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NARRATIVE REVIEW

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Control strategies for emerging infectious diseases: Crimean-Congo hemorrhagic fever management

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Abstract

Background and Aims: Crimean-Congo Hemorrhagic Fever (CCHF) is a significant public health concern transmitted by ticks. This study seeks to thoroughly grasp the epidemiology and transmission patterns of CCHF, which is caused by the CCHF virus (CCHFV), a member of the Nairovirus genus in the Bunyaviridae family.

Methods: The study investigates the global distribution and endemicity of CCHF, its mortality rates, modes of transmission (including tick bites, contact with infected animal blood, and limited person-to-person transmission), and factors influencing its prevalence across different regions. Genetic diversity within CCHFV and its impact on transmission dynamics are explored, along with efforts to control the disease through tick prevention, antiviral treatment, and the development of vaccines and diagnostics.

Results: CCHFV exhibits widespread distribution, particularly in the Middle East, Africa, Asia, and Eastern Europe, with an overall mortality rate of approximately 30% and a case fatality rate ranging from 10% to 40%. Transmission occurs primarily through tick bites and contact with infected animal blood, with limited person-to-person transmission. Livestock workers, slaughterhouse employees, and animal herders in endemic areas are most affected by their frequent interaction with sick animals and ticks. Genetic diversity within CCHFV contributes to variations in

transmission dynamics, complicating control efforts. Antiviral ribavirin shows efficacy in treating CCHF infection.

Conclusion: This study underscores the importance of further research to understand the enzootic environment, transmission routes, and genetic diversity of CCHFV for effective control measures, including the development of vaccines, treatment options, and diagnostics.

KEYWORDS

outbreak investigation, pathophysiology, public health, vector-borne diseases, viral hemorrhagic fevers, zoonotic diseases

1 | INTRODUCTION

A tick-borne virus causes CCHF, which is prevalent across various regions. The virus is a member of the genus Nairovirus, family Bunyaviridae.[1] This vector-borne viral disease affects multiple areas of the world.[2] Initially named "Crimean hemorrhagic fever" due to its first identification in Crimea in 1944, it later acquired its current name after being identified as the cause of disease in the Congo in 1969.[3] CCHF epidemics are spreading across Eastern Europe, Africa, Asia, and the Middle East, transmitted to humans through tick bites or contact with blood.[3,4] Additionally, contacting the blood or other bodily fluids of afflicted persons might spread the disease.[5] A 10% to 40% case fatality rate is associated with CCHFV-induced viral hemorrhagic fever outbreaks. It is estimated that approximately 30% of victims of CCHF will die. There are several characteristics of CCHF, including sudden onset, joint pain, headache, back pain, high fever, and nausea. As the disease progresses, there is a possibility of severe bleeding, liver damage, and kidney damage in patients. The CCHF virus is carried by and is stored in ixodid (hard) ticks. In endemic areas, there is a higher risk of CCHF for those who work in slaughterhouses, livestock operations, and animal herding.[5] The CCHFV, a spherical virus ~100 nm in diameter, possesses a lipid envelope derived from the host. Its genome comprises three segments: small, medium, and large. Surface glycoproteins Gn and Gc, found in the medium segment, encode key components, including the nucleoprotein and RNA-dependent RNA polymerase, facilitating receptor binding and entry.[6] (Figure 1).[7] One of the most genetically diverse arboviruses is the CCHFV, which exhibits geographic segregation linked to the virus's origin by having different genotypes categorized according to the investigated genomic area. The phylogenetic analysis of the S segment uncovers seven lineages: Asia 2, Asia 1, Africa 3, Africa 2, Africa 1, Europe 2, and Europe 1. Additionally, the M and L segments reveal nine and six extra genetic lineages, respectively, albeit with less consistency[8–10] Segment reassortment in CCHFV notably leads to variations in the phylogenetic tree structure for a single isolate when all three genomic segments are analyzed.[8,11] Control of CCHF in animals and ticks remains essential for preventing human infection.

Highlights

- Crimean-Congo Hemorrhagic Fever (CCHF) is prevalent in the Middle East, Africa, Asia, and Eastern Europe, with a mortality rate of ~30%.
- Transmission primarily occurs through tick bites and contact with infected animal blood, posing risks to livestock workers and animal herders.
- Genetic diversity within CCHFV influences its transmission dynamics, complicating control efforts.
- Antiviral ribavirin demonstrates efficacy in treating CCHF infections, highlighting potential therapeutic avenues.

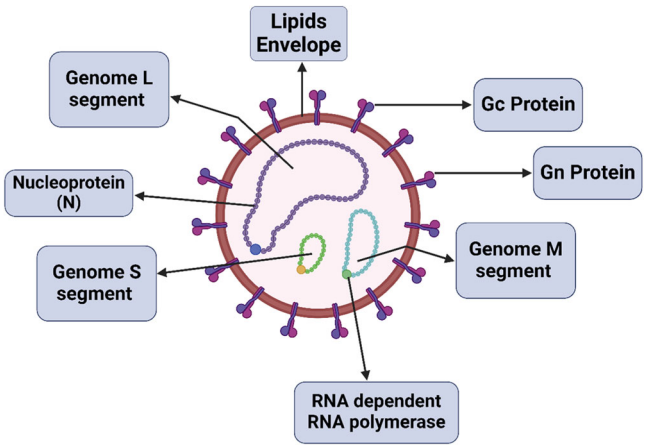

FIGURE 1 The genomic structure of CCHFV shows the three genomic segments and the proteins they encode each. [Created in Bio Render].

2 | HISTORICAL DISCOVERIES TO EMERGING PATTERNS

In 1944, scientists initially described Crimean hemorrhagic fever in the *Crimean Peninsula*. In 1969, they identified the pathogen responsible for this fever as the same one found in the Congo Basin

in 1956, leading to the naming of the disease and virus based on this linkage. Africa, the Balkans, and the Middle East are facing an ongoing spread of CCHF,.[12] with infection rates of 22.5% in humans, 2.1% in ticks, and 4.5% in other animal species in Europe and Asia.[13] Recent infections show a seroprevalence of 11.6% in humans and 0.4% in different animals. Infected humans typically remain viraemic for 2–15 days without exhibiting clinical symptoms,.[14] However, there could be hepatitis symptoms and serious side effects, including lung failure, rapid kidney decline, or sudden liver failure.[15] Hyalomma ticks mainly carry CCHF. Both oral and intravenous treatments worked well, and suspected CCHF samples should be handled safely in well-equipped labs by trained individuals.[16] The epidemiology of CCHF in Africa has not been fully defined. In Europe, CCHF has emerged as a significant pathogen, with outbreak case fatality rates ranging from 5% to 40%.[16] The majority of CCHF cases on the continent were documented in South Africa, where hospitalized patients had a case fatality rate of almost 30%.[14] CCHF exhibits seasonal patterns related to specific meteorological variables and is endemic in various regions. Studies have identified a seasonal pattern in Iran and an association between incidence and mean temperature in Bulgaria.[17,18] During the period when CCHFV is prevalent in the Northern Hemisphere, typically from May through September, with a peak in June and July, climatic conditions vary by location. In most parts of the Northern Hemisphere, meteorologists and climatologists generally define this time as the summer season, which encompasses the months of June, July, and August.[7] Surveillance and reporting of CCHF cases are crucial for monitoring its spread. The CDC and ECDC largely provide details about CCHF cases. In Africa, National Veterinary Services should continuously monitor and report CCHF information while improving data quality.[19] Overall, comprehensive surveillance and research efforts are necessary to understand and manage the spread of CCHF in various regions, particularly with regard to its relationship with climate variables.

3 | UNDERSTANDING THE SPREAD: CRIMEAN-CONGO HEMORRHAGIC FEVER

The transmission of CCHFV. Initially, infected tick bites transmit the virus to animals, while uninfected ticks become carriers when they feed on these animals. Human-to-human transmission occurs through close contact with infected individuals, which includes exposure to their blood, saliva, organs, or bodily fluids. Hospital-acquired infections may arise from problems such as inadequate sterilization of medical equipment, needle reuse, and contaminated medical supplies. Research, including modeling studies, contributes to our understanding of these transmission patterns. For example, a survey conducted in Afghanistan identified an endemic pattern of CCHFV transmission among cattle, closely mirroring human cases.[20] Another mathematical model demonstrated that tick populations remain infected for life, while infections in livestock and humans are temporary.[21] The Hyalomma genus of ixodid ticks serves as both a reservoir and vector for CCHFV, transmitting the virus to humans through various modes, such as contact with infected ticks or animal blood. In contrast, numerous domestic and wild animals serve as amplifying hosts.[22,23] Through transovarial and transstadial transmission during the larval, nymphal, and adult phases, the virus continues to exist in ticks.[24] Tick bites and direct contact with contaminated animal blood can infect humans; these situations frequently arise during veterinary treatments, animal slaughter, and hospital environments.[25] Notably, no approved CCHF vaccine is available, and therapy is limited to symptom management. Preventive measures, particularly for individuals engaged in high-risk livestock-related occupations, are essential. These measures include avoiding tick bites and contact with infected animal materials, as the virus can spread through multiple pathways, including from ticks to animals, from animals to humans, and between humans.[26] (Figure 2). Prominent symptoms of CCHF include headaches, high fever, stomach pain, and bleeding. High-risk individuals in the cattle industry, such as farmers, butchers, and veterinarians, are more susceptible to infection. The geographic range of the primary arthropod vector, the Hyalomma tick, correlates with the disease's endemicity. New populations are in danger of contracting CCHF due to the growing range of the Hyalomma tick vector.[26,27]

4 | OUTBREAK INVESTIGATIONS AND CASE STUDIES

Several recent outbreaks and investigations of CCHF in various regions have been reported, providing valuable insights into the current understanding of the disease. The Health Alert and Emergency Coordination Centre (CCAES) in Spain issued a study in October 2011 that predicted a low risk for human illnesses but suggested a multidisciplinary approach to surveillance and control.[22] A 2017 report in the World Health Organization's Eastern Mediterranean Region examined CCHF-related problems, difficulties, and potential future directions.[28] In Sudan, a retrospective study analyzing data from 2010 to 2020 identified five epidemics of CCHF, resulting in 88 cases and 13 fatalities,.[29] The significance of CCHFV as a cause of fever and bleeding in the area was underscored by another study conducted in Sudan in 2019 that found CCHF patients in an outbreak of severe undifferentiated febrile illness.[30] To stop future sporadic CCHF outbreaks in Uganda in 2021, studies were conducted to determine risk variables and suggest solutions.[31] The WHO reported an outbreak of CCHF in Iraq in June 2022, with 219 cases reported between January 1st and June 26th, 2022, prompting an epidemiological investigation and contact tracing.[32,33] To address CCHF outbreaks, the World Health Organization developed a Crimean-Congo Hemorrhagic Fever Outbreak Toolbox guiding investigation, risk assessment, and control measures[34] Following an epidemic including human patients, a study conducted in Uganda in January 2023 investigated the seroprevalence of CCHFV exposure in domestic animals. The results showed that CCHF is a developing concern for human health and is responsible for periodic outbreaks in Area.[35] Overall, CCHF remains a significant public health concern in various regions, necessitating further research and outbreak investigations to understand and control the disease better. Additionally, Table 1. presents information about disease transmission,

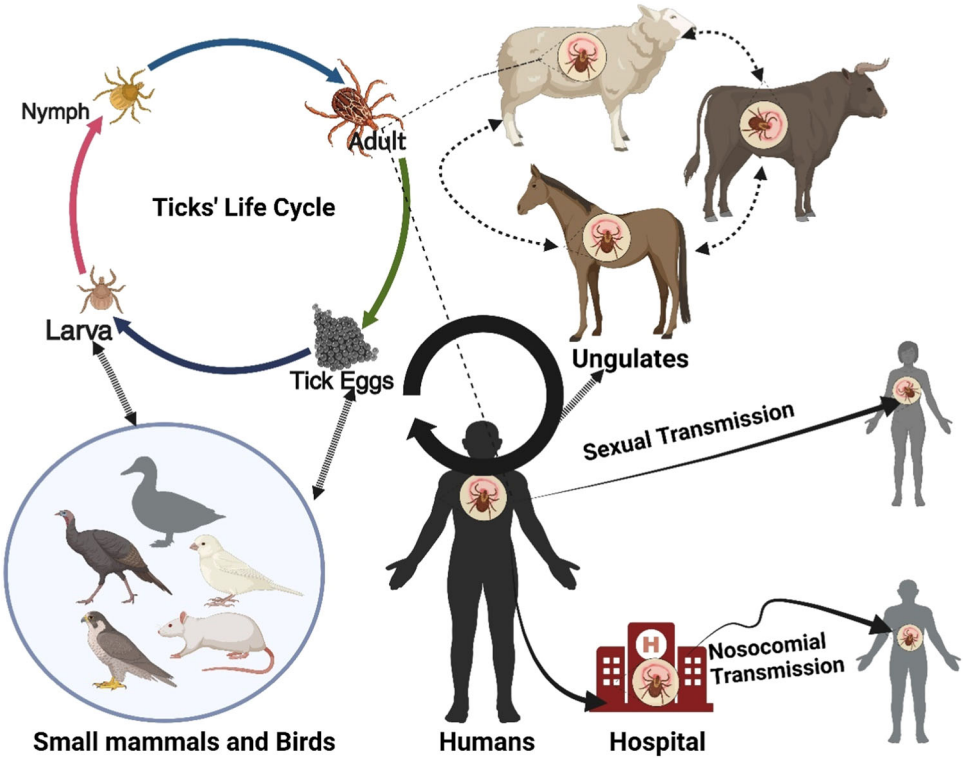

FIGURE 2 CCHFV Transmission Cycle: Human and Vector Interactions. [Created in Bio Render].

with the mode being either slaughtered animals or livestock in the region.[28] Between 2014 and 2020, the National Institute of Health, Islamabad, confirmed over 350 cases of CCHF, marking a significant increase in occurrences since 2010. In India, four states reported CCHF cases.[31] These studies emphasize the importance of continued surveillance and control measures to combat CCHF and mitigate its impact on human health and the livestock industry.

5 | PATHOGENESIS OF CCHF

Viruses causing hemorrhagic fever exert their pathogenic effects by turning off the host's innate immune function and exploiting the host's cellular machinery for rapid replication.[42] In the case of CCHF, this process primarily results in infection of the epithelium, which interferes with the vascular system's and lymphatic organs' proper function[43,44] Epithelial cells are harmed by viral replication, and the virus produces substances that are tissue-toxic and derived from the host, activating the endothelium and impairing cellular function.[44] Consequently, damaged endothelium attracts platelets, activating the intrinsic pathway of coagulation and causing hemostatic failure.[7] Cytopenia, marked by decreased blood cell counts and hemophagocytosis, is linked to the disease, alongside heightened activation of monocytes induced by elevated levels of Type-1 T helper cytokines and disseminated intravascular coagulation.[45–47] The CCHF virus enters host cells by interacting between its GC and GN glycoproteins and a receptor located on the surface of the host cell.[48] The viral RNA-dependent RNA polymerase engages with encapsulated genome segments within the host cell via clathrin-dependent endocytosis, resulting in the formation of positive-strand intermediates.[49] These intermediates serve as templates for the production of complementary negative strands, and the virus relies on the host's microtubules for internalization, assembly, and egress.[50] The Golgi body plays a crucial role in the synthesis and processing of viral surface glycoproteins, leading to the release of mature viruses through budding into the surrounding environment.[51] (Figure 3), the pathogenesis of CCHF, illustrating the intricate interplay between the virus and the host's cellular machinery. It outlines the entry of the CCHF virus into the host cell, its replication, and the host's immunological response. The figure highlights the interaction between viral glycoproteins and host receptors, the involvement of cytokines in pathogenesis, and the impact on endothelial cells and coagulation pathways. Additionally, it depicts the release of mature viruses from the Golgi body, their replication, and spread within the host, ultimately resulting in various degenerative changes and clinical manifestations of the disease.

6 | PHASES OF CCHF INFECTION AND CLINICAL MANIFESTATIONS

In CCHF, humans manifest clinical symptoms associated with the disease, making them the primary known host.[52] A study indicated that among five infected individuals carrying the virus, the chances

TABLE 1 CCHF outbreaks: comparative analysis of affected countries.

S. No	Country	Cases Reported	Mortality Rate	Key Information	Reference
1.	Pakistan	In June 2023, investigated 81 suspected cases.	Approx 30%	CCHF poses a significant public health concern in Pakistan because the disease is present in livestock and tick vectors and has been reported in human cases.	[36]
2.	China	As of 2021, reported 4,47,848 cases.	80%	Between 1951 and 2021, researchers reported 447,848 cases of bunyaviruses viruses, with CCHFV causing a significant disease burden alongside three other viruses.	[7]
3.	Kazakhstan	Approximately 16 cases occur per year.	14.8%	The study finds that the CCHF virus is present in 2.4% of sheep and 3.8% of the cattle population in the Zhambyl region.	[7]
4.	India	In 2019, reported 34 cases.	50%	The first case in Gujarat state is linked to Pakistan, while multiple outbreaks occur in Uttar Pradesh, Rajasthan, and Gujarat.	[37]
5.	Afghanistan	On September 20, 2023, there were 352 cases reported.	9.7%	Afghanistan's CCHF instances provide an unparalleled difficulty, particularly for women, children, and other marginalized populations.	[38]
6.	Iran	The Iran Ministry of Health announced in July 2019 that there had been 1501 cases of CCHF, including 195 fatalities.	13%	The worldwide distribution and re-emergence of CCHF underscore the necessity for conducting additional research on prevention and treatment agents, understanding pathophysiology, elucidating transmission routes, and evaluating the efficacy of drugs like favipiravir through double-blind, randomized clinical trials.	[39]
7.	Oman	Between 2011 and 2017, individuals reported 80 cases.	23.8%	From 2011 to 2017, the Eid-Al-Ahda festival, typically occurring during the summer months, contributed to around 23.8% of cases, highlighting increased transmission risk during this period.	[40]
8.	Iraq	In August 2023, authorities confirmed 511 cases.	12.7%	Increased temperatures influence vector behavior, and uncontrolled animal movement with neighboring countries contributes to variations in CFR among provinces during religious ceremonies, highlighting the necessity for a unified public health intervention strategy.	[34]
9.	Turkey	From 2014 to 2017, medical professionals identified 76 suspected cases, confirming CCHF in 46.1% of them.	9.6%	Turkey is considered a hub for CCHF, with increasing cases and a high fatality rate initially. The disease is highly prevalent in eastern regions.	[41]

of developing clinical disease ranged from 0.215 to 1.[53] The illness progresses through four main phases: first, the incubatory period, characterized by viral replication within the body; followed by the pre-hemorrhagic phase; then the hemorrhagic phase; and finally, the convalescent phase.[54] Following a tick bite, the incubation period commences immediately and typically spans from 3 to 7 days.[55] The viral load injected during the bite and the exposure route determine the length of incubation.[56] If the tick feeds directly into the bloodstream, the incubation period is shorter than other transmission routes. It takes about 5 days for the infection to manifest in the blood and tissues of affected animals. Additionally, human-to-human transmission typically takes 5 to 7 days.[57] Reports indicate that in the UAE, the average duration from symptom onset to hospital presentation is 3–5 days, while in Turkey, it extends to 5-6 days. Pre-hemorrhagic infection manifests with symptoms including a fever ranging from 39 to 41°C, intense headache, dizziness, and muscle pain.[58,59] After 4– days, the fever finally goes away.[60] A new set of symptoms, including diarrhea, vomiting, and nausea, could appear in some people.[61] Throughout this phase, which lasts around 3 days, the face and neck experience hyperemia along with other body regions. Conjunctivitis and sclera congestion are often reported symptoms.[62,63] During the hemorrhagic phase, characterized by hemorrhages, the illness typically manifests between the third and fifth day, making it shorter yet more clinically significant.[64] Normally, there is no connection between a patient's fever and hemorrhages.[65] The skin and mucous

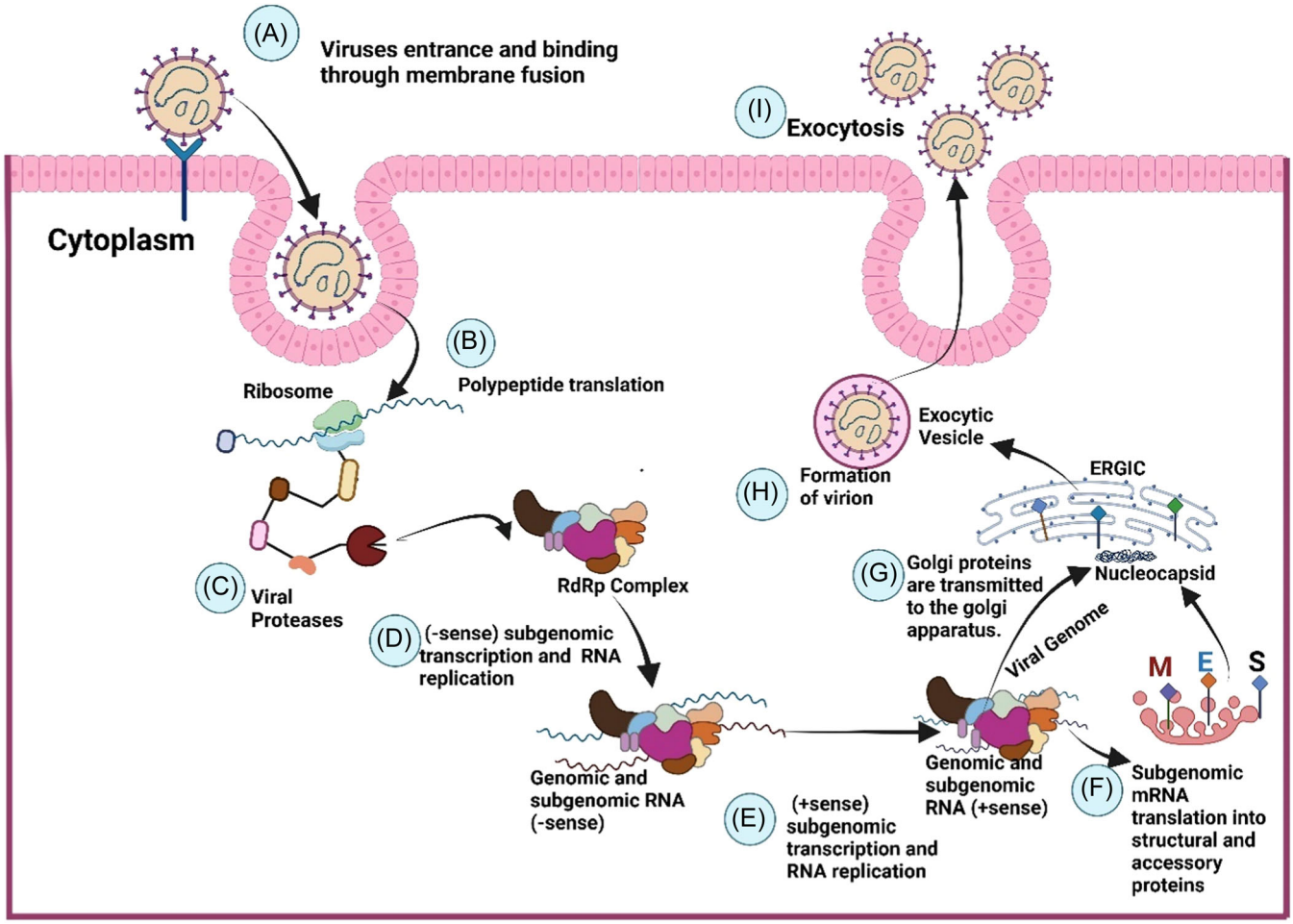

FIGURE 3 CCHF Viral Entry, Replication, and Host Response Mechanisms. [Created in Bio render].

membranes develop large hematomas.[66] In CCHF patients, the clotting time lengthens, and occasionally the blood gets so thin that it can leak through natural openings like the vagina, gingival tissues, and the nose.[67] Along with menorrhagia, which is the bleeding from the uterus, hematuria, or blood in the urine, and melena also happen.[68] During this stage, hemoptysis (bloody coughing) is also seen.[69] When the bleeding is internal only and not apparent, appendicitis may be misdiagnosed at this point.[70] The chronic pain that was initially misdiagnosed as appendix inflammation was actually caused by internal hemorrhages and bleeding in the cecum, internal oblique muscle, and external oblique muscle.[71] Although infrequently seen, hepatomegaly and splenomegaly are not always present.[72] CCHF patients who either survive this phase or pass away from severe bleeding and hemorrhages present these clinical characteristics.[73] The final stage, the recovery period, begins roughly 10 to 20 days following the illness.[74] During remission-stage CCHF, patients may experience a weak pulse, often with tachycardia, along with symptoms like partial or complete baldness, difficulty breathing, polyneuritis, dry mouth, hearing loss, memory impairment, blindness, or impaired vision.[75] Bradycardia and a reduction in blood pressure are additional symptoms that some people may experience.[76] Table 2.

7 | CHALLENGES IN DEVELOPING CCHF VACCINES AND VULNERABLE POPULATIONS

A small-scale trial of an inactivated, mouse-brain-derived vaccination against CCHF is now under place in Eastern Europe. However, there is not a human-useable vaccination that is currently safe and effective. Therefore, more investigation is required to create possible vaccines and evaluate the effectiveness of various treatment alternatives, such as ribavirin and other antiviral medications.[78] It is also very likely that laboratory workers who work with viral samples will be exposed to CCHFV.[2] A thorough analysis of CCHFV exposure in farming communities in Uganda found that livestock producers had very high CCHF seropositivity and that several regional risk variables, including consuming/collecting engorged ticks, were linked to exposures.[79] A concurrent increase in tick populations in Western Europe may help the spread of CCHFV as wild boar and deer populations grow there.[24] Vulnerable populations for CCHFV include anyone working in labs with viral samples, livestock workers, slaughterhouse employees, and animal herders in endemic areas since the virus has a high case fatality rate of (40-50%) emphasizes the importance of proper precautions and public health measures to

TABLE 2 The different phases of the disease progression.

S. No	Phase	Clinical Symptoms	Timeframe	References
1.	Incubatory Phase	Replication of the virus in the body	3 to 7 days	[54–56]
2.	Pre-hemorrhagic Phase	Fever (39°C to 41°C), headache, dizziness, muscular pain, diarrhea, vomiting, nausea	4 to 5 days	[58, 59, 61]
		Hyperemia in the face and neck, conjunctivitis	3 days	[62, 63]
3.	Hemorrhagic Phase	Hematomas and hemorrhages on the skin and mucous membranes that range in appearance from ecchymotic to petechialOozing of blood from natural orifices, hematuria, melena, menometrorrhagia, hemoptysisInternal bleeding resembling appendicitis, hepatomegaly, splenomegaly (in some cases)	3rd to 5th day	[64, 66] [67–69] [70–72]
4.	Convalescent Phase	Deafness, memory loss, blindness, weak eyesight, bradycardia, reduction in blood pressure, weak pulse, tachycardia, alopecia, dyspnea, polyneuritis, xerostomia	About 10 to 20 days after infection	[75–77]

prevent transmission and minimize the risk of infection among these high-risk populations.[80] Avoiding or reducing contact with infected ticks, employing tick repellents, and taking the necessary infection control precautions to prevent occupational exposure are all examples of prevention and control techniques.[79] To create safe and effective vaccines and treatment choices, more research is required.

7.1 | Occupational exposure and high-risk groups

Occupational exposure to CCHF poses a significant risk for certain professions, including slaughterhouse workers, veterinarians, healthcare personnel, butchers, animal breeders, and shepherds, due to their close contact with infected animals, animal products, or infected patients' secretions. In Turkey, a study conducted in the Eastern provinces revealed a CCHF infection rate of 6.94% among animal breeders, slaughterhouse workers, and veterinarians.[81] A similar survey in Turkey discovered that relatives of CCHF patients and those who work with animals have much higher rates of CCHF than persons in other groups.[82] Unprotected contact with infectious blood and body fluids also puts healthcare workers at risk of infection.[80] Additionally, contaminated medical supplies, reused needles, and insufficient cleaning of medical equipment have all been linked to reported incidents of CCHF spread within hospitals.[83] Thus, individuals in these high-risk occupational groups must take preventive measures to avoid exposure to the virus.

7.2 | Socioeconomic and environmental factors

CCHFV is a hemorrhagic fever virus that is disseminated by several environmental causes. Climatic factors that support tick survival and reproduction, as well as habitat fragmentation leading to increased human-animal contact, play crucial roles.[14] Increased CCHF risk was observed in Bulgarian areas where the illness has already spread due to rising temperatures, the normalized difference vegetation index, savannah-like cover, and habitat fragmentation.[18] The collection and consumption of engorged ticks was one of the previously unknown risk factors linked to CCHFV exposure in Uganda, underscoring the significance of additional surveillance and disease management strategies.[79] CCHF poses devastating economic impacts. Multiple risk factors, including globalization, unplanned urbanization, climate change, and socioeconomic issues, have contributed to the increase of CCHF in Sudan. CCHF occupational risks are common among those who work in agriculture, the meat industry, and veterinary medicine.[29] A population-based cross-sectional study in Turkey revealed higher CCHF seropositivity among livestock farmers, indicating the need for enhanced surveillance and control strategies.[84] Furthermore, nosocomial infection is another documented risk factor, particularly common among healthcare workers, especially during the hemorrhagic phase of the disease.[2] Vigilant surveillance and comprehensive control policies are crucial to mitigate the impact of CCHF in affected regions.

7.3 | Host genetics and immune response variability

The complexity of researching the immune response to CCHFV stems from its high contagiousness, the requirement for BSL-4 facilities, and the lack of appropriate animal models, making it not fully understood.[85,86] Research shows that T cells respond more actively to NP epitopes than to glycoproteins. NP is highly immunogenic, with antigenic epitopes distributed throughout the protein.[85] Additionally, severe illness and fatalities have been linked with low or absent antibody responses against CCHFV, and the levels of antibodies could potentially predict the outcome of the disease.[86] To understand the intricate host-viral response and viral pathogenesis in CCHF, researchers extensively investigated peripheral blood mononuclear cells from CCHF patients during both acute and convalescent phases. They employed system-wide network-based systems biology analysis alongside untargeted quantitative proteomics analysis of CCHFV-infected cells.[87] Additionally, a STAT-1 knockout mouse model was

used to study CCHFV pathogenesis and immune response, revealing the necessity of both host innate and adaptive immune responses for surviving CCHFV infection.[88] The scientific community has yet to grasp the immune response to CCHFV fully. Abundant T cell response to NP epitopes contrasts with low-to-absent anti-CCHFV antibody responses linked to severe disease. System biology analysis and mouse models have illuminated aspects of the immune response, but additional research is necessary to fully understand its complexities, particularly regarding the influence of host genetics.

8 | SURVEILLANCE STRATEGIES AND DISEASE CONTROL

WHO regional offices, collaborating centers, and laboratories coordinate national surveillance programs for CCHF in people worldwide. Additional support for surveillance comes from organizations such as FAO, WOAH, Médecins Sans Frontieres, the Wildlife Conservation Society, and academic partners. The effectiveness of human surveillance systems may vary significantly due to changes in surveillance tactics based on CCHFV prevalence in a nation, potentially leading to major gaps.[89] Since 2015, the province of Balochistan has operated an event-based surveillance system for CCHF, coordinating with WHO regional offices, cooperating centers, and laboratories as part of the global effort to monitor CCHF cases.[90] Europe, the Middle East, Asia, and Africa are among the regions where the WHO is working with partners to improve CCHF surveillance, diagnostic capability, and epidemic response operations.[91]

8.1 | Public health measures and outbreak response

Healthcare authorities should continue to prioritize and maintain robust CCHF capacity, surveillance, diagnostic, and outbreak response activities, as emphasized by the WHO.[92] A crucial element of this strategy involves implementing an early-preparedness plan with a One Health approach to prevent and manage CCHF outbreaks. Global collaboration and communication are imperative to prevent another CCHF pandemic. The WHO and international bodies are crafting research roadmaps for effective health technologies.[93] Implementing risk communication and community engagement strategies heightens awareness. Collaboration is vital for sharing knowledge and resources to enhance healthcare infrastructure and disease surveillance, particularly in CCHF-prevalent areas. This involves boosting laboratory and diagnostic capacity, enforcing infection control measures, and optimizing disease surveillance mechanisms.[94]

8.2 | Early warning systems

Surveillance systems play a vital role in preventing and managing CCHF by serving as early warning and detection systems, influencing actions, and furnishing crucial information for public health decision-making.[90] Nevertheless, there are insufficient monitoring systems for the early identification of cases and few CCHF diagnostic resources available.[94] Establishing CCHF surveillance programs is crucial to addressing this because they can evaluate possible dangers to populations of people living in endemic areas by tracking the frequency of cases, the possibility of disease transfer to humans, and the presence of surveillance systems.[89,95,96] National monitoring systems for CCHF in people are coordinated with WHO regional offices, cooperating institutions, and laboratories. Additionally, sentinel surveillance, a type of risk-based surveillance, has demonstrated some general success in predicting imminent outbreaks, making it a valuable early warning system.[97] Early warning and surveillance methods are crucial for the prevention and management of CCHF. The establishment of CCHF surveillance programs is critical in assessing potential risks to human populations in endemic areas. International surveillance efforts involve collaboration between various organizations to monitor and respond to the disease's spread effectively. Moreover, sentinel surveillance serves as a valuable tool in predicting and preparing for future outbreaks.

8.3 | Strategies for vector control and tick-borne disease prevention

Using tick repellents to avoid or reduce contact with infected ticks can help prevent and control CCHF illness.[98,99] Since there are many widespread tick vectors, the problem of CCHF transmission can only be partially resolved by using acaricides, which are substances intended to kill ticks, to control tick populations.[100] Developing CCHF virus diagnostic assays is crucial for early detection and surveillance, which is key to preventing diseases spread by ticks. Ascertain the disease's incidence in vectors and animal hosts in endemic areas to avoid and control CCHF.[101] To improve notifications and enable early warning for genetic and epidemiological alterations in the human, animal, and tick populations, a cross-sectoral “One Health” strategy for outbreak prevention is advised.[101] By avoiding or limiting contact with infected ticks by employing tick repellents, it is possible to prevent and control CCHF infection.

9 | CHALLENGES

Several issues need to be resolved about the epidemiology and transmission dynamics of CCHF. First, understanding the pathogenesis of CCHF beyond viral replication remains a significant challenge. Further research is required to uncover the precise mechanisms by which the CCHF virus causes disease, which can pave the way for the development of targeted drugs or candidate vaccines. The enzootic environment plays a crucial role in CCHF transmission, and comprehending its impact is a challenge. Investigating the intricate interactions between ticks, animal hosts, and the environment is essential to identify effective strategies for interrupting the

transmission cycle and reducing disease prevalence in specific regions. Developing antiviral drugs with higher efficacy against CCHF is another challenge. Advances in pharmacology are needed to produce drugs capable of directly killing the virus or blocking its replication pathways, thereby reducing viral load in patients. A primary cause of death in CCHF patients is diffused intravascular coagulation (DIC). Understanding how the virus induces DIC and the development of bacterial sepsis is crucial for developing targeted treatments. Exploring the use of anticoagulation factors, such as heparin and specific oxalates, may offer potential strategies to prevent DIC and manage clinical symptoms. Collaboration across various medical fields is essential. Pharmacologists, pathologists, parasitologists, microbiologists, and clinicians must work together to address the challenges of CCHF. Through their combined efforts, they may be able to fully comprehend the illness, create potent cures, and put prevention measures into action. Other challenges include implementing preventive and control measures, advancing diagnostic tools, and addressing the global burden of CCHF. By addressing these challenges, researchers and healthcare professionals can make significant strides in combating CCHF, leading to improved prevention, control, and treatment strategies for this severe tick-borne disease.

10 | FUTURE DIRECTION

The importance of adopting a sustainable One Health approach to prevent and mitigate CCHF. It advocates for concentrating efforts on surveillance, risk assessment, and risk reduction strategies targeted at tick vectors, animals, and human populations. Future research is urged to explore innovative and sustainable methods to implement this approach in CCHF-affected regions. Advances in vaccine development for CCHF are highlighted as a promising direction for future research. Ongoing clinical trials aim to identify vaccines with proven efficacy, with an emphasis on understanding the genetic diversity of the CCHF virus to develop effective vaccines. Supportive therapy for CCHF patients, particularly focusing on clotting abnormalities and transfusion of blood products or fresh frozen plasma, is underscored. Future research should continue exploring ribavirin's potential as a treatment and consider other antiviral agents or monoclonal antibodies to enhance patient outcomes. The importance of early pathogen identification and application of infection control measures is stressed, along with the need to improve surveillance systems, diagnostic capacity, and outbreak response strategies. Understanding CCHF epidemiology, including transmission risk factors and disease severity, is deemed crucial for targeted control strategies. Future research should explore the relationship between climate change and CCHF, ticks, animals, and human behavior. Effective public health education and awareness campaigns are emphasized to promote risk reduction strategies and infection control measures among the public. Lastly, the article emphasizes international collaboration in addressing CCHF, advocating for data sharing, resource exchange, and best practice dissemination among researchers, public health officials, and policymakers. Future efforts should continue fostering such collaboration to develop effective control strategies.

11 | CONCLUSION

This comprehensive analysis has shed important light on CCHF epidemiology and transmission dynamics. The CCHF is too responsible for the illness CCHFV, which poses significant challenges to public health globally. Through a comprehensive examination of the disease's characteristics, this analysis has highlighted important factors that contribute to its spread and impact. CCHF is globally spread, including endemic areas in Africa, Asia, Eastern Europe, and the Middle East, according to key results. The disease exhibits a range of case fatality rates and mortality rates, emphasizing the severity of CCHF and the need for effective control measures. The main methods of transmission are tick bites and contact with infected animal blood; person-to-person transmission is often ineffective. The genetic diversity of CCHFV, as well as segment reassortment, pose challenges to understanding the virus's evolution and developing effective vaccines. Further research is required to elucidate the host and viral determinants of pathogenesis, which can aid in the development of targeted therapeutic strategies and improved diagnostic tools. Addressing the epidemiology and transmission dynamics of CCHF requires a multidisciplinary approach. By focusing on surveillance, implementing vector control measures, improving diagnostics, strengthening healthcare systems, and raising public awareness, we can mitigate the impact of CCHF. These efforts will contribute to early detection, timely treatment, and effective prevention of the disease. This critical review concludes by emphasizing the significance of comprehending the epidemiology and dynamics of CCHF transmission for efficient management and control. Continued research, collaboration, and implementation of preventive measures are necessary to combat this severe tick-borne disease and safeguard public health.

AUTHOR CONTRIBUTIONS

Shriyansh Srivastava: Conceptualization; Writing—original draft; Writing—review and editing. **Sachin Kumar**: Conceptualization; Writing—original draft. **Pramod Kumar Sharma**: Conceptualization; Writing—original draft. **Sarvesh Rustagi**: Writing—original draft; Writing—review and editing. **Aroop Mohanty**: Writing—review and editing. **Suzanne Donovan**: Writing—review and editing. **Andres F. Henao-Martinez**: Writing—review and editing. **Ranjit Sah**: Writing—review and editing; Conceptualization; Methodology; Writing—original draft. **Carlos Franco-Paredes**: Writing—review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ETHICAL STATEMENT

Not applicable

TRANSPARENCY STATEMENT

The lead author Shriyansh Srivastava, Ranjit Sah affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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