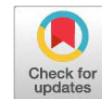


Mini Review



Crimean-Congo Hemorrhagic Fever (CCHF): A Comprehensive Review of Virology, Epidemiology, Pathogenesis, Clinical Features, Diagnosis, and Management

Md. Rimon Bhuiyan^{1,2*}

¹Department of Veterinary & Animal Sciences, University of Rajshahi, Rajshahi-6205, Bangladesh; ²Faculty of Veterinary & Animal Sciences, University of Rajshahi, Rajshahi-6205, Bangladesh.

Abstract | Crimean-Congo hemorrhagic fever (CCHF) is a severe tick-borne zoonotic disease caused by Crimean-Congo hemorrhagic fever virus (CCHFV) and remains a major public health concern across Africa, Asia, the Middle East, and parts of Europe. Its geographic distribution continues to expand because of climate change, ecological alterations, and increasing human–animal interactions. This review examines the current understanding of CCHFV virology, molecular biology, epidemiology, pathogenesis, clinical manifestations, laboratory diagnosis, treatment, prevention, and emerging research directions, with particular emphasis on translating virological and epidemiological knowledge into clinical diagnosis and patient management. CCHFV is maintained primarily through a *Hyalomma* tick–vertebrate transmission cycle and can cause illness ranging from a nonspecific febrile syndrome to severe hemorrhagic disease with high case fatality rates. Disease severity is closely associated with high viral load, dysregulated host immune responses, endothelial injury, and coagulation abnormalities. Real-time reverse transcription polymerase chain reaction (RT-PCR) remains the preferred diagnostic method during the acute phase of infection, whereas serological assays are most useful during later stages of disease. Clinical management is largely supportive, and the therapeutic benefit of ribavirin remains uncertain because high-quality randomized clinical trial evidence is limited. Although several vaccine platforms and antiviral candidates are under development, none has yet achieved universal clinical use. Continued investment in surveillance, rapid diagnostics, vaccine and therapeutic development, and integrated One Health strategies will be essential for reducing the global burden of CCHF and strengthening preparedness against future outbreaks.

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***Correspondence** | Md. Rimon Bhuiyan, Department of Veterinary & Animal Sciences, University of Rajshahi, Rajshahi-6205, Bangladesh;

Email: mdrimonbhuiyan1999@gmail.com, s1911168127@ru.ac.bd

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INTRODUCTION

Crimean-Congo hemorrhagic fever (CCHF) is one of the most geographically widespread tick-borne viral diseases affecting humans and carries one of the highest case-fatality rates among viral hemorrhagic fevers (Ergönül, 2006). First described in the Crimean Peninsula in 1944 during a military campaign and subsequently linked to a virus isolated in Congo in 1956, CCHF is now recognised as a significant global public health threat with an expanding geographic footprint (Whitehouse, 2004; Hoogstraal, 1979). The causative agent, CCHF virus (CCHFV), is a tri-segmented, negative-sense RNA virus maintained in nature primarily through a tick-vertebrate-tick transmission cycle involving *Hyalomma* species ticks (Flick and Whitehouse, 2005; Papa *et al.*, 2015).

The disease is endemic in Africa, Asia, Eastern Europe, and the Middle East, and has recently emerged in Western Europe, underscoring the risk of geographic spread driven by climate change, globalisation, and changes in tick and host ecology (Mertens *et al.*, 2013; Spengler, Bergeron and Spiropoulou, 2019; Portillo *et al.*, 2021). In humans, CCHFV causes a severe febrile illness that progresses to a haemorrhagic phase characterised by coagulopathy, multi-organ dysfunction, and high mortality (Swanepoel *et al.*, 1989; Shayan *et al.*, 2015). Healthcare workers are at particularly elevated risk owing to nosocomial transmission through exposure to infected body fluids (Smego, Sarwari and Siddiqui, 2004).

Despite decades of research, no universally licensed vaccine or antiviral therapy exists for CCHF (Keshtkar-Jahromi *et al.*, 2011). Ribavirin, an antiviral nucleoside analogue, is widely employed but evidence from randomised controlled trials remains lacking (Ergönül, 2006). The purpose of this comprehensive review is to provide a consolidated and updated account of the virology, epidemiology, pathogenesis, clinical presentation, diagnosis, and management of CCHF, integrating findings from a broad body of published literature. The aim of this review is to provide a mechanistically integrated, rather than purely descriptive, synthesis of CCHFV virology, epidemiology, pathogenesis, clinical features, diagnosis, and management, with the explicit objective of showing how molecular and epidemiological knowledge can be translated into improved clinical recognition, diagnosis, and patient management of

CCHF.

This review is deliberately organised around a single unifying narrative: that the molecular biology and pathogenesis of CCHFV directly determine, and should directly inform, how the disease is recognised, diagnosed, and managed. Accordingly, the specific objectives of this review are to (i) summarise current understanding of CCHFV virology and molecular pathogenesis, (ii) describe the epidemiological drivers that determine where and when human disease occurs, (iii) link these virological and epidemiological features mechanistically to clinical presentation and outcome, and (iv) critically evaluate the diagnostic and therapeutic tools available for translating this knowledge into patient care. Rather than treating virology, epidemiology, pathogenesis, clinical features, diagnosis, and management as independent topics, each subsequent section is written to build explicitly on the one preceding it, and areas of scientific controversy, methodological limitation, and unresolved research priority are highlighted throughout the review rather than confined to a single section.

Virology and molecular biology

Taxonomy and classification

Because the clinical and public health significance of CCHF ultimately stems from the molecular properties of its causative agent, this review begins with the virus itself. Crimean-Congo hemorrhagic fever virus (CCHFV) belongs to the species *Orthonairovirus* haemorrhagiae, genus *Orthonairovirus*, family *Nairoviridae*, and order *Bunyavirales* (Hawman and Feldmann, 2023; Kuhn *et al.*, 2024). The virus possesses a tri-segmented, negative-sense, single-stranded RNA genome consisting of three segments: small (S), medium (M), and large (L) (Morikawa, Saijo and Kurane, 2007; Deyde *et al.*, 2006). The S segment encodes the nucleocapsid (N) protein, the M segment encodes the surface glycoproteins (Gn and Gc), and the L segment encodes the RNA-dependent RNA polymerase (Flick and Whitehouse, 2005).

Genomic organisation and glycoproteins

The S segment encodes the nucleocapsid (N) protein, which encapsidates the viral genomic RNA to form ribonucleoprotein (RNP) complexes essential for viral replication and transcription (Morikawa, Saijo and Kurane, 2007). Beyond its structural scaffold role, the N protein actively interacts with host factors and plays a key role in modulating cellular immune responses

(Zivcec *et al.*, 2016).

The M segment of CCHFV encodes a large polyprotein that is co- and post-translationally cleaved to generate the two envelope glycoproteins, Gn and Gc (Sanchez, Vincent and Nichol, 2002). These glycoproteins are critical for viral entry into host cells and are primary targets of the host humoral immune response (Shepherd, Swanepoel and Leman, 1989). The unique mucin-like domain and GP38 fragment, derived from M-segment processing, distinguish CCHFV from other nairoviruses; while GP38 functions primarily as a molecular chaperone for PreGn maturation and trafficking, the mucin-like domain is implicated in immune evasion (Zivcec *et al.*, 2016).

The L segment encodes a large RNA-dependent RNA polymerase (RdRp) responsible for viral genome replication and transcription. Within the L protein, the N-terminal ovarian tumour (OTU) domain functions as a deubiquitinase and deISGylase, enabling CCHFV to suppress host innate immune signalling and evade type I interferon responses- a critical factor contributing to viral pathogenesis and virulence (Frias-Staheli *et al.*, 2007; Zivcec *et al.*, 2016) (Figure 1).

Genetic diversity and phylogenetics

CCHFV exhibits remarkable genetic diversity and can be grouped into at least nine distinct lineages (clades I–IX), which largely correspond to geographic origin

(Deyde *et al.*, 2006; Carroll *et al.*, 2010; WOA, 2024). Phylogenetic analyses demonstrate that reassortment events between different genome segments contribute significantly to CCHFV evolution and the emergence of genetically novel variants (Hewson *et al.*, 2004; Anagnostou and Papa, 2009). The highest genetic diversity is observed in African isolates, consistent with the ancient evolutionary origin of the virus on the African continent (Carroll *et al.*, 2010).

Furthermore, the geographic clustering and long-distance dispersal of CCHFV lineages are strongly influenced by tick vector distribution and migratory bird flyways (Mild *et al.*, 2010). Although most avian species are generally refractory to CCHFV infection and do not develop systemic viremia, migratory birds serve as long-distance transport hosts for CCHFV-infected ticks (e.g., *Hyalomma* spp.), facilitating the introduction and spread of novel viral genotypes into distant, non-endemic regions (Lindeborg *et al.*, 2012; Leblebicioglu *et al.*, 2014).

Epidemiology and global distribution

Global burden and geographic range

Building directly on the tick-vertebrate-tick maintenance cycle described above, this section examines the epidemiological factors that determine the geographic and temporal distribution of human CCHF cases. CCHF is the most geographically widespread tick-borne viral disease in the world (Ergönül, 2006). Messina *et al.* (2015) mapped the

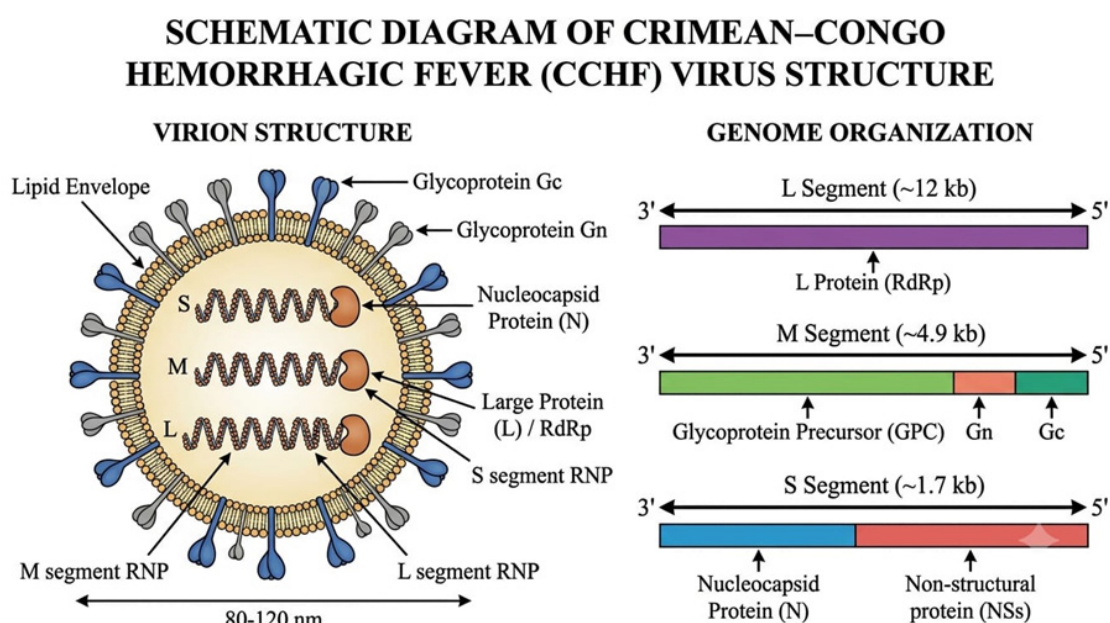


Figure 1: A schematic diagram of the CCHFV structure.

global distribution of CCHF and estimated that approximately 13 million km² of land across more than 50 countries falls within the geographic risk area of the disease. The endemic range spans sub-Saharan Africa, Central Asia, the Middle East, the Balkans, the Indian subcontinent, and parts of China. Recent decades have witnessed an expansion into Western Europe, with autochthonous cases confirmed in Spain and sero-evidence detected in tick populations in Portugal and France (Negredo *et al.*, 2017; Estrada-Peña *et al.*, 2012) (Figure 2).

Epidemiology in europe

Turkey represents the largest single-country burden of CCHF in Europe, reporting thousands of confirmed cases since the disease re-emerged in 2002 (Karti *et al.*, 2004; Yilmaz *et al.*, 2009). Vatansever *et al.* (2007) documented that the proliferation of *Hyalomma marginatum* ticks in Turkey, associated with changes in land use, livestock farming practices, and climate, has driven the explosive increase in cases. Leblebicioglu *et al.* (2016) identified significant seasonal clustering of cases between April and September, coinciding with peak tick activity.

In the Balkans, CCHF is endemic in Bulgaria, Kosovo, and Albania (Papa *et al.*, 2002; Papa *et al.*, 2004; Drosten *et al.*, 2002). The first autochthonous CCHF case in Western Europe was confirmed in Spain in 2016, representing a landmark in the westward expansion of the disease (Negredo *et al.*,

2017). CCHFV-infected ticks had been detected in southwestern Spain since at least 2010 (Estrada-Peña *et al.*, 2012), and a subsequent survey confirmed an established enzootic focus spanning multiple Spanish provinces (Negredo *et al.*, 2019). Portillo *et al.* (2021) discussed future scenarios for CCHF emergence in Western Europe, noting that changing climatic conditions are likely to expand the range of *Hyalomma* ticks northward (Portillo *et al.*, 2021).

Epidemiology in africa

Africa hosts the greatest genetic diversity of CCHFV and is considered the ancestral home of the virus (Carroll *et al.*, 2010). However, human cases in Africa have historically been underreported due to limited surveillance and diagnostic capacity. South Africa and Mauritania have the longest documented histories of CCHF in the continent (Swanepoel *et al.*, 1983; Nabeth *et al.*, 2004a). Dunster *et al.* (2002) described the first documented human case in Kenya, while Nabeth *et al.* (2004b) confirmed human CCHF in Senegal. Temur *et al.* (2021) demonstrated that CCHF in Africa has been significantly underestimated for decades, with modelling suggesting far greater transmission than official case counts indicate.

Epidemiology in the middle east and central asia

Iran is among the most affected countries in the Middle East, with multiple endemic foci identified across its provinces (Chinikar *et al.*, 2010; Keshtkar-Jahromi *et al.*, 2013; Chinikar *et al.*, 2009).

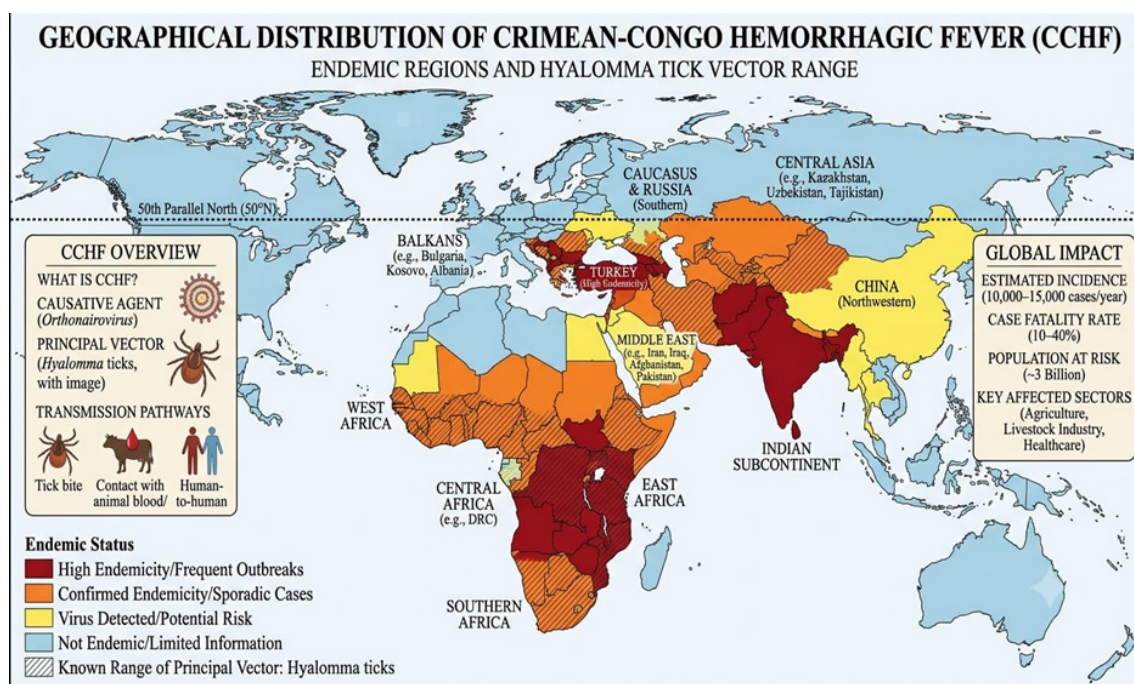


Figure 2: A world map showing the geographical distribution/endemic regions of CCHFV.

Mardani and Keshkar (2007) reviewed the Iranian CCHF experience and noted high case fatality rates in hospitalised patients. The disease is also endemic in Pakistan, Afghanistan, Iraq, the United Arab Emirates, and neighbouring states (Vorou, Pierroustakos and Maltezou, 2007; Appannanavar and Mishra, 2011). Across Central Asian republics of the former Soviet Union, CCHFV is maintained in large livestock populations managed in close proximity to *Hyalomma* tick-infested pastures (Watts *et al.*, 2019).

Transmission routes

The principal route of transmission to humans is through the bite of infected ticks, predominantly *Hyalomma* species, which serve as both the reservoir and the vector of CCHFV (Papa *et al.*, 2017; Hoogstraal, 1979). Occupational exposure during slaughter and processing of viremic livestock- particularly cattle, sheep, and goats- represents an important secondary route, as slaughterhouse workers can acquire infection through contact with animal blood and tissues (Spengler *et al.*, 2016). Nosocomial transmission through contact with infected blood, secretions, and bodily fluids has been responsible for numerous healthcare-associated outbreaks worldwide (Smego, Sarwari and Siddiqui, 2004). Spengler *et al.* (2018) further summarised additional emerging evidence of airborne droplet transmission in specific nosocomial settings (Spengler *et al.*, 2018).

Critical appraisal: Surveillance gaps and underestimation of burden

A critical limitation of the epidemiological literature is the substantial discrepancy between modelled estimates of geographic risk and the number of cases actually reported. Messina *et al.* (2015) estimated that approximately 13 million km² across more than 50 countries lies within the CCHF risk area, yet reported case numbers from large parts of this area, particularly sub-Saharan Africa, remain very low. Temur *et al.* (2021) and Ince *et al.* (2014) attribute this discrepancy chiefly to weak surveillance and diagnostic capacity rather than genuinely low transmission, implying that the true burden of CCHF in Africa and parts of Asia is substantially underestimated. This mismatch between modelled and reported burden is a recurring and unresolved problem in the CCHF literature: it limits the comparability of case-fatality and incidence figures across regions, and it represents a clear research gap, namely the need for standardised, prospective, population-based surveillance in under-resourced

endemic settings rather than continued reliance on retrospective case series or passive reporting systems such as ProMED.

Pathogenesis

Viral entry and immune evasion

The geographic and occupational exposure patterns described above translate into disease only once CCHFV establishes infection in the human host; the mechanisms by which it does so, and the reasons some infections progress to severe disease, are considered next. Following entry into the host, CCHFV primarily infects monocytes, macrophages, dendritic cells, and hepatocytes (Akıncı *et al.*, 2013). The virus replicates rapidly in these cells, generating a high viral load that correlates strongly with disease severity and outcome (Duh *et al.*, 2007; Çevik *et al.*, 2007). CCHFV suppresses the type I interferon (IFN) response through multiple mechanisms, including the OTU deubiquitinase activity of the L protein, which disrupts ubiquitin-dependent innate immune signalling pathways (Morikawa, Saijo and Kurane, 2007; Zivcec *et al.*, 2016).

Cytokine storm and endothelial dysfunction

A hallmark of severe CCHF is a dysregulated and exaggerated cytokine response- commonly referred to as a cytokine storm- which contributes significantly to vascular injury, coagulopathy, and multi-organ failure (Papa *et al.*, 2006). Papa *et al.* (2006) demonstrated markedly elevated serum levels of TNF- α , IL-6, IL-10, and IFN- γ in fatal versus non-fatal CCHF cases, highlighting the immunopathological nature of severe disease (Papa *et al.*, 2006). Connolly-Andersen *et al.* (2011) demonstrated in vitro that CCHFV directly activates endothelial cells, inducing expression of adhesion molecules and pro-inflammatory mediators, contributing to vascular permeability and the haemorrhagic diathesis characteristic of severe disease (Connolly-Andersen *et al.*, 2011).

Coagulopathy and haemorrhagic diathesis

Disseminated intravascular coagulation (DIC) is a central feature of severe CCHF and results from the interplay of direct viral endothelial injury, hepatocyte destruction causing impaired synthesis of coagulation factors, and platelet consumption (Swanepoel *et al.*, 1989; Akıncı *et al.*, 2013). Thrombocytopenia, prolonged prothrombin time, elevated D-dimer, and decreased fibrinogen are consistent laboratory hallmarks of this coagulopathic state (Çevik *et*

al., 2008). Karanam *et al.* (2025) provided an updated mechanistic account of CCHFV-mediated coagulopathy, emphasising the role of hepatic injury as an amplifier of haemorrhagic manifestations (Karanam *et al.*, 2025). Hawman and Feldmann (2018) further highlighted the role of platelet-activating factor and thrombin generation in sustaining the haemorrhagic cycle (Hawman and Feldmann, 2018).

Controversy: Direct viral injury versus immune-mediated pathology

The relative contribution of direct viral cytopathic injury versus dysregulated host immune responses to severe CCHF outcome remains a genuine point of scientific disagreement rather than settled fact. Duh *et al.* (2007) and Çevik *et al.* (2007) found that viral load on admission was the strongest single predictor of mortality, favouring a model in which disease severity is driven primarily by the extent of viral replication. In contrast, Papa *et al.* (2006) and Connolly-Andersen *et al.* (2011) demonstrated that markedly elevated pro-inflammatory cytokines and direct endothelial activation, independent of measured viral load, correlate with fatal outcome, supporting an immune-mediated model of pathogenesis analogous to the cytokine storm described in other viral haemorrhagic fevers. These two explanatory frameworks are not mutually exclusive, but the literature has rarely attempted to reconcile them within a single cohort using both quantitative viral load and cytokine profiling, and this remains an important research gap that limits the design of targeted host-directed therapies.

Clinical features

Clinical phases

The pathogenic events described above, namely high viral replication, cytokine dysregulation, and coagulopathy, are directly reflected in the clinical phases and severity patterns observed in patients, described below. The clinical course of CCHF has been classically divided into four phases: incubation, pre-hemorrhagic, hemorrhagic, and convalescence (Ergonul, 2007; Shayan *et al.*, 2015). The incubation period ranges from 1 to 13 days following tick bite (typically 1–3 days) or 5–6 days following exposure to infected blood or tissues (Swanepoel *et al.*, 1987). The pre-hemorrhagic phase (days 1–3) is characterised by the abrupt onset of fever, chills, severe headache, myalgia, and malaise. Nausea, vomiting, abdominal pain, and diarrhoea are also common. Flushing of the

face and neck, conjunctival injection, and petechiae on the palate are characteristic early findings (Vorou, Pierroutsakos and Maltezos, 2007).

The hemorrhagic phase (days 3–6) is the most severe stage and encompasses ecchymoses, petechiae, purpura, and frank bleeding from multiple sites including the gastrointestinal tract, nose, gingiva, and venepuncture sites (Ergonul, 2007; Öncü, 2013). Hepatomegaly, splenomegaly, and signs of hepatitis are frequently observed. Death, when it occurs, typically results from multi-organ failure during or shortly after the hemorrhagic phase, usually between days 5–14 of illness (Swanepoel *et al.*, 1987). Survivors enter a convalescent phase characterised by gradual clinical and laboratory recovery, though debilitating fatigue and neurological sequelae may persist for weeks to months (Elaldi and Kaya, 2014).

Severity predictors and case fatality

Case fatality rates (CFR) for CCHF vary widely, from approximately 5% in population-based surveillance studies to greater than 80% in small hospital-based series, with most large case series reporting CFRs between 15% and 40% (Whitehouse, 2004; Ergönül, 2006). Çevik *et al.* (2008) identified elevated AST, thrombocytopenia ($< 20 \times 10^9/L$), prolonged activated partial thromboplastin time, and high viral load as independent predictors of fatal outcome. Duh *et al.* (2007) confirmed that viral load on admission is the strongest single predictor of mortality, with fatal cases demonstrating significantly higher viraemia than survivors. Children appear to manifest a distinct clinical spectrum, with Tezer *et al.* (2010) reporting that the clinical course in paediatric CCHF is generally milder with lower mortality than in adults. This wide range in reported CFR is itself a methodological limitation rather than a true reflection of variable virulence: hospital-based case series, which enrol only the most severely ill patients, systematically inflate fatality estimates relative to population-based surveillance that captures mild and subclinical infections. Comparisons of CFR between countries and studies should therefore be interpreted cautiously unless case ascertainment methods are explicitly comparable, a caveat that is frequently overlooked in the wider literature.

Laboratory diagnosis

Molecular detection

Because the clinical features described above are frequently nonspecific, particularly early in illness,

laboratory confirmation is essential and, as discussed below, must be matched to the stage of disease and to the underlying virological and immunological events described earlier. Reverse transcription polymerase chain reaction (RT-PCR) targeting the S or L segment of CCHFV is the gold standard for diagnosis during the acute febrile and hemorrhagic phases, when viral titres are high (Vanhomwegen *et al.*, 2012; Raabe, 2020). RT-PCR is highly sensitive and specific and can detect CCHFV RNA within 24–48 hours of specimen collection, making it invaluable for early clinical management and isolation decisions (Duh *et al.*, 2007). Real-time RT-PCR platforms offer quantitative viral load estimation, which has prognostic as well as diagnostic utility (Çevik *et al.*, 2007; Vanhomwegen *et al.*, 2012).

Serological methods

Serological diagnosis employing enzyme-linked immunosorbent assay (ELISA) is the primary method for diagnosis in the convalescent phase, when RT-PCR sensitivity declines due to viral clearance (Vanhomwegen *et al.*, 2012; Raabe, 2020). IgM antibodies typically become detectable 7–9 days after illness onset, whereas IgG antibodies appear somewhat later and may persist for years (Shepherd, Swanepoel and Leman, 1989). Neutralisation assays, though labour-intensive and requiring biosafety level 4 (BSL-4) containment, offer high specificity for confirmatory testing and seroprevalence studies (Spengler *et al.*, 2016).

Laboratory findings

The haematological and biochemical profile of CCHF is characteristic, though not pathognomonic. Thrombocytopenia is an early and near-universal finding, typically falling below $150 \times 10^9/L$ by day 3–5 of illness (Shayan *et al.*, 2015). Leukopenia with lymphopenia is also common in the early febrile phase (Swanepoel *et al.*, 1989). Elevated aminotransferases (AST > ALT, which is characteristic), elevated creatine kinase, and prolonged coagulation parameters—including prothrombin time and activated partial thromboplastin time—become increasingly pronounced as the disease progresses (Çevik *et al.*, 2008; Öncü, 2013).

Critical comparison of diagnostic approaches and research gaps

RT-PCR and serology are best understood as complementary rather than competing tools, but each

carries limitations that are not always made explicit in the literature. RT-PCR offers high sensitivity only within a narrow early window of illness (Duh *et al.*, 2007; Raabe, 2020), so a negative result obtained later in the clinical course does not exclude infection, whereas ELISA-based serology (Vanhomwegen *et al.*, 2012) is unreliable in the first week of symptoms and in immunosuppressed patients who may fail to mount a measurable antibody response. Neither method is well suited to point-of-care use in the resource-limited, rural settings where most CCHF transmission occurs, since RT-PCR requires laboratory infrastructure and cold-chain reagent transport, while confirmatory neutralisation assays require BSL-4 containment (Spengler *et al.*, 2016). The development and field validation of rapid, low-cost, point-of-care molecular or antigen-based assays therefore remains an important and largely unmet research priority for CCHF-endemic regions.

Treatment and clinical management

Supportive care

Diagnosis alone does not alter patient outcome; translating the virological and pathogenic understanding outlined above into clinical benefit ultimately depends on the therapeutic and preventive options discussed in this and the following section. The cornerstone of CCHF management remains intensive supportive care, including fluid replacement, correction of electrolyte imbalances, transfusion of platelets and fresh frozen plasma for bleeding management, and meticulous monitoring of multi-organ function (Ergönül, 2006; Elaldi and Kaya, 2014). Strict isolation precautions with appropriate personal protective equipment are mandatory to prevent nosocomial transmission (Smego, Sarwari and Siddiqui, 2004).

Ribavirin

Ribavirin, a broad-spectrum antiviral nucleoside analogue with inhibitory activity against CCHFV in vitro, is the only antiviral agent widely recommended for CCHF treatment (Keshtkar-Jahromi *et al.*, 2011; Ergönül, 2006). Intravenous ribavirin is generally preferred over the oral route in severe cases. Observational data from Turkey and other endemic regions suggest a survival benefit when ribavirin is administered early in the clinical course (Leblebicioglu *et al.*, 2016; Vorou, Pierrotsakos and Maltezos, 2007). However, no randomised controlled trial has been completed, and evidence remains observational.

Spengler *et al.* (2018) reviewed emerging antiviral candidates, including favipiravir and monoclonal antibodies, which show promise in animal models but require clinical evaluation. This divergence between observational data suggesting benefit and the continued absence of confirmatory randomised evidence constitutes one of the longest-standing controversies in CCHF clinical management: observational studies are inherently vulnerable to confounding by indication, since patients treated earlier may simply have presented with milder disease, yet the ethical and logistical difficulty of conducting placebo-controlled trials during sporadic, geographically dispersed outbreaks has prevented this uncertainty from being resolved for over three decades. Until adequately powered randomised controlled trials are conducted, the routine use of ribavirin will continue to rest on clinical consensus rather than definitive evidence, a limitation that should be explicitly acknowledged in clinical guidelines.

Vaccines and future therapeutics

No universally licensed vaccine is available for CCHF, though several candidates are in various stages of development (Keshtkar-Jahromi *et al.*, 2011; Hawman and Feldmann, 2023). An inactivated CCHFV vaccine developed in Bulgaria and Russia has been used on a limited basis in endemic regions but lacks international regulatory approval. DNA vaccines, virus-like particle (VLP)-based platforms, and recombinant subunit vaccines targeting the glycoprotein antigens have demonstrated protective efficacy in rodent and non-human primate models (Hawman and Feldmann, 2018). The prioritisation of CCHF by the World Health Organisation (WHO) on its Blueprint list of priority pathogens has accelerated vaccine development efforts globally (Shahhosseini *et al.*, 2021).

Public health and prevention

Prevention of CCHF rests on integrated strategies addressing the tick vector, animal reservoirs, and human exposure pathways (Mertens *et al.*, 2013). Personal protective measures- including wearing protective clothing, use of tick repellents, and prompt tick removal- are central to individual protection in endemic areas. Occupational risk reduction in abattoirs and agricultural settings through appropriate personal protective equipment and animal dipping programmes to reduce tick burdens is equally important (Smego, Sarwari and Siddiqui, 2004; Swanepoel, 1994).

Strengthening laboratory diagnostic capacity, training healthcare workers in infection prevention and control, and establishing rapid alert and response systems are critical public health interventions (Maltezou *et al.*, 2010; Maltezou and Papa, 2010). Ince *et al.* (2014) analysed global CCHF outbreak reports submitted to ProMED and identified significant underreporting, particularly from Africa and parts of Asia, highlighting the need for enhanced surveillance infrastructure. Kuehnert *et al.* (2021) described CCHFV as a 'silent but widespread threat', emphasising that its cryptic spread in many regions poses a serious unrecognised public health burden.

Research gaps and future directions

Drawing together the critical discussion threaded through the preceding sections, four cross-cutting research gaps stand out. First, surveillance in Africa and parts of Asia is insufficient to distinguish genuinely low transmission from underdiagnosis, and standardised population-based studies are needed to resolve the discrepancy between modelled risk and reported case numbers (Messina *et al.*, 2015; Temur *et al.*, 2021). Second, the relative contribution of direct viral injury versus immune-mediated pathology to severe disease has not been resolved within single, adequately characterised patient cohorts, which constrains the rational design of host-directed adjunctive therapies (Duh *et al.*, 2007; Papa *et al.*, 2006). Third, no rapid, field-deployable point-of-care diagnostic exists for use in the rural, resource-limited settings where most transmission occurs, leaving both RT-PCR and serology dependent on laboratory infrastructure that is frequently unavailable where it is most needed (Vanhomwegen *et al.*, 2012; Raabe, 2020). Fourth, and most importantly for clinical practice, the therapeutic benefit of ribavirin remains unconfirmed by randomised controlled trials despite more than three decades of use, and no licensed vaccine has yet reached broad clinical deployment, although candidate platforms are in earlier-phase development (Keshtkar-Jahromi *et al.*, 2011; Hawman and Feldmann, 2018). Addressing these four gaps through internationally coordinated, adequately funded research, rather than continued reliance on retrospective and observational data, should be regarded as the principal priority for the CCHF research community over the coming decade.

Conclusions and Recommendations

Crimean-Congo hemorrhagic fever continues to

represent a major global zoonotic threat owing to its extensive geographic distribution, high case fatality rate, complex tick–animal–human transmission cycle, and increasing potential for emergence in previously unaffected regions. Advances in molecular virology and immunopathogenesis have substantially improved our understanding of CCHFV biology; however, significant gaps remain in the development of effective antiviral therapies and internationally licensed vaccines. Early diagnosis using molecular assays, prompt supportive management, rigorous infection prevention and control measures, and strengthened surveillance remain the cornerstones of disease control. Climate change, ecological alterations, expanding *Hyalomma* tick populations, and globalization are expected to further influence the epidemiology of CCHF, highlighting the need for continuous monitoring and international collaboration. Future research should prioritize vaccine development, evaluation of novel antiviral agents, improved point-of-care diagnostics, and integrated One Health strategies that address human, animal, and environmental health simultaneously. Such multidisciplinary efforts will be critical for reducing the burden of CCHF and improving global preparedness against this high-priority emerging infectious disease.

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Novelty Statement

This review integrates current knowledge of CCHFV virology, epidemiology, and pathogenesis with their practical implications for clinical diagnosis and management, providing a unified perspective rather than a purely descriptive overview. It also critically identifies major evidence gaps and future research priorities in therapeutics, diagnostics, surveillance, and One Health approaches.

Author Contributions

Md. Rimon Bhuiyan: Conceptualisation, literature search, writing- original draft, Data curation, writing-

review and editing, Supervision, critical revision. The author approved the final manuscript.

Generative AI and AI-assisted technology statement

The author declares that no generative AI and AI assisted technology was used in the creation of this manuscript.

Conflict of interest

The author declares no conflicts of interest.

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