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Crimean-Congo Haemorrhagic Fever Virus: From Genomic Insights to Control Strategies

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Highlights:

- Epidemiological trends of crimean-congo hemorrhagic fever (CCHFV)
- Zoonotic reservoirs of CCHFV
- Public health implications

Keywords:

- Crimean-Congo haemorrhagic fever (CCHFV)
- Viral haemorrhagic fevers
- Tick-borne
- Zoonosis
- One health

ABSTRACT:

Crimean-Congo hemorrhagic fever virus (CCHFV) is a life-threatening arthropod-borne virus transmitted by tick bites or contact with blood or tissues of viraemic individuals and animals. CCHFV continues its existence in a broad region with sporadic cases or outbreaks. CCHFV infection is observed frequently as an asymptomatic, but sudden severe disease characterised by haemorrhagic can occur. Diagnostic methods employ enzyme-linked immunosorbent assay (ELISA) and real-time reverse transcription-polymerase chain reaction (RT-PCR). Although ribavirin has been recommended in treatment besides supportive therapy approaches, no antiviral or vaccine for CCHF is currently approved. This review demonstrates general knowledge of CCHFV, summarising its molecular biology, pathogenesis, diagnosis, epidemiology, sustaining and transmission, treatment and prevention strategies, including vaccine candidates.

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INTRODUCTION

Diseases transmitted by arthropod vectors caused by parasites, bacteria, or viruses constitute over 17% of all infectious diseases, resulting in more than 700,000 deaths yearly (World Health Organization (WHO), 2020). This review focuses on one of the infectious diseases transmitted by arthropods, the Crimean–Congo haemorrhagic fever virus (CCHFV).

In 1944, the haemorrhagic fever disease was first defined in Crimea (Crimean haemorrhagic fever) (Watts et al., 2019). However, the initial isolation of the virus dates back to the 1960s in Congo (Simpson et al., 1967). Subsequent investigations unveiled that the virus responsible for these cases shared antigenic similarities with the pathogen that causes diseases in the Congo (Casals, 1969).

CCHFV, a virus transmitted predominantly by infected ticks (mainly of the *Hyalomma* genus) or through contact with the blood or other bodily fluids from an infected animal or individual, can induce haemorrhagic fever in humans. This disease presents a mortality rate that can reach 40% (Bente et al., 2013). While CCHFV can infect various wild and domestic animals, it typically induces viremia without causing apparent disease in these hosts. Consequently, these animal species play a crucial role as significant amplifying hosts. In human infections, CCHFV can lead to a spectrum of outcomes, ranging from asymptomatic or mild manifestations to fatal cases (Bente et al., 2013).

CCHFV is prevalent across Africa, the Middle East, Southeast Asia, and southern and eastern Europe, closely mirroring the distribution of its reservoir host, the *Hyalomma* tick (Messina et al., 2015). Furthermore, the range of *Hyalomma* ticks, specifically *Hy. marginatum* and *Hy. rufipes,* has extended as far north as Sweden (Grandi et al., 2020). Currently, there is no specific vaccine and therapeutics for CCHFV. Therefore, understanding CCHFV infection is vital for protecting public health, preventing outbreaks, getting knowledge of its pathogenesis, and developing diagnosis, treatment, and prevention strategies.

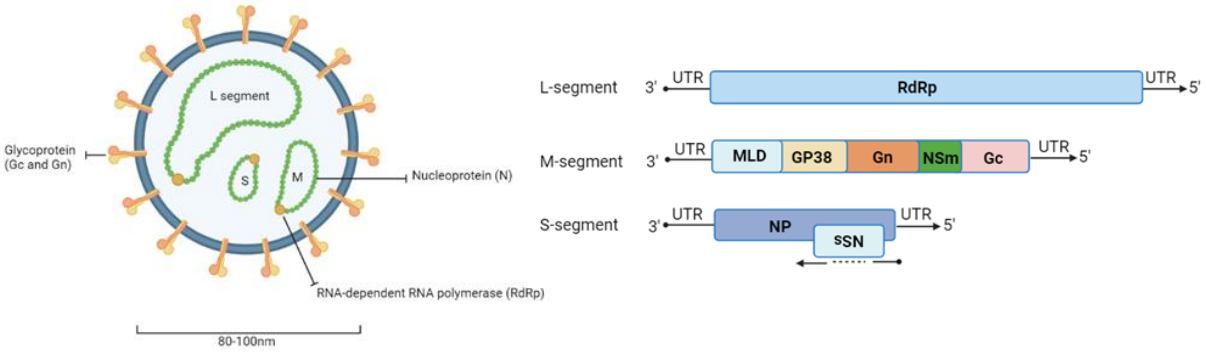
Genome and Structure

Crimean–Congo Haemorrhagic Fever virus (CCHFV), tri-segmented (-) ssRNA, belongs to the genus *Orthonairovirus* (family *Nairoviridae*, order *Bunyavirales*) (Garrison et al., 2020).

The small (S) segment is responsible for encoding the nucleoprotein (NP) and the non-structural S (NSs), the medium (M) segment encodes the glycoprotein precursor (GPC), giving rise to mature Gn and Gc glycoproteins, along with three non-structural proteins; mucin like protein/domain (MLD), GP38, and NSm. The large (L) segment carries the genetic code for the L protein, which includes the RNA-dependent RNA polymerase (RdRp) responsible for viral RNA synthesis (Zivcec et al., 2016) (Figure 1). In addition, the virus contains an ovarian tumour (OTU) protease domain, which may contribute to its evasion of host innate immune responses (Tchesnokov et al., 2020). However, the virus replication was determined not to be reliant on the protease activity of OTU (Bergeron et al., 2010).

The CCHFV NSs protein is likely to trigger apoptosis by activating both the intrinsic (mitochondrial death pathway) and extrinsic (the death receptor pathway) pathways during infection (Barnwal et al., 2016). Gn and Gc are incorporated into the virion's membrane, where they facilitate cellular attachment and entry (Whitehouse, 2004). Additionally, Gn is believed to be involved in the assembly of the virion (Estrada & De Guzman, 2011). GP38, alongside the MLD (also known as GP85), is involved in processing and directing the movement of structural glycoproteins, playing a crucial role in viral replication. NSm (GP160) has been implicated in the processing of Gc but is not essential for viral replication (Freitas et al., Hulswit et al., 2021). Due to its high contagion and ability

to induce severe illness, the virus should be exclusively managed in high-containment (BSL-4) laboratories (Weidmann et al., 2016).



(a) (b)

Figure 1: Diagram illustrating the CCHFV virion (a) and the CCHFV genome structure (b) The figure was created with BioRender.com)

Clinical Manifestations

Initial manifestations of CCHFV infections appear as a non-specific febrile illness (Bente et al., 2013), with over 80% of infections estimated to be subclinical (Ergonul, 2008). Human infection with CCHFV is marked by four noticeable phases: incubation, pre-haemorrhagic, haemorrhagic, and convalescence (Hoogstraal, 1979).

The shortest incubation period occurs after a tick bite, typically within 1–3 days, while exposure to infected livestock and human blood, tissue, and secretions results in a slightly more extended incubation period of 5–6 days (Vorou et al., 2007), during which the virus replicates and disseminates.

The pre-haemorrhagic phase can last up to one week. This stage typically initiates symptoms including fever (ranging from 39 to 41 °C), headache, myalgia, dizziness, neck pain, stiffness and photophobia (Vorou et al., 2007). Extra symptoms such as abdominal pain, nausea, vomiting and diarrhoea might be observed. Noteworthy, CCHFV infection led to neuropsychiatric changes, including abrupt mood changes, along with feelings of confusion and agitation individuals (Whitehouse, 2004). In this phase, viremia reaches its peak, and reverse transcription-PCR (RT-PCR) can be employed to define the circulating virus and the virus isolation is also feasible (Drosten et al., 2002; Drosten et al., 2003).

Haemorrhage usually begins 3-6 days after the initiation of symptoms appear. Haemorrhagic symptoms may manifest, varying from small red or purple skin spots (petechial) caused by bleeding from ruptured capillaries, nosebleeds (epistaxis), and bruising (ecchymosis) at injection sites to substantial bleeding from different bodily systems (Ergonul et al., 2006). Bleeding has also been reported in the genital-urinary tract and brain (Whitehouse, 2004). Elevated levels of liver enzymes, creatinine phosphokinase, and lactate dehydrogenase, along with prolonged bleeding markers (thrombocytopenia, leukopenia) are observed. In the most severe instances, fatalities are linked to cerebral and profound gastrointestinal haemorrhage, as well as kidney, liver, or pulmonary failure, along with the shock (Hawman & Feldmann, 2023). Mortality is linked to various factors, including age, viral strain, viral load and endemic conditions (Leblebicioglu, 2010; Stähelin-Massik et al., 2008; Tezer et al., 2010).

Survivors of CCHFV infection typically undergo a convalescence period lasting approximately 9-20 days. While some transient symptoms like weakness, tachycardia or bradycardia, and hair loss may manifest during the recovery phase, they are generally temporary (Hawman & Feldmann, 2023).

Individuals who survive usually acquire both humoral and cellular immunity to combat CCHFV (Fels et al., 2022; Goedhals et al., 2017).

Diagnosis

CCHF suspected cases are assessed by considering clinical symptoms (e.g., observations of skin and mucosal bleeding), patient history (e.g., a history of tick attachment), and diagnostic laboratory tests (e.g., finding of virus RNA). Differential diagnosis for CCHFV should be considered if the cases happen in the endemic region for other viral haemorrhagic fevers (VHFs) such as Hantavirus pulmonary syndrome (Onder Ergonul, 2012).

The disease's extensive geographic spread and rising incidence in new regions have elevated CCHF to a public health emergency. Swift diagnosis is crucial for effective patient care, particularly in rural and remote areas where most cases occur. The World Health Organization (WHO) has designated CCHF as a priority disease for research and development, specifically focusing on advancements in diagnosis, prevention, and control measures (World Health Organization (WHO), 2022a). The importance of early patient identification is underscored by the inverse relationship between mortality rates and patients' accessibility to healthcare services (Komut et al., 2023).

Direct diagnosis approaches involve the detection of the viral RNA and virus isolation, but the latter requires a biosafety level 4 (BSL-4) (Onder Ergonul, 2012).

PCR-based molecular methods can be chosen for rapid laboratory diagnosis of CCHF virus infection (Drosten et al., 2003). The approach is highly sensitive for identifying a viral genome and potentially quantifying the viral load in a sample within a short timeframe (Schwarz et al., 1996). Over the past years, various PCR systems have been established to diagnose the CCHFV (Albayrak et al., 2012; Drosten et al., 2002, 2003; Duh et al., 2006; Kamboj et al., 2014). Although PCR-based diagnostic system provides quick, definite diagnosis, a limitation of these tests is the extremely narrow diagnostic window. PCR outcomes might yield negative results if the sample is collected beyond nine days post-symptom onset (Fillâtre, Revest, & Tattevin, 2019). Furthermore, due to the intricacy and expense associated with RT-PCR platforms and PCR kits, there has been extensive development of isothermal nucleic acid amplification assays, particularly loop-mediated isothermal amplification (LAMP). LAMP enables the process to occur at a consistent temperature (60-65°C) for a short duration, eliminating the necessity for a thermal cycler (Hema & Konakalla, 2021). This makes LAMP particularly suitable for applications in the field and point-of-care diagnostics. The integration of LAMP with a reverse transcription step, facilitating the detection of RNA, led to the establishment of LAMP with reverse transcription (RT-LAMP) for the detection of CCHFV (Febrer-Sendra et al., 2023).

Similar to other isothermal amplification methods, isothermal recombinase polymerase amplification (RPA) eliminates the need for a thermal cycler, as the reaction occurs at a constant temperature. This assay was effectively designed for the molecular detection of CCHFV (Bonney et al., 2017).

Serological techniques detect virus-specific IgG and IgM antibodies, including immunofluorescence, hemagglutination inhibition, complement fixation, and ELISA. Typically, these offer a prolonged diagnostic timeframe, spanning from the haemorrhagic phase of CCHF to the recovery period (Fillâtre et al., 2019). There are commercially accessible kits for identifying human IgM and IgG CCHFV-specific antibodies, involving enzyme-linked immunosorbent assay (ELISA) indirect immunofluorescence tests (IIFTs) (Emmerich et al., 2021). The IgM tests primarily diagnose acute infections, while IgG tests are used for detecting advanced disease stages and for

epidemiological and disease surveillance purposes (Schluederberg, 1965). Furthermore, the recombinant nucleoprotein (NP) of the CCHFV has proven to be an effective antigen for the diagnosis of CCHFV in ELISA and immunofluorescence assays (Dowall et al., 2012; Emmerich et al., 2018; Saijo et al., 2005; Tang et al., 2003).

In addition to these systems, aptamer-based diagnostics have recently attracted attention as highly sensitive, specific, and rapid (Moshref et al., 2023). In one study, diagnosis of CCHFV infection was shown using specific aptamer-antibody ELASA for CCHFV NP protein. The choice of the NP protein for this assay is based on its superior stability across various strains of the CCHFV, its status as the primary protein of the virus, inducing a high immune response and its abundance as the most readily detectable antigen in CCHFV positive sera (Jalali et al., 2021; Liu et al., 2014).

Epidemiology

CCHF exhibits endemicity in regions situated south of the 50th north parallel latitude, encompassing Africa, the Balkans, the Middle East, and Asia (Bente et al., 2013) (Figure 2), with over 30 countries documenting cases since its initial emergence in Crimea (Blair et al., 2019; Hoogstraal, 1979; Spiropoulou & Bente, 2020). Endemic foci are present in all regions except Western Hemisphere, northern Europe and Australia. CCHF manifests in established geographic areas and adheres to a predictable seasonal trend, typically reaching a maximum of 1000 cases annually per nation (World Health Organization (WHO), 2018).

Over the years, the epidemiology of CCHFV has undergone dynamic changes, with sporadic outbreaks, localized endemicity, and the emergence of new cases reported in various countries (García Rada, 2016).

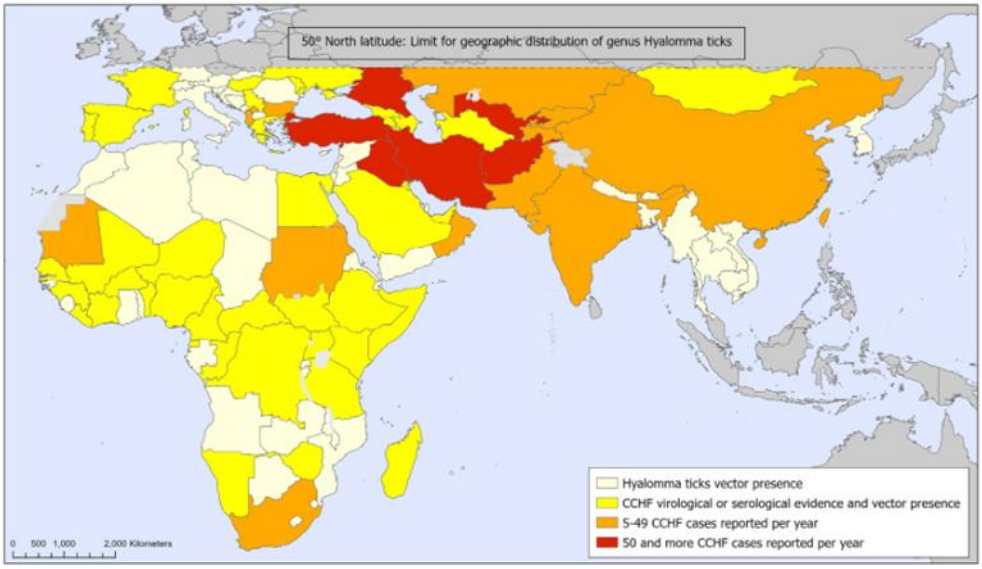


Figure 2: Worldwide map of the CCHF distribution, adapted from (World Health Organization (WHO), 2022b)

The following outlines the brief epidemiology of CCHF across three geographical areas: Africa, the Middle East and Europe.

Africa

While CCHF was first documented in Africa in 1956 (Simpson et al., 1967), publications and reports on CCHF epidemiology in Africa are scarce. However, since 2000, nine countries, namely Kenya, Mali, Mozambique, Nigeria, Senegal, Sierra Leone, South Sudan, Sudan, and Tunisia, have recorded their initial CCHF cases (Omoga et al., 2023 Temur et al., 2021). The reported cases directly correlate with improving diagnostic capabilities in these countries. Notably, South Africa has reported

the most substantial caseload on the continent, with 215 cases documented from 1981 to 2019 (Grard et al., 2011; Temur et al., 2021). This discrepancy in reported cases reflects variations in diagnostic capacities among African nations, emphasizing the importance of a thorough comprehension of CCHFV cases in humans, animals, and vector circulation across countries.

The Middle East

The presence of CCHF in Iran, Afghanistan, Pakistan, Iraq, United Arab Emirates, Tunisia, Oman, and Saudi Arabia has been documented. Iran has been consistently identified cases of either nosocomial infections or tick bites of CCHF annually, primarily in the south-eastern region (Chinikar et al., 2012, 2013). After first report in 1998, Afghanistan faced the first multifocal outbreak in 2008 (Mofleh & Ahmad, 2012) and a seroprevalence study illustrated that the incidence was high in livestock population (%75) and 11.2% of humans (Mustafa et al., 2011). In Iraq, nosocomial transmission plays a role in both sporadic cases and outbreaks (Ibrahim et al., 2014).

Seroprevalence studies showed CCHFV antibodies in the sera of humans and various animals in the United Arab Emirates (Khan et al., 1997). Exposure to CCHFV was observed in humans (approximately 8%) (Wasfi et al., 2016) and camels (89.7%) (Bouaicha et al., 2021) in Tunisia. In Oman, a heightened prevalence of CCHFV antibodies was observed in diverse animals and ticks: cattle, camels, goats, sheep, and ticks, 17.5%, 15.7%, 4.8%, 4.3%, and 5.1%, respectively. (Body et al., 2016). From 2011 to 2017, there was a steady increase in human cases of CCHFV infections, with the primary risk factor being contact with animals (Al-Abri et al., 2019).

Regarding sporadic cases and outbreaks, the circulation of CCHFV is evident in the region.

Europe

In Europe, particularly in the Balkan Peninsula, there have been reports of outbreaks as well as sporadic or imported cases of CCHF. In Bulgaria, in southeastern Europe, CCHF was defined initially within its borders in 1952 (Nekliudov, 1952). Bulgaria recorded over 1500 diagnosed cases of CCHF from 1953 to 2000s (Papa et al., 2004). Since the initial case in 1954 in Kosovo, there has been a persistent reporting of outbreaks (Ahmeti et al., 2019; Vesenjak-Hirjan et al., 1991).

In 1975, the CCHFV strain (AP92) was isolated from ticks of the *Rhipicephalus bursa* species, which were gathered from goats in Northern Greece (Papadopoulos & Koptopoulos, 1980) and revealed that the AP92 strain is distinct from all other strains of CCHFV (Vorou et al., 2007). Although different seroprevalence studies showed AP92 CCHFV strain circulation in the population, it does not cause severe illness in humans (Antoniadis et al., 1991; Sargianou et al., 2013). Notably, the initial domestic CCHF case documented in Greece in 2008 (Maltezou et al., 2009), and this CCHFV infection was fatal. Moreover, molecular analysis showed that the causative strain (Rhodopi) differs genetically from the AP92 strain (Papa et al., 2011).

In 2010, evidence of CCHFV circulation was identified in ticks of the genus *Hyalomma* collected from deer in Spain (Estrada-Peña et al., 2012). Later on, two autochthonous cases (fatal and non-fatal) were addressed in the country (García Rada, 2016; Negredo et al., 2017). In asymptomatic blood donors from Spain, there were between 0.58% (3/516) and 1.16% (6/516) IgG antibodies against CCHFV (Arteaga et al., 2020).

Interestingly, while no human cases have been reported thus far, infected *H. marginatum* ticks have been found on cattle and horses in southern France (Bernard et al., 2024). Additionally, antibodies against the virus were detected in ruminant sera in Corsica, a French island (Bernard et al., 2022).

Serological evidence of CCHFV in Türkiye dates back to 1975, the initial officially confirmed CCHF case in the north of Türkiye was documented in 2002 (Karti et al., 2004; Pattyn, 1978). Following, cases with comparable clinical and laboratory manifestations were documented in Tokat and its surrounding municipalities (Shahhosseini et al., 2021). These regions provide favourable habitats for tick species, vectors of CCHFV (Leblebicioglu et al., 2016). From 2002 to 2007, Turkish hospitals, mainly in the Middle and Eastern Anatolia of Türkiye, recorded 1820 confirmed cases with a mortality rate of 5% (range 4.5–6.2%) (Ozkaya et al., 2010). From 2002 onward, over 9,000 verified cases have been noted, resulting in a mortality rate of 5% (Shahhosseini et al., 2021). Apart from clinical cases, a serosurvey study brought attention to a significant proportion of subclinical CCHFV infections in the epidemic hotspots (Bodur et al., 2012).

Given that CCHF cases have predominantly been recorded in the Balkan Peninsula and Türkiye, there exists a potential for this virus to emerge as an infectious threat across the rest of Europe influenced by various factors, including climate change.

Sustaining and Transmission of CCHFV

Vectors of cchfv

Ticks are blood-feeding arthropods, and there are approximately 900 species classified into medically important tick families: the Argasidae and the Ixodidae (Guglielmone et al., 2010). *Hyalomma* ticks, members of the Ixodidae family, serve as vectors and reservoir for CCHFV (Spengler et al., 2016; Whitehouse, 2004). Even though CCHFV has been identified in at least 35 tick species (Shahhosseini et al., 2021), which includes soft ticks from the Argasidae family, the role of these ticks should be evaluated within the framework of their vector capacity (Gargili et al., 2017). Vector competence applies to the ability of ticks to be infected via feeding on an infected host, maintaining, replicating, and transmitting the virus (Papa et al., 2017).

Ixodid ticks progress through three active stages in their life cycle: larva, nymph, and adult (Bonnet et al., 2023). Most ticks of the *Hyalomma* spp possess a three-host cycle that involves each of the three life stages seeking a new host to obtain a blood meal, but some exhibit two-host behaviour, with larvae and nymphs feeding on the same host (Bonnet et al., 2023). Larvae hatch, feed, moult to nymphs while attached to the host, and then drop to the ground for further development. Adults, resulting from this process, find a host, feed, mate, and lay eggs in protected sites with high humidity. Each blood meal integrates ticks into the CCHFV transmission cycle through transstadial or transovarial transmission. Transmission occurs between ticks and mammals or through co-feeding ticks. Human infection can result from the bite of an infected tick or exposure to the body fluids of a viraemic animal or CCHF patient (Bente et al., 2013).

Medically important ticks typically take a blood meal from small mammals and birds during their immature stages, while adults feed on larger herbivores and carnivores. This diverse feeding behaviour allows ticks to acquire pathogens from various vertebrate hosts and subsequently transmit them to humans. Human exposure to ticks, often characterized by generalist host behaviour, increases the risk of pathogen transmission (Salim Abadi et al., 2010).

Vertebrate hosts of cchfv

CCHFV is widespread in both wild and domestic animals, and importantly, CCHFV infection without apparent symptoms has been documented in these species (Spengler et al., 2016). CCHFV has been isolated from domestic animals (e.g., horses, livestock, chickens, dogs, camels), small mammals (e.g., hedgehogs, rabbits) and large mammals (e.g., buffalos, rhinoceroses, giraffes, deer) (Espunyes et al., 2021; Spengler, Bergeron, et al., 2016; Whitehouse, 2004).

Notably, higher seropositivity of CCHFV antibodies in domestic animals increases the risk of human infection. As such, higher levels of CCHFV IgG antibodies in livestock frequently align with occurrences of CCHF cases in individuals engaged in the livestock sector, such as butchers and farmers (Mustafa et al., 2011; Sharifi-Mood et al., 2014). Moreover, the recent seroprevalence study highlighted the high CCHFV seropositivity in camels, 97% (179/184), in an abattoir in Nigeria (Adamu et al., 2024).

Most bird species are likely resistant to CCHFV infection, but antibodies against CCHFV have been detected in ostriches and exhibited viremia after experimental infection (Cooper et al., 2004). Migrating birds play a crucial role in transmitting diseases by providing blood meals to ticks, thereby aiding the spread of infected ticks and the emergence of disease hotspots. For instance, the potential entry route of CCHFV into Spain is believed to involve migratory birds transporting immature forms of infected ticks from Africa (Palomar et al., 2013). Nevertheless, the virus has been detected in only a minor percentage (0% to 3.2%) of ticks in Spain (Spengler et al., 2018).

Treatment Strategies

The majority of CCHFV infections either manifest as asymptomatic or lead to a non-specific febrile illness, typically not necessitating hospitalization or targeted treatment. In rare instances where patients experience life-threatening outcomes of the infection, such as haemorrhage, the existing medical approach primarily revolves around providing supportive care. There is currently no specific approved antiviral treatment or vaccine for CCHF. Patients are often given intravenous fluids to maintain hydration, pain relievers for fever and discomfort, and other supportive measures to address specific symptoms, closely monitoring the patient's hematologic status and involves the administration of thrombocytes, fresh frozen plasma, and erythrocyte preparations (Ergönül, 2006; Fillâtre et al., 2019).

Ribavirin, a nucleoside analogue that interferes with the replication of viruses, including RNA viruses such as respiratory syncytial virus and Lassa virus, is the only therapeutic agent for the CCHF treatment recommended by the WHO (Graci & Cameron, 2006; World Health Organization (WHO), 2022b). It is available in both oral and intravenous formulations (Johnson et al., 2018). Ribavirin inhibits viral replication in Vero cells (Watts et al., 1989) and reduces the average time to mortality in a suckling mouse model of CCHF (Tignor & Hanham, 1993). Retrospective studies in Türkiye and Iran indicated a lower mortality rate, but ongoing research and clinical evaluation are still discussing its effectiveness (D'Addiego et al., 2023; Ergönül et al., 2004; Mardani et al., 2003). WHO suggests a dosage of 17 mg/kg (up to a maximum dose of 1 g) every 6 hours from day 1 to day 4. Subsequently, the recommended dosage is 8 mg/kg (up to a maximum dose of 500 mg) every 8 hours from day 5 to day 10 (Fillâtre et al., 2019). Additionally, a meta-analysis suggested that administering ribavirin as a prophylactic post-exposure treatment in health workers reduces the risk of infection (Ergönül et al., 2018).

Favipiravir, a broad-spectrum viral polymerase inhibitor, has shown effectiveness against several pathogenic RNA viruses, including Lassa fever (Rosenke et al., 2018; Safronetz et al., 2015). Studies on CCHFV in mice demonstrated that Favipiravir effectively suppressed viral replication and prevented mortality, even when administered late after the onset of symptoms. These findings suggest that Favipiravir may have potential efficacy in treating advanced cases of CCHF (Hawman et al., 2018; Oestereich et al., 2014).

Besides these, alternative therapeutic options reported in individual cases or experiment results include steroids, convalescent serum, monoclonal antibodies, and specific immunoglobulins, including

hyperimmune globulins derived from the serum of recovered patients (Bertolotti-Ciarlet et al., 2005; Keshtkar-Jahromi et al., 2011; Kubar et al., 2011). However, there is inadequate evidence to evaluate the effectiveness of these treatments.

Prevention and Control

Developing preventative measures and vaccines to protect against infection is of great importance, particularly critical in regions where the virus is endemic or emerging to mitigate its impact on public health (Fletcher et al., 2017; Hawman & Feldmann, 2023).

The most effective approach to preventing the disease is to steer clear of or reduce exposure to the virus, and there are several ways to achieve this. Individuals in high-risk professions (e.g.,, veterinarians, farmers, slaughterhouse workers, etc.) should utilize suitable attire, including long sleeves, pants and socks to cover ankles.

Furthermore, the spread of CCHF in hospitals can be restricted by employing appropriate personal protective equipment (PPE). Standard barrier PPE, including a lab gown, gloves, a face shield, and a mask, reduces the risk of healthcare personnel coming into contact with potentially infectious bodily fluids (Ergönül, 2006). Further, trained personnel in adequately equipped laboratories should manage samples collected from individuals suspected of having CCHF (Bartolini et al., 2019). Needle stick injuries and exposure to mucous membranes through splashes were common causes of high-risk nosocomial infections among healthcare personnel and several cases reported from different countries (Burney et al., 1980; Conger et al., 2015; Leblebicioglu et al., 2016).

It is also essential to manage the tick population, particularly *Hyalomma* ticks, in the context of prevention and control of CCHF infections. Various methods, such as chemical, biological, genetic, and ecological approaches, have been developed for tick control. The deployment of acaricides is recommended on farms and livestock, as well as using approved repellent on the skin and clothing (Bonnet et al., 2022; Kumar et al., 2020).

Moreover, anti-tick vaccines, implemented in livestock populations and focusing on the vector, offer a dual advantage by addressing both the ticks and the life cycle of CCHFV (de la Fuente & Contreras, 2022). Additionally, regular examination and quarantine measures for livestock that may carry CCHFV or harbour CCHFV-infected ticks, conducted before transportation or slaughter, can decrease exposure and restrict the introduction of CCHFV to new regions (Hawman & Feldmann, 2023).

In the absence of a vaccine, the primary approach to reducing CCHFV infection in humans is through public health-focused educational campaigns. These campaigns should highlight information on the CCHFV and its tick vectors, transmission routes, using suitable repellents, recognition of the disease's clinical signs, and the importance of admission to a hospital as soon as possible after suspicion. Thus, health-focused educational initiatives can raise awareness regarding the risk factors and prevention of CCHFV infection. Recognizing the significance of the infection also increases the likelihood of successful recovery when individuals with early symptoms of CCHF seek admission to a hospital (Hawman & Feldmann, 2023).

Vaccines

The extensive spread of CCHFV, the risk of person-to-person transmission, the severity of the disease, and the high fatality rate, coupled with challenges in treatment, collectively establish CCHF as a significant public health issue. In addition to this, there are numerous vaccine potential candidates,

but none has received official approval (Ahata & Akçapınar, 2023). Having a vaccine against CCHFV benefits individuals residing in endemic areas and engaging in activities such as working with livestock or agriculture, where the risk of infection is higher (Tipih & Burt, 2020).

In 1974, Bulgaria pioneered the development of an inactivated vaccine derived from suckling mouse brains, which was administered to several hundred human volunteers, predominantly in the military and medical personnel. Although this vaccine is still in use on a small scale in Eastern Europe and has demonstrated elevated antibody levels, its limited adoption and lack of official recognition for use in other countries highlight the need for further evaluation (Papa et al., 2011). Moreover, it has been shown that the vaccine triggered both cellular and humoral responses to CCHFV. However, the levels of neutralising antibodies were low, even among individuals who had received up to four doses (Mousavi-Jazi et al., 2012).

Indeed, it is important to note that there is currently no officially approved and widely available vaccine for human or animal use; however, several experimental vaccine candidates exist (Garrison et al., 2017; Hawman et al., 2021), plant-expressed vaccines, transgenic tobacco leaves expressing the CCHFV viral glycoproteins (Ghiasi et al., 2011), and recently mRNA-based vaccine efficacy against CCHFV has been highlighted in various studies (reviewed in detail in refs. Ahata & Akçapınar, 2023; Ozdarendeli, 2023; Tipih & Burt, 2020).

CONCLUSION

In conclusion, this thorough investigation of Crimean-Congo Hemorrhagic Fever provides insights into its genome, molecular characteristics, epidemiology, and pathogenesis. The discussion encompassed the virus's transmission dynamics, the crucial role of ticks in its life cycle, and the significant impact of various host species on its circulation. The review delved into diagnostic techniques, emphasizing the importance of accurate and rapid detection methods for effective management.

Furthermore, insights into the global distribution of CCHFV underscore its endemicity in various regions, prompting the necessity for region-specific preventive measures. The evaluation of vaccination strategies, antiviral treatments, and the importance of public health interventions emphasized the need for a multifaceted approach to combat CCHF. This review serves as a foundation for future endeavours, urging the scientific community to remain vigilant and proactive in the face of emerging infectious threats like CCHFV.

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Conflict of Interest

The article author declares that there is no conflict of interest.

Author’s Contributions

The authors declare that they have contributed equally to the article.

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