine development, including traditional methods and new approaches, while highlighting advancements in antigen formulation, delivery methods, and adjuvant technology. It also addresses the primary obstacles to clinical translation and suggests priorities for future advancements.

Historical Development of CCHF Vaccines

The sole vaccine administered to people for Crimean-Congo Hemorrhagic Fever (CCHF) was created in the Soviet Union in 1970 and implemented in Bulgaria starting in 1974 [13, 14, 15]. This vaccine was made by using a virus that was killed with formalin and grown in the brains of baby mice, then mixed with aluminum hydroxide $Al(OH)_3$ to help boost the immune response. The immunization regimen comprised two subcutaneous doses administered 30 days apart, succeeded by a booster at one year and additional boosters every five years thereafter. It was authorized for adults aged 16 and older and largely distributed to high-risk populations, including military personnel, healthcare workers, agricultural laborers, and inhabitants of endemic areas [15, 16].

Epidemiological data from Bulgaria indicate a notable reduction in reported occurrences of CCHF subsequent to the vaccine's use. Between 1953 and 1974, 1,105 cases were documented, exhibiting a 17% case fatality rate. From 1975 to 1996, merely 279 instances were documented, with a death rate dropping to 11.4%. No illnesses were recorded among immunized military or laboratory workers. Nonetheless, it is probable that enhancements in tick management, diagnostic capabilities, and overall awareness probably played a role in the noted reduction [17].

The vaccine was never authorized outside Bulgaria due to concerns over its safety and efficacy. Vaccines made from mouse brain tissue pose a risk of allergic encephalomyelitis and further autoimmune problems. Moreover, research indicated that while the vaccination might provoke T-cell responses to the CCHF nucleoprotein, neutralizing antibody titers were typically low, necessitating frequent boosts for prolonged protection [18, 19].

The aforementioned restrictions, along with the requirement for biosafety level 4 (BSL-4) facilities for vaccine manufacture, have hindered worldwide adoption. Recent research endeavors have transitioned toward recombinant subunits, viral vectors, and nucleic acid-based vaccine platforms. Nonetheless, the Bulgarian vaccination serves as a significant historical reference and exemplifies a rare instance of practical implementation of a CCHF vaccine.

After the original vaccine, successive decades experienced disjointed and regionally separated research initiatives. Multiple experimental vaccines – comprising recombinant subunit, modified vaccinia Ankara-based vectors, viral vector vaccines, and nucleic acid-based platforms – have demonstrated encouraging immunogenicity in animal models but have not yet attained licensure [13, 14].

The lack of broadly recognized animal models, along with biosafety constraints and the significant genetic heterogeneity of the virus, has consistently hindered vaccine development. Recent global teamwork efforts, like the CCHF Vaccine [20] collaboration and clinical studies started by the University of Oxford in 2023 [21], show a renewed worldwide interest and joint efforts to create a vaccine for CCHF that works for everyone.

Live-Attenuated and Inactivated Vaccines

Live-Attenuated Vaccines

Even though live-attenuated vaccines for the CCHF virus could offer strong immune responses, they haven't moved forward much because of serious safety concerns. The possible risks – especially viral reversion to virulence or genetic reassortment – have hindered clinical advancement. As a result, existing research and clinical studies demonstrate limited engagement or enthusiasm in the advancement of live-attenuated vaccines for CCHF [13].

Inactivated Vaccines

Recent studies have concentrated significantly on inactivated vaccines derived from safer cell culture techniques. A formalin-inactivated, cell culture-based vaccination (CCVax) has demonstrated encouraging preclinical outcomes. CCVax given to BALB/c mice produced strong CCHF-specific IgG antibodies that lasted for at least 12 months after vaccination, which was much better than the results from mouse brain-derived vaccines (MBVax). Also, a study with mice that had temporary immune suppression found that CCVax provided complete protection (100%) against a deadly virus, and it led to more neutralizing antibodies and T-cell responses compared to MBVax [22, 23].

Despite these promising early results, increasing production is held back by safety issues related to handling the live virus, as well as logistical problems such as the need for strict temperature control to keep the vaccine effective in areas with limited resources.

Subunit Vaccines and Protein-Based Approaches

Subunit vaccines, which employ isolated viral proteins to elicit immune responses, are regarded as one of the safest vaccination platforms. The main parts studied for Crimean-Congo Hemorrhagic Fever (CCHF) vaccines are the viral proteins Gn and Gc, the nucleoprotein (NP), and the non-structural protein GP38. These components are generally generated through recombinant expression systems and combined with adjuvants to augment immunogenicity.

A detailed study of glycoprotein subunits was conducted using the outer parts of Gn and Gc from the CCHFV strain IbAr10200. Antigens were made in *Drosophila* insect cells and given to STAT1-knockout mice in two doses of 1.4 μg, spaced three weeks apart, using the Sigma Adjuvant System. Even though the Gc-e vaccine triggered an average antibody level of 1:333, all the vaccinated mice showed signs of illness and eventually died from the virus after being exposed to a serious challenge. A similar outcome was observed with Gn-e, suggesting that high antibody levels alone might not protect against the virus without a strong cellular response [24].

Conversely, vaccinations utilizing the nucleoprotein (NP) have exhibited more favorable outcomes. A modified adenovirus type 5 that makes NP (Ad-N) provided some protection in mice lacking STAT1, with just one shot given in the muscle leading to 33% survival after being exposed to the virus. The protective effect is probably due to the strong $CD8^+$ T-cell responses triggered by the NP antigen, which is mostly similar in many CCHFV strains [25].

A contemporary method entails the amalgamation of several antigens. A 2024 study involved giving mice shots under their skin with either recombinant NP, GP38, or both, using AddaVax and monophosphoryl lipid A to boost their immune response. When faced with a different strain of CCHFV, all the mice that were vaccinated only with NP survived, while 83% of the mice that received both NP and GP38 survived. The dual-antigen group demonstrated fewer clinical symptoms and weight loss, indicating additional protective effects from the combination of humoral and cellular targets [26].

Although subunit vaccines are safe and versatile, they frequently necessitate enhanced delivery mechanisms and adjuvants to elicit strong protection. Furthermore, immunogenicity does not consistently correlate with protection, as evidenced by the glycoprotein investigations. Future improvements should focus on using multiple antigens, better ways to present antigens (like virus-like particles or nanoparticle platforms), and testing in relevant animal models, including non-human primates.

Nucleic Acid-Based Vaccines

Nucleic acid vaccines – DNA and RNA – are very promising options for Crimean-Congo Hemorrhagic Fever (CCHF) because they can be designed quickly, are safe, and can activate both parts of the immune response. However, their efficacy is heavily contingent upon the chosen antigen, delivery method, and the immunological pathways they engage.

DNA vaccines aimed at the viral glycoprotein precursor (GPC) have demonstrated limited efficacy in protection. A study injected a plasmid that contains the full GPC of the IbAr10200 strain into the muscles of mice in three doses of 50 μg each, using electroporation. The vaccinated mice produced neutralizing antibody titers and attained over 60% survival after a fatal challenge. The result validates the protective efficacy of DNA vaccines while underscoring the necessity for enhanced delivery and boosting protocols to ensure consistent protection [27].

Importantly, better results were achieved with a DNA vaccine targeting GP38, which is a non-structural protein released from the M segment. After receiving three identical doses, animals vaccinated with GP38 showed an 80% survival rate after being challenged. Following three identical dosages, GP38-vaccinated animals exhibited an 80% survival rate after challenge. Even though there wasn't strong neutralizing action, the protection was still steady, suggesting that Fc-mediated effector functions or increased T-cell activation might be involved. These findings establish GP38 as a formidable and hitherto undervalued immunogen [28].

RNA-based platforms, especially self-replicating RNA (repRNA), seem increasingly promising. A single dose of repRNA that produces NP or GPC, combined with a LION™ nanocarrier, provided full protection for mice. In contrast to DNA vaccines, these designs necessitated minimal boosting and generated strong T-cell responses and IgG binding titers; however, they exhibited low or negligible neutralizing antibodies. This study highlights the significance of cellular immunity in CCHFV protection and the efficacy of repRNA in inducing it [29].

Traditional mRNA vaccines encased in lipid nanoparticles have exhibited immunogenicity. Mice vaccinated with glycoprotein-expressing mRNA generated antigen-specific IgG and IFN-γ+ T lymphocytes. Formulations that included the NSm protein showed weaker immune responses, which might be due to changes in the immune system or competition between different parts of the antigen, highlighting the importance of carefully choosing the right antigens [30, 31].

RNA vaccines, especially the replicon-based types, offer better protection with fewer doses than DNA vaccines and more effectively activate the T-cell responses needed for CCHFV immunity. In several studies, GP38 and NP are more effective than GPC as antigens, challenging the usual focus on neutralizing antibodies. These data underscore that effective CCHFV vaccinations may depend more on the breadth and quality of T-cell immunity than only on elevated antibody titers.

Viral Vector-Based Vaccines

Viral vector-based vaccines constitute an innovative and swiftly evolving platform for CCHFV vaccination. These vaccines use modified viruses to deliver CCHFV proteins directly into host cells, which boosts both antibody and cell-based immune responses. Various vector systems have been examined, demonstrating differing efficacy based on the vector type and antigen employed.

The ChAdOx2 CCHF vaccine, which uses a harmless chimpanzee virus to deliver the complete glycoprotein precursor (GPC) of CCHFV, is one of the leading options. In early tests, mice given the ChAdOx2-CCHF vaccine showed strong antibody and T-cell responses, leading to 100% survival after being exposed to a deadly virus. The protection was even better when this vaccine was given first, followed by a booster shot of Modified Vaccinia Ankara (MVA) CCHF. A detailed tissue examination confirmed complete protection, showing no signs of the virus or any changes in the tissues [32, 33].

A different adenoviral method used a human Ad5 vector that carries the nucleoprotein (NP) of CCHFV. In IFNAR−/− mice, one dose gave 30% protection, while a prime-boost method increased protection to 78%. In IFNAR−/− mice, a single administration provided 30% protection, whereas a prime-boost strategy enhanced it to 78%. Even though there were only a few neutralizing antibodies, strong NP-specific IgG and T-cell responses were found, showing that cell-mediated immunity played

an important role in protection [13, 32, 34]. These findings highlight the importance of choosing the right antigens: while GPC-based vaccines offered full protection, NP-based ones only gave partial protection.

Besides adenoviruses, other different viral vectors have been investigated:

• Bovine Herpesvirus Type 4 (BoHV-4) has surfaced as a viable candidate owing to its minimal human toxicity and robust immunogenicity. A modified version of BoHV-4 that makes CCHFV NP (called BoHV4-ΔTK-CCHFV-N) triggered strong immune responses andspecific antibodies in both BALB/c and IFNα/β/γR−/− mice. Even though there were no detectable neutralizing antibodies, the vaccine completely protected against serious infections with the Ank-2 strain. Tests showed that giving antibodies and checking T-cells resulted in 75% protection, confirming that both antibody and T-cell responses are involved [35, 36].

• Vesicular Stomatitis Virus (VSV) vectors have demonstrated significant efficacy. A recombinant VSV expressing the CCHFV glycoprotein was evaluated in STAT1−/− mice. The vaccinated mice produced strong anti-GP IgG and neutralizing antibodies, but all of them died after being exposed to a dangerous strain of CCHFV. The VSV platform's rapid replication and elevated antigen expression may enhance its robust immunogenicity [37].

Adenoviral vectors are the most advanced regarding translational potential and continuing clinical study; yet, these other systems have significant advantages. BoHV-4 can hold large genetic changes and triggers a variety of immune responses, while VSV allows for effective single doses and higher levels of expression. However, there are still limitations, like the need for cold storage, the chance of existing immunity (especially for Ad5), and the lack of information about how long the effects last in large animals or humans.

In summary, vaccines that use viral vectors, like adenoviruses, BoHV-4, and VSV, show great promise for treating CCHFV. Their effectiveness will depend on improving how we choose antigens, the amount given, and how they are delivered, as well as comparing different options to find the best ones for use in humans. Their success will hinge on the ongoing optimization of antigen selection, dosage regimens, and administration methods, along with comparative assessments across platforms to identify the most dependable candidates for human application.

Adjuvants and Delivery Systems

The efficacy and nature of the immune response generated by CCHFV vaccines are contingent upon both the antigen and the method of its delivery and processing. Diverse platforms activate unique pathways − some promote antibody responses, while others enhance T-cell activation. Figure 2 summarizes these pathways, illustrating how inactivated, subunit, nucleic acid, and viral vector vaccines activate the immune system.

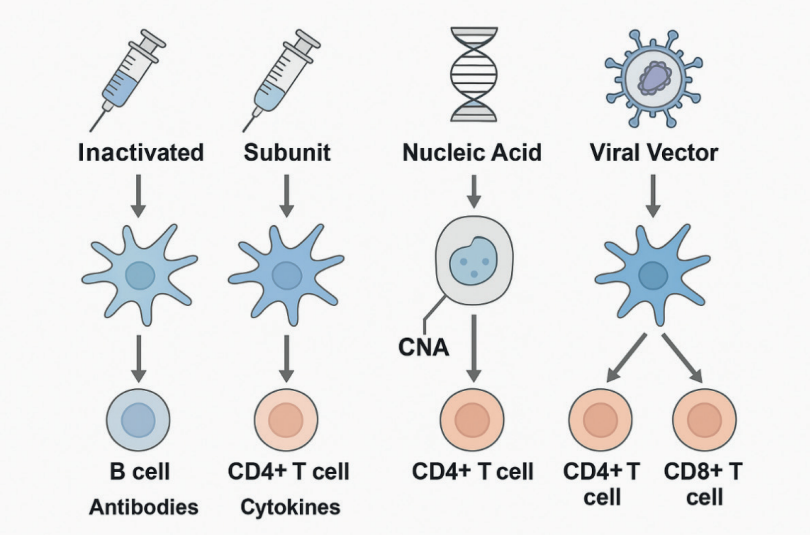

Figure 2 – Schematic depiction of immune response pathways elicited by several CCHFV vaccination platforms. Inactivated and subunit vaccinations predominantly stimulate antibody synthesis, frequently necessitating adjuvants. DNA, RNA, and viral vector platforms induce more extensive responses by activating both helper and cytotoxic T cells. Comprehending these distinctions is crucial for the selection and optimization of vaccination candidates

The effectiveness of CCHFV vaccine candidates, especially those using subunit and nucleic acid methods, often needs to be improved with adjuvants and better delivery systems. These components improve how strong and effective the immune response is, which is especially important for viruses like CCHFV that need both antibody and cell-based immunity for good protection.

Adjuvants

Adjuvants are agents that enhance the immunological response to an antigen. Various adjuvants have been assessed for CCHFV vaccines:

• Aluminum-based adjuvants (alum) continue to be the predominant choice in inactivated CCHFV vaccinations. In IFNAR−/− mice, alum-adjuvanted cell culture-derived vaccinations induced specific IgG responses and conferred partial protection after viral challenge. However, their ability to create strong cellular immunity is limited, which may explain the moderate level of protection seen in some models [34, 38].

• To address this, more effective adjuvant compositions have been investigated. A good example is the combination of Montanide ISA 201VG with Poly (I:C), which is a man-made version of double-stranded RNA that activates TLR3. This two-adjuvant method was used to create glycoprotein subunit vaccines, which produced a balanced immune response shown by higher levels of IFN-γ and antigen-specific IgG in BALB/c mice. The formulation additionally facilitated cross-presentation, crucial for effective cytotoxic T-cell activation [39].

Delivery Systems

Antigen delivery strategies are essential in influencing the immunological result. Numerous advanced techniques have been created to enhance antigen stability, absorption, and presentation:

• Gram-Positive Enhancer Matrix (GEM) particles, originating from Lactococcus lactis, have been utilized for the surface display of CCHFV glycoproteins through a protein anchor system (PA). The GEM-PA platform facilitates high-density antigen presentation and rapid purification without requiring adjuvants. In mouse studies, vaccines made with GEM-displayed Gn and Gc parts triggered strong immune responses, including specific IgG and IFN-γ, showing that this system could be useful for both mucosal and overall vaccination methods [40].

• Zera® Protein Fusion Technology employs plant-derived fusion tags to facilitate the self-assembly of antigens into protein bodies. This method enhanced protein expression, aggregation, and immunogenicity when applied to CCHFV Gn and NP antigens. Mice that received Zera-fused nanoparticles showed strong IgG responses and produced IFN-γ from splenocytes, suggesting that this technology could improve the effectiveness of vaccines made from both DNA and protein subunits [40, 41].

Together, these adjuvants and delivery methods help overcome important challenges in developing CCHFV vaccines, like the weak immune response from purified proteins, the need to lower doses, and the activation of cellular immunity. As vaccination methods improve, carefully mixing antigens with effective adjuvants and smart delivery systems will be key to achieving long-lasting and broad protection.

Key Insights and Future Directions

Recent advancements in CCHFV vaccine research indicate a distinct trend: cellular immunity, especially T-cell responses, seems more vital for protection than only neutralizing antibodies. Subunit vaccines targeting GP38 or NP, even though they don't produce strong neutralizing antibodies, often perform better than glycoprotein-based vaccines in tests. This view shifts the focus from just measuring antibody levels to looking at the overall immune response when evaluating how well a vaccine works.

Replicating RNA (repRNA) and viral vector vaccines have shown the best effectiveness (up to 100%) in early tests, often needing just one dose, highlighting their ability to be given quickly and with fewer doses. In contrast, DNA vaccines need multiple doses and electroporation to reach similar effectiveness, which limits how they can be used in practice. Conversely, DNA vaccines necessitate numerous administrations and electroporation to achieve similar efficacy, thereby constraining their practical application.

Adjuvants and delivery methods are essential components. Technologies like GEM particles, Zera® fusion, and effective combinations of adjuvants (like Montanide with Poly I:C) have significantly

improved how well subunit vaccines work. These technologies enhance antigen presentation and provide practical benefits such as simplified formulation and needle-free alternatives.

Notwithstanding this advancement, obstacles persist. Most research concentrates on select virus strains, and the mechanisms of cross-genotype protection remain inadequately comprehended. The absence of standardized animal models and established immunological correlates of protection impedes cross-platform comparisons. Significantly, no vaccine has progressed to advanced human trials; nevertheless, the ChAdOx2 CCHF candidate represents a crucial advancement.

Future research should emphasize broad-spectrum antigens, multi-antigen formulations, and scalable delivery systems appropriate for endemic environments. Coordinated worldwide investment could expedite the development of a safe, effective, and accessible CCHFV vaccine.

Conclusion

Despite extensive study over several decades, there is presently no licensed vaccination available for Crimean-Congo Hemorrhagic Fever. Recent advancements – especially in RNA replication, viral vector technology, and antigen-specific subunit platforms – have substantially progressed the area. The focus has shifted from just targeting antibodies to also building strong cellular immunity, improving delivery methods, and creating widely protective antigens. The creation of a vaccine is both a scientific advancement and a public health imperative in endemic nations like Kazakhstan, where the circulation of CCHFV is thoroughly recorded in southern areas. Connecting preclinical achievement with clinical application is essential for ensuring protection for high-risk populations in Kazakhstan and elsewhere.

Authors' Contributions

AT, BM and LK: Conceptualization, formal analysis, designed the study, writing - original draft. AT GZh, TT, KB: Conducted an extensive literature review and analyzed the data. AT, BM and LK: Data Curation, Writing Review & Editing. MR, KZh and BM: Supervision. All authors have read, reviewed, and approved the final manuscript.

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