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NARRATIVE REVIEW

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The current pathogenicity and potential risk evaluation of Crimean-Congo hemorrhagic fever virus to cause mysterious "Disease X"—An updated literature review

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Abstract

Background and Aims: Crimean-Congo hemorrhagic fever (CCHF) is a severe and potentially lethal illness. Tick bites of the Hyalomma genus are the primary source of transmission of CCHF to humans. The virus responsible for CCHF is the CCHF virus (CCHFV). It is a single-stranded negative sensed RNA virus. The virus belongs to the Orthonairoviridae genus within the Nairoviridae family. It occurs in an extensive geographical area spanning the Middle East, western China, southern Asia, southeastern Europe, and much of Africa. The current study aimed to evaluate the pathogenicity and potential risk of CCHFV to cause a public health emergency of international concern.

Methods: We searched updated relevant information from PubMed, Google Scholar, and Scopus databases using Crimean-Congo hemorrhagic fever, tick-borne virus, and Nairovirus as keywords.

Results: The case fatality rate (CFR) varies by region. It can be more than 30% in some cases. Three segments in the genome of CCHFV (L, M, and S) are different in size and function. It is unknown whether the pathogenicity of CCHFV varied based on the genomic diversity. CCHFV can be transmitted through tick bites, handling of infected ticks, contact with infected humans, contaminated body fluids, and so on. A wide range of severity is associated with CCHF, ranging from a moderate fever with no apparent cause to increased vascular permeability, failure of several organs, bleeding, and shock. Hospitals with high-level isolation units should be the first choice for treating CCHF patients. Individual safety equipment is crucial in healthcare to prevent the spread of the virus. In the farm environment, using integrated pest management techniques, minimizing activity in tick-infested regions, and dressing appropriately in long sleeves and pants will help to reduce the risk of CCHFV infection via tick bites.

Conclusion: There are no approved vaccinations or therapeutics for CCHF except supportive therapeutic approaches. Therefore, scientists recommend early ribavirin therapy for cases of high-risk exposures.

KEYWORDS
Disease X, Crimean-Congo hemorrhagic fever, hemorrhagic fever, tick-borne virus, Nairovirus, Bunyaviridae

1 | BACKGROUND

The impact of unexpected infectious disease epidemics has often shaken the confidence of the medical world and caused widespread panic and loss of life.[1] For instance, the recent COVID-19 caused by SARS-CoV-2 has reached pandemic proportions. By the end of February 2021, COVID-19 has claimed the lives of around 2.5 million individuals globally.[2] The World Health Organization (WHO) claims that numerous prioritized illnesses have the potential to become epidemics for which there are insufficient or no medicinal interventions. In that category of illnesses, Disease X is occupying a place along with Crimean-Congo hemorrhagic fever (CCHF), Ebola, Zika, and COVID-19. The WHO stated that pathogen X is responsible for causing Disease X. An epidemic or pandemic outbreak in the future might be induced by pathogen X.[3] The pathogen under investigation is anticipated to be a zoonosis, most probably an RNA virus that originates from a region where a particular set of causative determinant markedly raises the possibility for persistent transmission.[4] Although some writers have referred to Zika as a Disease X, other specialists have stated that COVID-19 meets the criteria to be designated the first Disease X.[5,6] The CEO of the Coalition for Epidemic Preparedness Innovations (CEPI), Richard Hatchett, stated that although Disease X may seem like science fiction, we still need to be ready for it.[4] The growing human population, biodiversity loss, climate change, aggressive land use for agriculture, human habitation, and other factors that contribute to the expanding interfaces between humans, animals, and the environment increase the possibility of these developing threats.[2]

2 | EPIDEMIOLOGY OF CCHF

CCHF is a severe and potentially fatal disease transmitted to humans through tick bites. We see the CCHF virus (CCHFV) in a wide geographical area from western China to southern Asia, the Middle East, southeastern Europe, and much of Africa. Ticks of the genus *Hyalomma* (*Hyalomma marginatum*, *Hyalomma anatolicum*, *Hyalomma truncatum*, *Hyalomma impeltatum*, and *Hyalomma impressum*)[7] are stated to be the principal source of CCHFV transmission, probably because to fulfill their obligation to consume blood, ticks from both young and mature stages rapidly search for hosts. The widespread occurrence of the CCHF virus in both ticks and other animals around southeastern Europe, Africa, and southern Asia suggests that human infections have been occurring for thousands of years, even though several narratives about CCHF depict it as a disease that has only just emerged. The initial record of CCHF dates back to the 12th century in Tajikistan.[8] In 1944, CCHF was identified as a distinct human sickness in the previously known Soviet Union, specifically on the Crimean Peninsula; however, the virus was not isolated until 1956, when it was discovered in a patient who was feverish in Belgian Congo. The viruses were initially identified as "Crimean hemorrhagic fever virus" and "Congo virus," and scientists thought of them as two separate organisms. As the two viruses eventually showed no differences the term "Crimean-Congo hemorrhagic fever" was adopted.[7]

Since 2000, there has been a noticeable increase in both the occurrence and geographical representation of verified incidents of CCHF, with new cases being recorded in Iran, Turkey, Greece, India, the Republic of Georgia, and other Balkan countries. Surprisingly, in the ensuing 10 years since the initial CCHF cases in Turkey that were discovered in 2002, approximately 6300 instances were documented. There has also been a significant increase in CCHF cases in Iran after the initial human infection occurred in 1999.[9] Occasional incidents of CCHF have been recorded in Iraq. According to data from the Iraqi Ministry of Health, CCHF cases have significantly increased in the past 2 years, with 19 laboratory-confirmed CCHF cases in 2021 and 108 laboratory-confirmed CCHF cases in the initial half of 2022.[10] Nonetheless, in recent years, outbreaks have been less frequent throughout Africa. The CCHF is indigenous throughout Africa, and its case fatality rate (CFR) is 40%. A few weeks before COVID-19 made its way to Africa, on February 2, 2020, in Mali, 14 cases of CCHF were documented with seven fatalities. The authority of Mauritania reported a case of CCHFV-infected 60-year-old patient on May 2, 2020.[11]

3 | MUTATIONAL HISTORY OF VIRUS

The CCHFV is a single-stranded RNA virus that is negative (−) sensed. It is categorized as the Orthonairoviridae genus within the Nairoviridae family. The genome of CCHFV consists of three segments that are different in both size and function called large (L), medium (M), and small (S), which encode for the L RNA-dependent RNA polymerase, the glycoprotein precursor (GPC), and the nucleoprotein (NP), respectively.[7] CCHFV strains are categorized into seven genetic lineages (Africa 1, Africa 2, Africa 3, Asia 1, Asia 2, Europe 1, and Europe 2) and show significant variation at the sequence levels of RNA and protein. The illness is often transmitted by ticks of the Hyalomma genus. All lineages Africa 1, Africa 2, Africa 3, Asia 1, Asia 2, and Europe 1 are reported to cause serious illness in humans except Europe 2. On the other hand, the Europe 2 lineage is a genetic anomaly because it is not linked to any serious illness. It is currently unknown if the pathogenicity of the CCHF virus varied with its genomic diversity. Although experts are unsure of the precise

alterations that make the CCHF virus more or less lethal, they believe that genetic variations across viral strains may be the cause of the variations in mortality rates. In one study a variation in the strain of Europe 2 lineage was found in one investigation. Its genome was sequenced after it was extracted from Bulgarian ticks carrying the CCHF virus. The name Malko Tarnovo was adopted for the virus strain. The virus's ability to infect human cells appears to be reduced by a single amino acid alteration in its genomic sequence. The mutation stops a surface protein of the virus from combining with human cells which is a necessary stage of infection.[12]

4 | VIRAL TRANSMISSION AND SPREAD

Researchers have delineated the main characteristics of the causative agent's circulation among ticks and a category of small and big animal species in the roughly seven decades since CCHF was identified as a human illness.[8] Due to their ability to spread several illnesses, ticks are of great medical importance. Ticks are called hematophagous arthropods because they consume blood. Despite the possibility that other tick species contribute to the persistence of CCHFV in endemic areas, studies have shown that ticks belonging to the Hyalomma genus serve as the primary source and repository of the virus.[13] The distribution of outbreaks is strongly correlated with environmental aspects, for instance, elevated humidity and favorable temperature (around 28°C). Because the tick's proliferation is encouraged by these climatic variables,.[7] There are several ways that CCHFV may infect human hosts, including tick bites, handling of infected ticks, and contact with viremic human and animal body fluids and tissues by percutaneous method. As a result, people who participate in outdoor activities or have direct interactions with livestock are at increased risk of exposure. Healthcare professionals and close family members who are involved in inpatient treatment are in danger of exposure due to reports of nosocomial and intra-family transmission by needle sticks or contact with patient blood and secretions.[14] Routes of human transmission were determined according to patient exposure records and the identification of CCHFV antibodies in blood samples from endemic communities.[8]

5 | DISEASE PATHOGENESIS

During the Crimean Epidemic in 1944, patients who were hospitalized displayed various symptoms that included an unexpected rise in temperature, accompanied by headache and weakness, muscular pain, as well as vomiting. Also, we see severe hyperemia of the oropharynx and face, gastrointestinal tract bleeding, bleeding from the nasopharynx and other parts of the body, and a hemorrhagic rash with the formation of ecchymoses among the infected individuals.[8] Initial signs of CCHF include fever with generalized malaise. These may progress to more severe symptoms, for instance, bleeding from the gastrointestinal tract, urinary tract, and respiratory tract, which frequently result in death.[7] The clinical presentation of CCHF is categorized by four successive phases of illness, defined as incubation, prehemorrhagic, hemorrhagic, and convalescence. Incubation time depends on the viral dosage and exposure route and is often less than a week. The symptoms of the prehemorrhagic stage include fever (39–41°C), dizziness, headache, myalgia, stiffness and discomfort in the neck, backache, sore eyes, and photophobia. The hemorrhagic phase can last up to 2 weeks, although it generally lasts just 2 to 3 days. Death occurs as a result of fatal circumstances such as shock, multiple organ failure, and hemorrhagic conditions. It is also possible to experience cerebral hemorrhage, bleeding from the stomach and vagina.[15] In survivors, convalescence usually starts in 9–10 days following the onset of the disease (range 9–20 days).[14]

Due to the frequent low number of reported cases of outbreaks and the deficiency of diagnostic skills, the case fatality ratio of CCHF fluctuates, making it challenging to guarantee that all individuals with benign illnesses were identified and incorporated in the denominators. Around the last 10 years, Turkey has had around 6000 cases; the average CFR for these cases is roughly 5%, indicating that prior outbreaks' higher reported rates may have resulted from a failure to identify less severe diseases.[8] Massive bleeding, thrombocytopenia, and fulminant hepatitis are causes of mortality. The CFR of CCHFV varies, and some regions reported more than 30%.[16] With a 40% CFR, CCHF is prevalent throughout Africa.[11] However, in Iraq, the CFR of CCHF was 16.4% in 2022.[10]

6 | THERAPEUTIC AND PREVENTIVE MEASURES

The CCHFV is classified as a biosafety category IV pathogen that is viable and capable of creating nosocomial epidemics with an elevated death ratio.[16] Majorities of CCHFV infections have no symptoms or cause a nonspecific fever that does not require to be admitted to the hospital. The majority of current medical care is supportive for a relatively limited proportion of patients who experience low blood pressure and bleeding. Increased vascular permeability causes reductions in organ perfusion and blood pressure, which requires close supervision to avoid the onset of pulmonary swelling and volume replacement, typically with intravenous fluids.[8] To avoid hematomas and localized bleeding at punctured sites, drugs should not be injected intramuscularly.[16] Transfusions of blood are necessary in the event of severe bleeding; however, coagulation disorders can be treated with fresh frozen plasma and platelets.[8] Only supportive therapy is necessary due to the lack of a successful specialized etiological treatment. However, nonsteroidal anti-inflammatory medicines should be avoided because of their probable effects on coagulation.[17]

In the most severe instances, high-dose ribavirin is advised, even though its usage is debatable because no trials have shown it to be effective. It is an analog of guanosine and a synthetic antiviral. It has a broad spectrum of antiviral action against DNA and RNA viruses. Additional therapies, such as hyperimmune serum from recovering patients, showed promising outcomes, particularly in patient groups

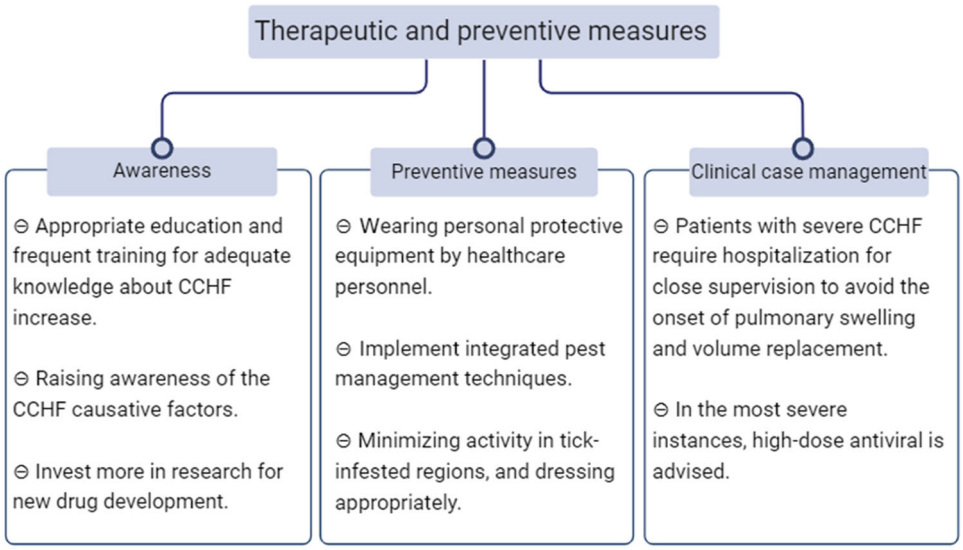

FIGURE 1 Key preventive measures against Crimean-Congo hemorrhagic fever (CCHF).

with extremely high virus loads, where 90% of sick patients survived. Recommendations for their routine usage are hampered due to their inadequate medical experiments and observational studies with a control group.[16] Numerous risk factors for CCHFV exposure must be addressed to prevent CCHFV infection. For farmers, this means using integrated pest management techniques, minimizing activity in tick-infested regions, and dressing appropriately in long sleeves and pants. Additionally, appropriate education and frequent training in wearing and removing personal protective equipment should be provided to healthcare personnel. Raising awareness of the CCHF causative factors (like tick bites and occupational hazards) through educational programs may encourage those who are already at risk to lower their exposure risk and identify and report any early signs of CCHF.[14] Moreover, no vaccination is safe or effective in people. Conducting clinical studies is challenging since the infrequent outbreaks have variable numbers of patients.[18] We presented our recommendations for awareness, preventive, and therapeutic measures in Figure 1.

7 | RISK EVALUATION OF CCHFV TO CAUSE GLOBAL PANDEMICS

Arboviral infections are becoming a greater global concern to public health and are spreading geographically. Most arboviral infections are zoonotic, mostly spread throughout populations of humans and animals. Arboviral infections have developed through several spillover and spillback events to constantly increase their host range. Arboviral epidemics are becoming more likely on a worldwide scale. CCHF is a zoonotic illness that affects not only humans but also animals. Although it seldom causes illness in animals, 40% of CFR and a significant proportion of asymptomatic infections make it potentially lethal in humans.[19] According to the WHO, vector bionomics and climate change may be contributing factors to the high incidence of CCHF, making it one of the most contagious illnesses worldwide. Additionally, they stated that throughout the world most viral hemorrhagic fever outbreaks are caused by CCHFV.[20] It is also regarded as a developing arboviral zoonotic disease in numerous regions. In the WHO's Eastern Mediterranean Region, the incidence of CCHF has recently increased rapidly, and outbreaks and sporadic human cases have been reported from several countries in the region.[21] The incidence of diseases in Sudan is increasingly spreading beyond its original endemic region of Central Sudan, resulting in a wider geographical distribution.[22] Similarly, Iran has experienced a significant surge in CCHF cases after the first human infection was discovered in 1999.[8] CCHF cases surged in Iraq from 33 in 2021 to 511 by August 2023.[23] Due to its high death rates, CCHF was formerly categorized as a category C illness. Ticks are the primary vectors of CCHFV transmission, can spread to new areas, and become endemic due to the variety of animals they feed on. The virus may continue to be a persistent hazard in the future if globalization keeps growing and climate change keeps changing disease patterns. The virus is highly contagious and virulent and can be easily cultivated and spread, making it a possible bioterrorism agent.[7]

8 | CONCLUSION

CCHF is a severe transmissible illness with a 30% or higher CFR and a wide geographical distribution. Incubation, prehemorrhagic, hemorrhagic, and convalescence are the four successive phases of the disease that describe the clinical presentation of CCHF. Implementing preventative actions for at- risk populations in endemic locations is necessary to prevent the spread of CCHFV. These include education, reducing tick contact, treating livestock to minimize the infestation of ticks, quarantining animals, and providing protection from activities with elevated hazard exposure. Currently, no specific antivirals or

vaccines are available for CCHFV. Therefore, preventive and control measures for CCHFV are vital. Also, the most often prescribed medication for CCHF is ribavirin for high-risk populations during the early stages of exposure.

AUTHOR CONTRIBUTIONS

Sanjida Jannath: Conceptualization; data curation; writing—original draft. **Md. Rabiul Islam**: Conceptualization; supervision; visualization; writing—review and editing.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

TRANSPARENCY STATEMENT

The lead author Md. Rabiul Islam 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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