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CRIMEAN CONGO HEMORRHAGIC FEVER (CCHF): A PROMISE FOR THE FUTURE

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ABSTRACT

Crimea-Congo hemorrhagic fever (CCHF) is a deadly tick-borne zoonosis caused by the Crimean-Congo hemorrhagic fever virus (CCHFV), with the highest case-fatality rate and with widespread distribution. This review synthesizes the disease with respect to zoonotic origins, transmission routes, clinical manifestation, and current progress in vaccine development. CCHF is transmitted mainly through ticks of the genus Hyalomma or through close contacts with infected animals or humans' blood and body fluids. People involved in handling livestock, agriculture, and health care are particularly at risk. The illness begins with nonspecific symptoms and may develop into hemorrhagic complications. Indian epidemiological data between 2011 and 2023 have revealed 63 confirmed cases and 31 deaths, with Gujarat recording maximum cases. Major outbreaks worldwide have also been recorded, including Afghanistan (950 cases, 96 deaths), Iraq (545 cases, 70 deaths), and Turkey (2,508 cases, 133 deaths), revealing the deadly potentials of the disease.

KEYWORDS: Crimean-Congo Hemorrhagic Fever (CCHF), zoonotic disease, tick-borne infections, vaccine development, epidemiology.

INTRODUCTION

Crimean-Congo Haemorrhagic Fever (CCHF) is an infectious zoonotic disease caused by the Crimean-Congo Hemorrhagic Fever Virus (CCHFV) from the Nairoviridae family. Zoonotic diseases are disease transmitted naturally from a vertebrate animal to humans and based on their reservoirs/transmission can be classified into three categories: anthropozoonoses (animal to human), zooanthroponoses (human to animal), and amphixenoses (bidirectional transmission); zoonoses can also be classified based on the life cycle of the disease: direct zoonosis (direct contact), cyclozoonoses (includes more than one vertebrate hosts), metazoonoses (involves more than one host, vertebrate and invertebrate), and saprozoonoses (have environmental reservoirs such as soil).[1] The causative agents of zoonoses typically are bacteria (e.g., Bacillus anthracis, Leptospira spp.), viruses (e.g., rabies virus, CCHFV), parasites (e.g., Toxoplasma gondii), fungi (e.g., Trichophyton spp.), and pathogen (e.g., vector borne pathogens - dengue virus). CCHF is of particular interest because it has a high fatality rate and distribution across the planet.

CCHF was first described in the former Soviet Union in 1944 and has been reported since then in many countries including Turkey, Iran, India, Greece, Georgia, and some regions in the Balkans.[2] CCHF is usually transmitted through the bite of an infected Hyalomma tick but can also be transmitted by contact with infected animal or human blood, or other body fluids. Importantly, airborne transmission does not occur during this process.[2] The groups at highest risk include agricultural workers, livestock handlers, veterinarians, and health care workers. Environmental factors can impact the prevalence of CCHF disease, evidenced by a retrospective study linking precipitation, humidity, temperature, and seasonal mobility with confirmed cases in case distributions. Most cases (41.13% of a total of 547) occurred during the months of August and September, when there was a high movement of humans and animals in the region where the cases were reported. The overwhelming majority (84.6%) of cases were males, implying gender-related occupational exposure.[4]

Clinically, CCHF begins with flu-like symptoms such as fever, headache, sore throat, dizziness, mood changes, and muscle pain. Gastrointestinal issues like nausea,

vomiting, diarrhea, and abdominal pain are also common in the early phase. As the disease progresses, patients may develop severe manifestations including bleeding (petechiae, ecchymosis, epistaxis, gum bleeding), hepatomegaly, jaundice, and organ failure. Diagnostic confirmation relies on virus isolation, ELISA, and RT-PCR, while biosensor-based tools are being developed to improve detection.[5] No specific antiviral treatment exists for CCHF, and current management is supportive, aiming to relieve symptoms and support vital organ functions. Ongoing research is investigating experimental therapies, including immunotherapy and novel antiviral agents, for future clinical use.[5]

METHODS

This review synthesizes findings from peer-reviewed articles, retrospective studies, and preclinical vaccine trials from scientific databases including PubMed, PLOS One, and institutional repositories. Publications from 2011 to 2024 were screened for relevance to the development, evaluation, and clinical prospects of CCHF vaccines. Both animal model studies and epidemiological reports were included. The key criteria for inclusion were studies discussing vaccine platforms (mRNA, DNA, inactivated, subunit, and plant-based), immunogenicity, protective efficacy, and public health relevance. Data on outbreaks were also extracted from official health agency reports.

RESULT AND DISCUSSION

Several vaccine candidates are undergoing various stages of research and development, although there is currently no approved vaccine for human use against CCHF. The nucleoside-modified mRNA vaccine encapsulated in lipid nanoparticles (mRNA-LNP), which encodes the CCHFV nucleoprotein (N) or glycoproteins (Gc and Gn), is among the most promising strategies. Research on mice lacking the interferon alpha receptor (IFNAR) revealed a strong humoral and cellular immune response, with Gc exhibiting higher immunogenicity than Gn. In mice, this vaccine offered complete protection against virulent CCHF infection.[6]

A different strategy involves a DNA vaccine expressing ubiquitin-tagged CCHFV antigens (Gc, Gn, and N) alongside transcriptionally competent virus-like particles (tc-VLPs). Not only did this combination generate high titres of neutralizing antibody but it also highlighted the significance of a dominant Th1 and well-balanced Th2 type immune response. The research also identified conserved linear B-cell epitope areas among various CCHFV strains, finding that the presence of a robust Th1 response in addition to neutralizing antibodies dramatically improves survival rates in mice.[7] The DNA vaccine encoding the M segment glycoprotein precursor gene of CCHFV was also tested in both IFNAR and transiently immune–suppressed (IS) mouse models. Delivered by intramuscular electroporation, the vaccine generated a strong humoral immune response and high titre neutralizing antibodies. The vaccine protected more than 60% of immunized animals against disease, with IS mice having somewhat superior Th1 and Th2 responses to the IFNAR model.[8]

Another novel technique was the plant-based vaccine strategy where transgenic roots and leaves expressing glycoproteins of CCHFV were fed to mice followed by a booster injection subcutaneously. Immunized groups revealed higher IgG and IgA titres in serum and urine, respectively which evidenced encouraging mucosal and systemic immunity.[9] A comparative study of two inactivated vaccine preparations—cell culture-derived vaccine (CCVax) and mouse brain-derived vaccine (MBVax)—proven that CCVax produced a greater dose-related humoral response than MBVax. Given in three doses (5 µg, 10 µg, and 20 µg), CCVax performed similar to MBVax based on IgG titres and production of neutralizing antibodies. The process of developing vaccines included virus isolation, purification, formalin inactivation, ultracentrifugation, and adjuvant addition, with CCVax having a superior immunoprofile in preclinical models.[10] Finally, a subunit multi-epitope vaccine was created through reverse vaccinology and immune informatics. The construct, comprising 427 amino acids, was formulated based on selected B-cell and T-cell epitopes screened for antigenicity, allergenicity, and population coverage. Molecular docking simulations showed stable binding with immune receptors, indicating that it could be a potentially effective global vaccine, although preclinical work is required to confirm its safety and efficacy.[11] Cumulatively, these reports show significant advancement in CCHF vaccine research, albeit ongoing work in clinical assessment and optimization is necessary. The epidemiological trend of CCHF outbreaks, both in India and globally, highlights the persistent and expanding nature of this zoonotic threat. Table 1 summarizes reported cases in India from 2011 to 2023, with a predominant concentration in Gujarat, as well as additional cases in Rajasthan and a single report from Kerala. These outbreaks have varied in intensity, with the largest cluster recorded in Gujarat in 2019 (34 cases, 17 deaths).[12-18] Table 2 presents global data, reflecting widespread outbreaks across Asia, Europe, and Africa. Particularly severe occurrences were documented in Turkey (2002–2008; 2,508 cases), Afghanistan (2023; 950 cases), and Iraq (2023; 545 cases), with significant mortality. This underscores the urgency for sustained surveillance, cross-border data sharing, and accelerated vaccine development as a long-term solution.[19-26]

Table 1: Reported CCHF Cases and Deaths in India (2011–2023)

Year	State	District / Location	Cases	Deaths
2011	Gujarat	Ahmedabad (Sanand)	4	3
2011	Gujarat	Ahmedabad	2	2
2013	Gujarat	Amreli (Karyana village)	14	5
2014	Rajasthan	Sirohi (Veravilapur village)	1	1
2015	Rajasthan	Jodhpur	4	2
2016	Gujarat	Kutch (imported case from Oman)	1	0
2019	Gujarat	Multiple districts	34	17
2019	Kerala	Thrissur	1	0
2022	Gujarat	Sabarkantha	1	0
2023	Gujarat	Kutch (Lakhapar village, Anjar Taluka)	1	1

Table 2: Global CCHF Outbreaks (2002–2023)

Year(s)	Country	Region / Province	Cases	Deaths
2023	Iraq	Multiple governorates	545	70
2023	Afghanistan	Nationwide	950	96
2023	Iran	Multiple provinces	60	3
2023	India	Gujarat	1	1
2022	Iraq	Thiqar & others	212	27
2022	Kazakhstan	Kyzylorda Region	15	N/A
2013–2021	Spain	Salamanca & others	10	N/A
2002–2008	Turkey	Tokat, Yozgat, others	2508	133
2003	Mauritania	Nouakchott	38	11
2010–2020	Sudan	Kordofan, D arfur	88	13
2010	Uganda	Agago, Nansana	4	4
2012	Iran	Multiple provinces	71	8
2010	UK	Glasgow (imported case)	1	1

CONCLUSION

There are many limitations of the currently available vaccines. Some of the limitations are due to genetic variability of the virus because of which it to modify itself, adjust to a new host, escape the immune system, and develop resistance to antiviral drugs or vaccines. There is a lack of a susceptible animal model to understand the pathology of the disease. The understanding of the specific protective epitope is unclear. There is no clear relationship between vaccine protection and neutralizing antibody levels. Studies on diverse populations result in external challenges like environmental factors, social determinants, medication response, etc. There is no global team of experts working together in an organized way to do the research work.

CCHF Virus is lethal for our society because of its high infectivity and mortality rate. Various institutions, pharma companies, and government projects regarding the control of CCHFV prevention and its spread. Vaccination is 1 of the best prevention modalities, but because of a lack of adequate knowledge, manpower, resources as well as awareness acts as an obstacle. Many vaccines are under trial, but still not up to the mark for the safety of people. With study of recent advancements in the field of genetics and medical science signifies a promising future for effective vaccine development and safety for all.

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