Veterinary Integrative Sciences 2026; 24(1): e2026013-1-20. DOI: 10.12982/VIS.2026.013

Veterinary Integrative Sciences
ISSN; 2629-9968 (online)

Review article

Crimean–Congo Hemorrhagic Fever (CCHF): An integrated overview

Afrah Ali Dakhil[1], Wessam Monther Mohammed Saleh[2,*] and Saad Shaheen Hamadi Al-Taher[3]

[1]Medical Devices Technology Department, College of Health and Medical Technology, Al-Ayen Iraqi University, Thi-Qar, 64001, Iraq.
[2]Department of Veterinary Internal and Preventive Medicine, College of Veterinary Medicine, University of Basrah, Basra State, 61004, Iraq.
[2]Department of Internal Medicine, College of Medicine, University of Basrah, Basra State, 61004, Iraq.

Abstract

CCHF (Crimean-Congo hemorrhagic fever), is an illness transmitted by a lethal virus with a high case mortality rate and widespread geographic distribution, is transmitted by ticks. Nations in Africa, the Middle East, Asia, and southern and eastern Europe all report cases of CCHF. The public's health is seriously threatened by the lack of study and the possibility of the endemic spread of the disease. The current review aimed to highlight the information gaps beside the undiscovered areas when researching the virus that causes Crimean-Congo hemorrhagic fever. Additionally, it included information on the epidemiology, etiology, transmission, clinical traits, diagnosis, therapy, and preventative and control strategies of the virus. Animals are asymptomatic, so this illness does not affect them as much. However, domestic livestock are crucial in the spread of disease to people. Therefore, people who work in slaughterhouses, farms, or as veterinarians run a risk of catching this illness. A rapid diagnosis is crucial since the condition has significant public health implications. Real-time PCR enables fast diagnosis of CCHF. Future studies should concentrate on the molecular causes of CCHFV infection and how to treat it because there are still many unanswered questions in these fields. In endemic locations, an array of preventative measures must be placed in place, including education, lowering tick contact, minimizing tick infestations in livestock, controlling tick infestations, quarantining livestock, and shielding populations at risk from high-risk exposure activities.

Keywords: Bunyaviridae, CCHF, Hemorrhagic Fever, Tick Vector, Zoonosis

[*]**Corresponding author**: Wessam Monther Mohammed Saleh, Department of Internal and Preventive Medicine, College of Veterinary Medicine, University of Basrah, 57 Baghdad Street, Garmat-Ali, Basra state *61004,* Iraq.
E-mail: Wessam.Mohammed@uobasrah.edu.iq, wessamgm@gmail.com

Article history; *received manuscript: 6 October 2023,*
revised manuscript: 26 December 2023,
accepted manuscript: 4 January 2025,
published online: 6 May 2025,
Academic editor; *Korakot Nganvongpanit*

GENERAL OVERVIEW

Crimean-Congo hemorrhagic fever (CCHF), a lethal human disease triggered by a zoonotic virus transmitted by ticks with a high fatality rate, is characterized by hemorrhagic symptoms and multiple organ failure (Ergonul et al., 2006; Carroll et al., 2010). The geographical ranges of CCHFV is extraordinarily extensive and reflects the wide availability of the tick vectors, which are present in thirty countries across Southern Europe, the Middle East, Africa, and Asia (Mild et al., 2010). Recent CCHFV outbreaks in Turkey, southwestern Russia, and numerous Balkan republics imply that CCHFV activity is rising, especially in Southern Europe (Maltezou and Papa, 2010), Turkey (Maltezou and Papa, 2010), Pakistan (Maltezou and Papa, 2010) and Iraq (Al-Rubaye et al., 2022; Sah et al., 2022). The sole way to cure CCHFV infection is to administer ribavirin post-exposure, while its effectiveness as a preventative measure is debatable (Al-Rubaye et al., 2022; Sah et al., 2022). However, Public health and biodefense organizations currently prioritize the creation of efficient treatments for the prevention of CCHFV-mediated illness. CCHFV is a member of the Bunyaviridae family, and because it has many genome segments, along with *Orthomyxoviridae* and *Arenaviridae* family's members, it is referred to as a sNSV (segmented negative-strand RNA virus). Over 350 identified isolates belonging to the five genera Hantavirus, Nairovirus, Orthobunyavirus, Phlebovirus, and Tospovirus make up the Bunyaviridae family (Schmaljohn and Nichol, 2007). The segments that make up the nairovirus known as CCHFV's genome are: S (small), M (medium), and L (large). By the L-Segment, "RNA Dependent RNA polymerase" (RdRp; the L-Protein) is encoded, while M-Segment encodes the glycoproteins of the virus, and S-Segment encodes the nucleocapsid protein (N).

HISTORY

Blood samples from ancient Celtic communities in Germany's Upper Danube region had the CCHF virus, proving that the disease was prevalent at the time (Wiktorowicz et al., 2017). The virus might have developed between 1500 and 1100 BC. Its evolution is believed to have been influenced by the localized effects of changing climatic conditions and agricultural methods (Carroll et al., 2010). The first known instance of Crimean-Congo hemorrhagic fever may have occurred in the XII century, when a situation of hemorrhage sickness was recorded from what is now Tajikistan. As a result, the first case of CCHF may have been recorded in the 12th century from what is now Tajikistan (Shapiro and Barkagan, 1960). Between 1944 and 1945, 200 Soviet military agricultural workers had infected by Crimean hemorrhagic fever (CHF), conducting researches revealing the tick-borne viral microorganism (Whitehouse, 2004). A physician at the Provincial Medical Laboratory in Stanleyville, in the Belgian Congo, Ghislaine Courtois isolated the Congo virus in 1956. When Courtois isolated strain V3010, it was sent to the Rockefeller Foundation Virus Laboratory in New York City where it was found to be identical to another strain from Uganda, but not to any other viruses at that time (Vorou et al., 2007). In February 1967, virologists John P. Woodall, David Simpson, Jessalyn Courtois, and others published preliminary reports of a virus they named Congo virus (Simpson et al., 1967; Woodall et al., 1967). A Samarkand fatal case was the source of an isolate that Soviet virologist Mikhail Chumakov submitted to the List of Viruses Spread by Arthropods in June 1967 (Chumankov et al., 1968). In the year 1969, the "Russian strain" was found to be identical to the Congo-Virus, when Chumankov had transmitted this strain to the Rockefeller Foundation Virus Laboratory (RFVL) (Casals, 1969). Interestingly in 1973, Crimean-Congo Hemorrhagic Fever Virus (CCHFV) was chosen as the formal name of this unique virus through the "international committee on taxonomy of the viruses" (Woodall, 2007). Viral and/or antibodies detection to CCHFV were detailed in different

researches, which being present in Madagascar, Portugal, Greece, South Africa where the initial detection of the disease came from, Iraq, Saudi Arabia, Morocco, UAE, and Kuwait (Al-Tikriti et al., 1981; Okorie, 1991; Crowcroft et al., 2002; Dakhil et al., 2024; Saleh, et al., 2025).

CCHFV STRUCTURE

The small (S), medium (M), and large (L) RNA segments make up the nairovirus known as CCHFV's genome. The L-segment encodes an RNA-dependent RNA polymerase (RdRp; the L-protein), the M-segment encodes viral glycoproteins, and the S-segment encodes the nucleocapsid protein (N). The genomes of sNSVs are formed ribonucleoprotein (RNP) complexes after being encapsidated by the viral N protein. rather than existing as naked RNAs. In order to create active templates for the production of viral RNA, RNPs link up with their homologous RdRp. This results in the production of mRNAs that are not encapsidated and replication products that are. RNP packaging into progeny virus particles additionally needs genome encapsidation, and for bunyaviruses, virus assembly occurs by between viral glycoproteins and the RNP directly. (Overby et al., 2007; Shi et al., 2007; Snippe et al., 2007; Ribeiro et al., 2009; Hepojoki et al., 2010). As a result, RNP synthesis is crucial for viral reproduction and so provides a possible therapeutic target. Baghdad-12-Crimean-Congo Hemorrhagic Fever Virus strain's N-Protein was described as having a "1.2-Crystal Structure". Comparing the Crimean-Congo Hemorrhagic Fever Virus N-Structure to the most recent report on the CCHFV strain's N-Structure (GenBank accession number: YL04057), considerable variations in domain positions may be seen (Carter et al., 2012; Guo et al., 2012). All these discrepancies might have significant effective repercussions, which detailed below, and are geographically distant from China. The key RNA binding and N-Protein functions of N-N oligomerization are revealed by the structure, and these activities have been investigated in a minigenome assay in mammalian cells. As a result of the strong and unexpected structural similarity between the N-Structure and the N-Protein belong Arenavirus Lassa Virus "LASV", it is also possible that the present classification of sNSVs has to be revised (Carter et al., 2012).

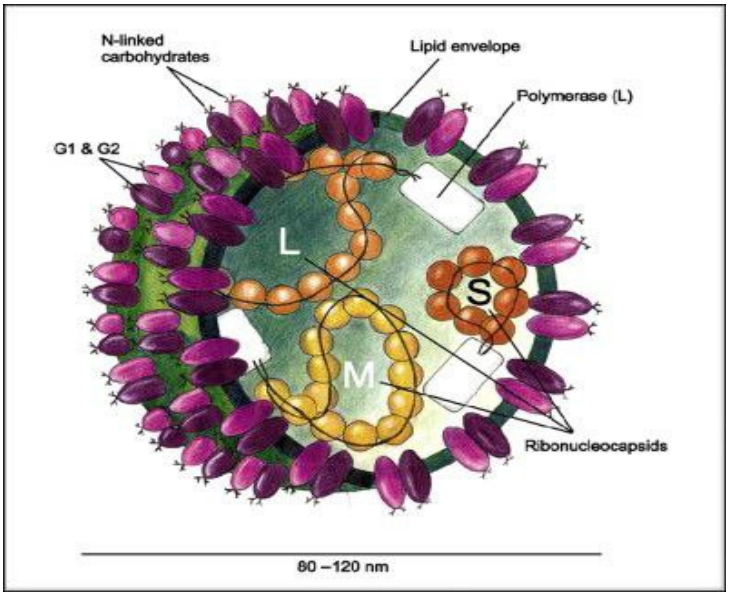

Figure 1 Shows the typical shape of the CCHF virus, source: (Ergönül, 2o14).

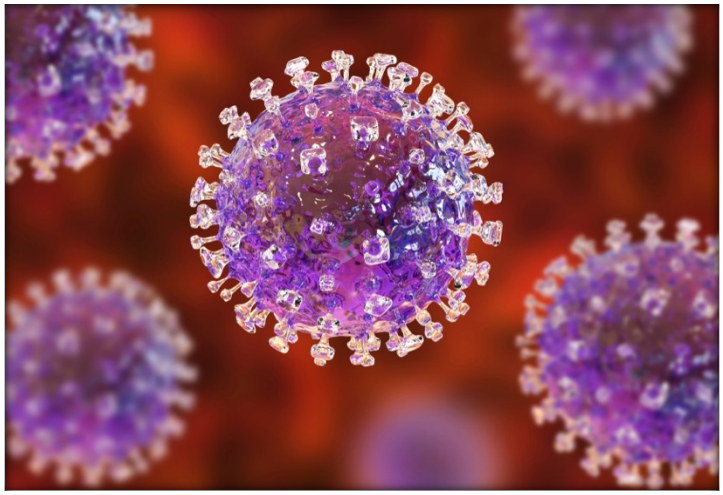

Figure 2 Recombinant CCHFV main glycoprotein Gc isolated from culture supernatant and generated in HEK293 cells. A fifteen amino acid glycine-serine linker and the human IgG1 Fc region have been added to the protein in place of the tail of the intravirion and the C-terminal transmembrane domain. https://thenativeantigencompany.com/products/crimean-congo-hemorrhagic-fever-virus-gc-protein-human-fc-tag/

Disease Transmission

Ticks serve as the virus's "environmental reservoir" and vector, passing it from wild animals to pets and, human (Gonzalez et al., 1992; Whitehouse, 2004). A true tick-associated arbovirus, the CCHFV is transstadially lives [larva-to-nymph-to-adult], and lives seasonally by many tick species. Transovarially transmission is commonly occur in F1, and rarely in F2 generations of tick species; *Hyalomma marginatum marginatum, Hyalomma marginatum rufipes, Rhipicephalus rossicus,* and *Dermacentor marginatus*. CCHF virus reservoirs/vectors have been identified in 25 tick species and subspecies (*Argas persicus* has confired as the one reporting from the avian parasitic argasid). Noticeably, *Boophilus microplus, Boophilus decoloratus, Boophilus annulatus,* and may be *Boophilus geigyi* are one-host tick species that they maintain intensive viruses last for several weeks or sometimes months while infesting artiodactyls (particularly cattle). *Hyalomma marginatum marginatum*, *Hyalomma marginatum turanicum*, *Hyalomma marginatum rufipes*, and maybe *Hyalomma marginatum isaaci* are the two-host vectors; as immatures, they consume hedgehogs, hares, or birds; as adults, they predominately feed on artiodactyls (but occasionally also on humans). *Hyalomma detritum, Hyalomma anatolicum,* and *Rhipicephalus bursa* (the two-host tick) are feed also on artiodactyls like adults or juveniles. For their aggressiveness in seeking out the human host with their abundance at particular times, *Hyalomma* marginatum complex along with *Hyalomma antomical* are particularly essential for starting CCHF outbreaks and epidemics in human being. Other tick species, such as the thirteen species of the three-host ticks; (*Amblyomma variegatum, Haemaphysalis punctata, Hyalomma* [five species], *Rhipicephalus* [four species], *Dermacentor* [two species]) that they often less aggressively strive for human being host than the mentioned *Hyalommas*. They primarily preserve epizootic foci of Congo-Crimean Hemorrhagic Fever Viruses proliferating among ticks with domestic and wild animals (Hoogstraal, 1979). In addition to *Argas reflexus*, *Rhipicephalus sanguineus*, *Hyalomma anatolicum*, *Hyalomma detritum*, and *Hyalomma marginatum*, the virus has also been discovered in tick species in the Middle East (Telmadarraiy et al., 2015). However, there are at least thirty-one different worldwide tick species carrying the virus. *Hyalomma* and *Haemaphysalis* genera

are identified to have the virus in southeast Iran (Mehravaran et al., 2013). The "amplifying hosts" for wild animals and small mammals are affected by the virus including multimammate rats, Middle-African hedgehogs, and European hares. The only species of bird that is not sensitive to CCHF is the ostrich. Even though presence of high circulating antibody titter of CCHFV in domesticated animals such as cattle, sheep and goats, they rarely get sick from it (Ergönül et al., 2004). A bite from the tick *Hyalomma* often results in human "sporadic infection". The virus can infect humans from animals; however, this usually occurs in conjunction with a number of other disorders. When disease clusters form, humans typically treat, slaughter, or eat diseased livestock, particularly ruminants. Ostriches as well, contaminated blood and feces from animals or people, have exposed workers to outbreaks in abattoirs and other locations (Vorou et al., 2007; Blacksell et al., 2023). Humans can contract diseases from other humans, and clinical settings can also experience epidemics due to contaminated medical equipment and blood (Vorou et al., 2007; Bodur et al., 2010).

Vertical transmission

The tick-borne CCHF virus is transmitted during fertilizing, both from adult females to males and from adult females to their eggs. CCHF grows in ticks' midgut linings and spreads to many bodily tissues, including the ovaries and salivary glands. Transovarian transmission occurs when thousands of female ticks lay eggs, which sustains a huge population of infected ticks (Hoogstraal, 1979).

Horizontal transmission

The virus enters the human body via tick-bite or due to direct contact with blood of animals (veterinarians, slaughterhouse workers, farmers, etc.). Blood, semen, and saliva have all been reported to be the primary bodily fluids used for transmission from person to person (Bodur et al., 2010). Recently, three instances of sexual transmission between spouses have been reported (Pshenichnaya et al., 2016).

PHYLOGENETICS AND GENETIC DIVERSITY

Through phylogenetic analysis of the L and S-RNA, two genetic clades from Asia, two from Europe, and three from Africa were discovered portions of the CCHFV (Wahid et al., 2019). Based on recent outbreaks reported in Iraq, the United States, Pakistan, Saudi Arabia, India, Bulgaria, Turkey, Congo, Mauritania, Uganda and the Middle East; Table 1 presents eight distinct clades (Appannanavar and Mishra, 2011).

The CCHFV moved from the Middle East to Asia in two different paths, the first of which was dispersed in Central Asia and China and the second of that was identified in Pakistan and Iran. Finally, two very distinct strains which were believed to be Turkish infiltrated Europe. Based on a phylogenetic study of the sequencing data of the S-RNA segment, the genetic diversity of multiple CCHFV strains from various geographic locations is shown in Figure 3. According to Shayan et al. (2015), China, Russia, and Tajikistan all have phylogenetically separate groupings, according to the genetic analysis of M-segment. Only in the short genomic portions of the S-segment does crossover occur, based on different natural evaluations. Drosdov, HY-13 from China, JD206 from Pakistan, TI10145 from Uzbekistan, and STV/HU29223 from Taiwan are CCHFV strains that go through recombination Russian strain (Alam et al., 2013).

Table 1 Eight distinct clades of CCHFV are distributed geographically (Wahid et al., 2019).

Geographical origin	Clades
Uganda	1
Nigeria and the Central African Republic	2
Senegal, Mauritania, and South Africa	3
strains from Turkey, South Russia, and Europe	4
Uzbekistan, Tajikistan, China, Central Asia, and Kazakhstan	5
Greece (A92strain isolated from *Riphicephalus bursa*)	6
Group1(Iran, Pakistan and Madagascar)	7
Group2 (Iran, Mauritania, and Senegal)	8

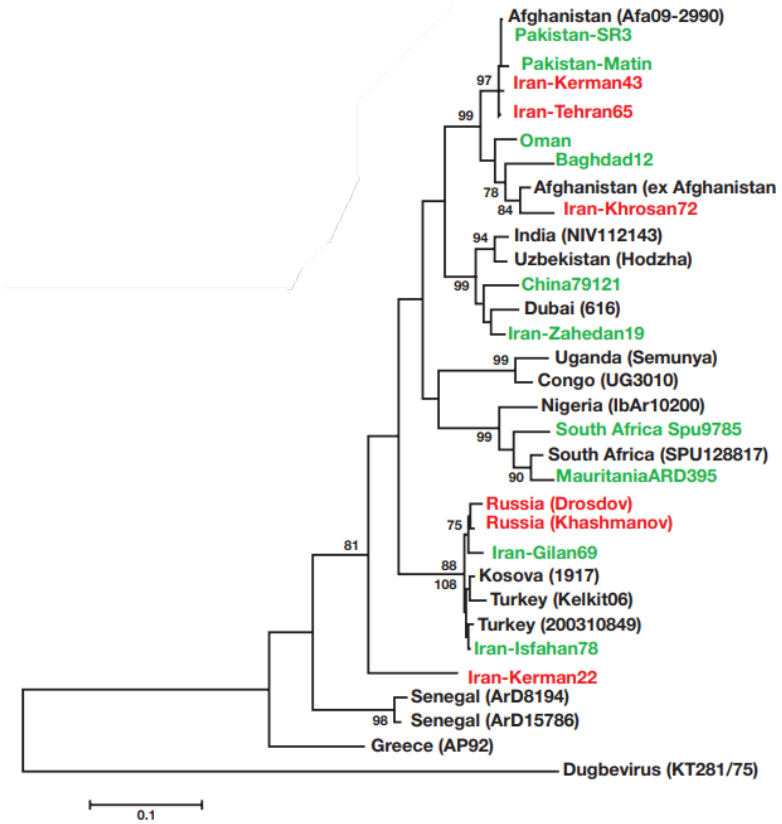

Figure 3 Showing the genetic diversity of multiple CCHFV strains from various geographic locations. The tree was constructed using Molecular Evolutionary Genetic Analysis (MEGA5) using a small segment of Crimean-Congo hemorrhagic fever virus (CCHFV). Bootstrap values are shown above the branches in percentages (of 1000 replicates). Recombination is shown by strains highlighted in green, and reassortment is shown by strains highlighted in red (Shayan et al., 2015).

EPIDEMIOLOGY PREVALENCE WITH SPECIAL TOPICS IN IRAQ

According to Ergönül et al. (2004), CCHFV, which is a member of the Bunyaviridae family and the Nairovirus genus, causes serious illnesses in humans with a documented fatality rate of 3–30% (Ergönül et al., 2004). Ticks, especially belonging to the *Hyalomma* genus, naturally transmit the virus to hosts that are not vertebrate during the enzootic sylvatic life cycle. Considering that they can prolong the virus's life for months or even years, these ticks serve as a pair of reservoir and vectors (biological) to CCHFV (Gargili et al., 2017). The disease has the widest geographic spread of the medically significant viral infections spread by ticks,

having been described in more than thirty countries. Humans can become ill from tick bites, intimate contact with sick people, and animals that have viremia. There have been reports of healthcare workers developing CCHF as a result of inadvertent needle sticks and when they come into contact with the bodily fluids, blood, or droplets of CCHF patients (De La Calle-Prieto et al., 2018). The clinical symptoms of CCHF appear post a short incubation period, usually during lower than seven days. Significant elevation of body temperature, headache, myalgia with disorders in gastro-intestinal system are among the early warning signs. Hemorrhagic syndrome can happen in the second stage of infection. There may occasionally be bleeding from the mucous membranes and skin (Fillâtre et al., 2019).

As early as 1979, when ten people were initially diagnosed with the illness, CCHF became known in Iraq. Then, between 1990 and 2009, a total of six instances was documented; in 2010, eleven instances; in 2018, three fatal cases; and, most recently, 33 confirmed cases, including 13 deaths (case fatality rate [CFR] = 39%), were reported in 2021 (Ahmad et al., 2022). An arbovirus known as Crimean-Congo hemorrhagic fever virus (CCHFV) is the cause of the tick-borne disease Crimean-Congo hemorrhagic fever (CCHF), which has a high mortality rate and has recently spread to Iraq (Mukherjee et al., 2022). According to Fillâtre et al. (2019), CCHF is widespread over parts of Asia, Africa, and Europe (Fillâtre et al., 2019). It has previously been reported that Iraq has been affected by CCHF, first in 1979, then in 1992, 1996, 2012, and until 2023 (Al-Shauwreed et al., 2023). According to a seroepidemiological study conducted in 1996, the prevalence of IgG antibodies to CCHF in rural residents of Basrah is below the endemic level. However, CCHF seropositivity was 9.7% among northern Basrah inhabitants, while 20% of sheep and 37% of cattle were seropositive (S Al-Yabis et al., 2005). To avoid or contain the current CCHF outbreak in a timely manner and avoid it from spreading further, immediate action is needed (Ahmad et al., 2022). Despite CCHFV has recently spread throughout Iraq, causing high mortality and morbidity rates in humans, the prevalence and distribution of CCHFV in Iraq are poorly understood, making it impossible to quantify the risk of infection (Nubgan and Al-Saadi, 2023). In order to progress development of vaccinations, treatments, and control measures for effective control and prevention, the situation with the CCHF outbreak in Iraq right now has not been adequately documented, nor have the primary characteristics of this significant disease.

A confirmed CCHF outbreak that was occurring in the Saint-Louis region of Senegal (a country where CCHF is prevalent) was recorded to the WHO August 12th, 2022 (Sah et al., 2022). The surveillance system for viral hemorrhagic fever (VHF) identified. The index case was a 38-year-old female patient who had hemorrhagic symptoms, a fever, a headache, myalgia, and tiredness. Track record of successfully visiting Mauritian, where CCHF is endemic before the onset of symptoms, and the index case died from the illness. On the fourteenth of August 2022, a second case that was a contact of the index case received a positive confirmation (Sah et al., 2022). 1112 probable CCHF patients were reported in the WHO Report for week 32 on August 14, 2022 have been identified in Iraq, of which 295 were laboratory verified. Of the verified cases, 53 deaths (comprising 17.9% of the positive case fatality rate) and 86 linked suspected deaths were recorded. Since there was a 14% increase in cases from the previous week, the current number likewise showed an upward tendency (WHO, 2022b). A confirmed record of having the polymerase chain reaction (PCR) revealed direct contact with animals. Verified cases or 84% of individuals reported to be sick were homemakers, butchers, breeders, and traders of livestock. On the fourteenth of August 2022, it was established that positive results were obtained in a second case, which was a contact of the index case (Sah et al., 2022). The WHO reported 1112 probable CCHF cases as of the week ending on August 14, 2022 have been identified in Iraq, 295 of them have been verified in laboratories. 53 fatalities (comprising 17.9% of cases that result in fatalities) and 86 related suspected deaths have been identified

among the confirmed cases. The present statistic also demonstrated an upward tendency because there had been a 14% increase of cases from the prior week (WHO, 2022b). In the polymerase chain reaction (PCR) verified instances or 84% of the people reported to be ill, there was a verifiable record of having direct contact with animals. These people included homemakers, butchers, livestock breeders, and traders.

PATHOGENESIS

Since there is not an animal model for the illness, pathophysiology is mainly unknown. Typically, laboratory animals lack any overt symptoms of disease (Van Leeuwen et al., 2022). To research CCHFV pathogenesis, a new small-animal model that displays clinical illness resembling that found in people without the virus adapting to the host was developed (Bente et al., 2010). Because of this, mice lacking the signalling proteins for STAT-1 were highly vulnerable to infection and died within three to five days. Mice with CCHF virus infection showed fever, thrombocytopenia, and leukopenia, and significantly increased liver enzyme levels. Significant histopathologic alterations in the liver and spleen have been linked to rapid viremic dispersion and extensive replication in these organs. The blood of the animals had dramatically increased proinflammatory cytokine levels, which is indicative of a cytokine storm. The results of the immunologic investigation showed extensive lymphocyte depletion and delayed immune cell activation. Furthermore, this study showed that mice are protected from lethal CCHFV challenge by ribavirin, a medication that is suggested for use in human circumstances. Interferon response thus becomes essential in controlling the mouse model of Crimean-Congo Hemorrhagic Fever (CCHF) replication. This brand-new mouse model displays crucial traits of lethal human CCHF, demonstrates value in assessing the efficacy of therapeutic approaches, and can be used to research how viruses weaken. However, the pathogenesis of CCHF is poorly understood because there is no reliable animal model for researching the illness, it primarily affects areas with outdated medical infrastructure, and it requires work to be performed under biosafety level 4 (BSL-4) containment due to its high virulence (Garrison et al., 2019). The majority of what is currently understood comes from case studies involving humans, some in vitro research, and extensive extrapolation from what is other viral hemorrhagic fevers are well-known. Since the initial virus isolation in 1956, an array of household and lab animals have been examined as potential animal models (Woodall et al., 1967; Whitehouse, 2007). Hamsters, rabbits, guinea pigs, calves, and horses that were infected experimentally do not show any clinical symptoms of illness despite developing little to having large amounts of neutralizing antibodies without any viremia (Shepherd et al., 1989; Whitehouse, 2007). Contrary to the vast majority CCHFV family hemorrhagic fever viruses are not known to frequently infect utilized nonhuman primate species with sickness (Fagbami et al., 1975; Smirnova, 1979). Adult immunocompetent mice exhibit no symptoms of illness and are not vulnerable to CCHFV infection (Smirnova, 1979). On the other hand, high viral titers in the blood and liver have been observed in a mouse infection model in a young animal (Tignor and Hanham, 1993). The virus could not be isolated from the spleen, which is home to numerous mononuclear phagocytes, despite the fact that these animals exhibit signs of systemic viral dispersion and infection of macrophages and this is compatible with the viral hemorrhagic fever paradigm (Gowen and Holbrook, 2008). Furthermore, due to the difficulties of frequent sample collection for pathogenesis investigations and animal husbandry, using a neonatal mouse in a BSL-4 environment is not very practicable.

Human interferons (IFNs) have been shown in earlier research to antiviral properties that can combat bunyaviruses (Morrill et al., 1989). Additionally, IFN response is critical for controlling Crimean-Congo Hemorrhagic Fever (CCHFV) replication, as evidenced by the results of in vitro study, and a recent study has

revealed that IFN receptor knockout (KO) mice are especially susceptible to CCHFV infection (Andersson et al., 2008; Bereczky et al., 2010).

In a related investigation, the researchers discovered that inhibiting CCHFV replication required a functional IFN response. The signal transducer and activator of transcription 1 (STAT1), an essential component of the IFN signalling pathway, was disrupted homozygously in the mice utilized in the study (Meraz et al., 1996).

IFNs come in three different types: type I (alpha interferon [IFN-] and type II (IFN-), type III (IFN-), and type II (IFN-). Despite using STAT1 and STAT2 receptor complexes of various types are activated and transported to the nucleus in response to IFN / and IFN- stimulation, where they then bind to the IFN response genes' promoters. STAT1 is triggered by IFN- whereas not STAT2, in comparison. Hence, the intracellular IFN response is entirely abolished in STAT1 KO mice in response to all three types of IFNs through selective signaling abnormalities (Akira, 1999). As a result, STAT1 knockout mice are highly vulnerable to even low doses of CCHFV challenge, and this novel mouse model shows many symptoms of human illness. Additionally, animals are protected from CCHFV challenge by ribavirin.

CLINICAL FEATURES

According to serological data, CCHFV can silently infect a wide range of wild and domestic animals. Furthermore, even in people, CCHFV infection is frequently asymptomatic or subclinical (Rodriguez et al., 2022). But symptomatic sickness only occurs in people. Humans with CCHF may experience an array of symptoms, from mild infections with no signs to severe, occasionally lethal diseases. In humans, hemorrhaging fever in its most serious stage is the clinical disease linked to CCHFV (Whitehouse, 2004). The incubation period following a tick bite typically lasts two to three days but can extend to nine days, compared to five to six days for the incubation period after coming into touch with infected blood or tissues but can extend to a maximum of 13 days (WHO, 2022a) The pre-hemorrhagic phase's fast onset of symptoms includes fever, myalgia (muscle aching), dizziness, stiff neck, Suhash sickness, a headache, itchy eyes, and photophobia (light sensitivity). At the beginning of the acute infection phase, common signs include nausea, diarrhea, pain in the abdomen, or sore throat. These symptoms are then abruptly followed by anxiety, confusion, and variations in mood (WHO, 2022a), which can be fatal if left untreated. After a short period, the agitation may subside and be replaced by lethargy, depression, and lassitude. The upper right quadrant of the stomach may also experience the pain, which is often accompanied by visibly enlarged liver tissue. Large patches of bleeding, severe nosebleeds, and bruising that is uncontrolled at places of injection may be observed. When the sickness starts to hemorrhage, starting on approximately starting on the 4th day of the illness and lasting for around 2 weeks. Among the additional clinical signs is tachycardia (rapid heartbeat), Petechiae (a rash brought on by bleeding into the skin) with lymphadenopathy (enlarged lymph nodes) on external mucosal surfaces, such as the skin and mouth. The petechiae could progress into ecchymoses, which are greater rashes, in addition to other hemorrhagic manifestations. Hepatitis is typically present, and after the fifth day of sickness, critically sick individuals may quickly develop kidney damage, failure of the liver, or respiratory failure (WHO, 2022a). Although According to the WHO, the typical range is between 10 and 40%, with deaths commonly happening in the second week of sickness, Hospitalized patients' death rates have ranged from 9% to 70% in reported outbreaks of CCHF. Improvement typically starts in individuals who recover on the 9th or 10th day following the start of their sickness. There has not been enough research carried out on the effects of CCHF infection over time in survivors to identify any specific issues. Recovery, however, takes time. The four unique stages of CCHFV infection are incubation, pre-hemorrhagic, hemorrhagic, and convalescence. Following a

tick bite, the incubation period lasts 1 to 5 days, and it persists for 5-7 days after coming to contact with contaminated blood or tissues (Ergönül, 2006; Bente et al., 2013). The pre-hemorrhagic stage lasts for between four and five days and is defined by a sudden appearance of an array of generalized signs that match those of other diseases. Certain individuals may have subclinical or asymptomatic CCHFV infections; for instance, high seroprevalence was observed in some parts of Turkey and Greece (Bodur et al., 2012; Papa et al., 2016). The hemorrhagic phase typically lasts two weeks and features hemorrhaging that develop quickly. Patients who are critically ill may rapidly deteriorate, go into shock, or suffer from multiorgan failure (Mazzola and Kelly-Cirino, 2019). Hospitalized patients have seen death rates up to 50% in known outbreaks, with an 30% of deaths, on average, occur in the second week of sickness (Charrel et al., 2004). Recovery for survivors typically starts 10–20 days after the sickness starts, although complete recovery could take up to a year (Ergönül, 2006; Bente et al., 2013). There has not been enough research conducted on the long-term impact of CCHFV infection in survivors to identify any specific issues.

Furthermore, CCHFV infection affects mice's hepatocytes and endothelium cells (Bente et al., 2010; Oestereich et al., 2014; Lindquist et al., 2018; Hawman et al., 2019), and the liver damage and vascular dysfunction may be the result of viral replication in these tissues observed in CCHF patients. Hamsters lacking STAT2 are also vulnerable to CCHFV infection, which can be fatal. According to these models (Bente et al., 2010; Zivcec et al., 2013; Lindquist et al., 2018), illness is often accompanied by unchecked viral proliferation, inflammation immune-mediated responses, liver damage, and ultimately mortality rates.

DIAGNOSIS

Among the laboratory methods used to find CCHF are IFA (immunofluorescence assay), ELISA (antigen-capture), and antibody (IgG, IgM) tests, reverse transcriptase (RT)-PCR, and virus isolation. Patients with Crimean-Congo Hemorrhagic Fever are often diagnosed using RT-PCR tests because they offer the high rate of sensitivity for detection the recent active infection. The broad spectrum and CCHFV development in situ may make it challenging to pinpoint a specific lineage, especially for RT-PCR methods that depend on a conserved genomic sequence (Vanhomwegen et al., 2012; Koehler et al., 2018). Small modifications to the genome have little of an effect on serological detection. Given the wide range of CCHFV strains, it is suggested that should be used immunological assays when combined with RT-PCR and this is one example of NAAT (nucleic acid amplification test) for the highest detection sensitivity (Drosten et al., 2003; Mertens et al., 2013; Fernandez-Garcia et al., 2014). Even at the beginning of an outbreak, it’s possible that PCR testing is not feasible in many low-resource environments. Because a strict BSL-4 biosafety containment level is needed, rarely is viral isolation utilised as a diagnostic tool method. The majority ELISA and IFA can be carried out on a benchtop in a relatively basic lab setting, whereas NAAT typically calls for a high level of laboratory equipment, a PCR station or clean room, as well as biosafety hoods (Roberts et al., 2012; Wang et al., 2016). Point of care (POC) NAAT tests should ideally be samples are transferred to a cartridge that is integrated and contains all the chemicals and is entirely automated required for the analysis and processing of samples. Biosafety hoods are not required for this procedure, if the sample preparation criteria are met (here defined as BSL-2 for human illnesses) (Wang et al., 2016). There will be no more manual steps needed after the cartridge has been inserted into the device. RDTs (rapid diagnostic tests) are frequently developed for application in the field or in the home. The manufacturer specifies the time it takes to complete each test; for each result, it may also take a few days to a few weeks for the sample to be transported and processed at the reference lab.

Rapid diagnosis tests

ELISA-compatible antibody/antigen capture agents can be utilized in RDTs, however, they do so in a lateral flow strip configuration and require only small specimen processing (blood, plasma, or swabs). Because of the smaller sample amount, it has a less sensitive detection than ELISA but a shorter time to result (10–30 min) (Filippone et al., 2013). Although follow-up confirmatory testing is frequently necessary (Table 2), RDTs are excellent screening tests which are acceptable for field testing and limited infrastructure settings (Burt et al., 1994). RDTs were effectively used to identify and rank possible high-risk disease outbreaks involving dengue and ebola, (Saluzzo and Le Guenno, 1987; Shepherd et al., 1988). However, there is no proof of CCHF RDT formation in the literature. Since the IgG/IgM serological response is often only visible for five days after an infection, and frequently goes undetected in severe and deadly illnesses, the main problem is detection sensitivity.

Table 2 Comparison of the diagnostic infrastructure (Mazzola and Kelly-Cirino, 2019).

Test format	Infrastructure necessities	Requirement Of training	Reaction time	In house or Prototype	Trade source	Goal population
Segregation and eradication of the virus	(Reference laboratory) (BSL-4) High	expert laboratory technician, high	three days, seven	different	-	Animal, Human
Reference for NAAT (multiplex included)	(BSL-3/4) high (reference lab-regional lab)	Moderate- high (expert laboratory technician	Two-. five hours 0ne-two hours of preparation	>ten	>five	Ticks, Human-animals
POC, NAAT	BSL-2 (Moderate, District Hospital)	(Lab Technician) Moderate	0ne-two hours	one	-	Ticks-Human culture
IFA, ELISA	High - moderate (District hospital, regional lab)	(Laboratory Technician) Moderate	Three-four hours	>ten	sex	Human, culture-, animal
R-D-Ts	Low (Clinic, health center, field settings)	Low (nurse, medical professional)	<thirty min	-	-	-

*BSL is for biosafety containment level. IFA stands for immunofluorescence assay. NAAT stands for nucleic acid amplification test.

Molecular diagnostics

The more stable part of The S region of the nucleoprotein gene section is shared by geographically distinct isolates of the CCHFV genome, which is the target of most RT-PCR-based approaches (Burt et al., 1998; Bodur et al., 2010). Based to several studies (Burt et al., 1998; Drosten et al., 2003; Duh et al., 2006; Bodur et al., 2010), The first week after the onset of symptoms is when CCHFV RNA peaks, and it can be found for up to three weeks beyond that. Viral load, which differs significantly between CCHF patients (Drosten et al., 2002; Çevik et al., 2007; Hasanoglu et al., 2018), can be a sign of severity. For mild instances, serum viral counts are typically 102–104 copies/mL, yet in severe cases, initial viral loads are often 104–107 copies/mL, with a fatal result predicted by viral burdens of 108–1010 copies/mL (Çevik et al., 2007; Duh et al., 2007; Akinci et al., 2016). In comparison to traditional RT-PCR or nested RT-PCR, quantitative real-time RT-PCR (qRT-PCR) performs better due to lower contamination rates, increased sensitivity and specificity, and improved time-effectiveness (Escadafal et al., 2012; Fernandez-Garcia et al., 2014). To improve the efficiency of tests and determine the amount of virus, it is being recommended that laboratories that exclusively use nested or traditional RT-PCR implement qRT-PCR. In order to allow amplification

at a single temperature in a more "crude" material, a NAAT test that uses recombinase polymerase for isothermal amplification has been developed (Bonney et al., 2017). This type of test may be more suitable as a field diagnostic or in laboratories with limited resources. While CCHFV phylogeny has already been investigated with next-generation sequencing (NGS) (Brinkmann et al., 2017; Papa et al., 2018), this time-consuming and expensive method has yet to be widely utilized. Currently, the approach is not workable for diagnostic screening.

TREATMENT

Supportive care is the mainstay of CCHF treatment, as there are very limited pharmacological options available (Jabbari et al., 2006; Vorou et al., 2007; Ascioglu et al., 2011). Patients with CCHF require close monitoring of the fluid and electrolyte balance, support for adequate oxygenation during ventilation, light sedation, and hemodynamic support as needed during the early stages of the disease. Delays in diagnosis and supportive care reduce treatment effectiveness and worsen the course of the disease. Depending on their state of homeostasis, a few of the patients required preparations of erythrocytes, platelets, and fresh frozen plasma. The care of severe CCHF cases requires replacement therapy using blood products, as determined by the findings of the complete blood count. The CCHF virus's ability to replicate itself in vitro has been demonstrated to be inhibited by ribavirin, a synthetic analogue of purine nucleosides (Ascioglu et al., 2011). Currently, the World Health Organization (WHO) recommends taking ribavirin, either orally or intravenously, as a viable medication for treating CCHF, however, there is a debate over its effectiveness in the course of therapy and certain studies have shown that oral ribavirin treatment in CCHF patients does not affect viral load or disease progression (Jabbari et al., 2006; Ascioglu et al., 2011; Bodur et al., 2011). According to our research, prescribing ribavirin to patients who received an early diagnosis was linked to greater survival rates, quicker recoveries, and an earlier return to normal levels of laboratory markers (Jabbari et al., 2006). Healthcare personnel who may have been exposed to the CCHF virus should think about receiving treatment with ribavirin in suspected instances and undergoing post-exposure prophylaxis (Smego Jr et al., 2004). It was determined that this strategy could be regarded as a standard treatment or prophylactic protocol according to the clinical responses that were observed in a majority of patients who have been prescribed ribavirin along with corticosteroids for treatment or prophylaxis (Jabbari et al., 2006; Jabbari et al., 2008; Ascioglu et al., 2011). According to Ascioglu et al. (2011) and Vorou et al. (2007), there is actual doubt regarding the benefits of intensive care unit preparedness CCHF treatment with this medication in addition to intravenous ribavirin and corticosteroid prescription (Vorou et al., 2007; Ascioglu et al., 2011). Because treatment protocols and disease prevention measures are more advanced in intensive care units, intensive care for admitted patients simultaneously improves the patient's outcome and plays a significant role in disease control.

CONTROL AND PREVENTION

The only strategy to decrease CCHF infection because there is currently no vaccination is to promote public awareness of the disease's risk factors and possibilities (Aslam et al., 2016). preventive measures involving controlling the spread of sickness and reducing virus exposure. Because the tick's life cycle passes unnoticed by animals, the infection is frequently undetectable in animals, and only viremia occurs, managing CCHF infection in animals and ticks is challenging (WHO, 2022a). During tick season, avoiding tick-infested areas and taking extra precautions might lessen the risk of tick-to-human communication. By using glove and staying free of direct skin contact with fresh-blooded animals and other tissues, butchers, veterinarians, and shepherds can reduce their exposure to

virus-infected ticks or virus-contaminated animal blood and tissues. Use permethrin spray on clothing to prevent tick bites, acaricides on animals, and commercial insect repellents such diethyl toluamide on exposed skin to minimize the number of infected ticks. Medical staff should employ usual barrier nursing practices and separate the patient to lower the potential of transmission from an infected human to another human (Whitehouse, 2004). In addition to avoiding touching each other directly, they should also routinely wash their hands. Healthcare workers must use surgical masks, high-efficiency air respirators, face shields, safety goggles, and other protective equipment when they are closer to patients than three feet away (Leblebicioglu et al., 2012) and wash their hands frequently and properly while doing so (WHO, 2013). Use only disposable instruments and materials, such as syringes and needles, and follow correct burial protocols (Lloyd and Perry, 1998.) By heating at 56°C for 30 minutes, disinfectants such 2% glutaraldehyde and 1% hypochlorite can be rendered ineffective (Appannanavar and Mishra, 2011). Milk that is raw should not ever be consumed, while only fully prepared meals should be eaten. Animals should be routinely administered insecticides and preventative precautions should be made to prevent animal-to-human transmission when importing them, maintaining clean surroundings while slaughtering animals at home or in commercial slaughterhouses. Gloves must be utilized when working with meat. Before reuse, knives as well as other equipment should be cleaned after an animal has been slaughtered (WHO, 2013).

CONCLUSIONS

CCHFV has a wide geographic distribution and a big population at risk, but the factors that determine its understanding of the host and viral factors of pathophysiology is still lacking. Prevention measures like schooling, decreased vector contact, tick therapy, animal isolation, and protection against dangerous exposures activity must be put into place in endemic areas. quick diagnosis is crucial since the condition has significant public health implications. Real-time PCR enables rapid diagnosis of CCHF. Future research should concentrate on understanding the molecular basis of CCHFV infection and how to cure it because there are a number of knowledge gaps in these areas. Despite the fact that pets play a crucial role in the sickness' transmission to humans, farmers, and slaughterhouse employees, the disease is less common in animals since they are asymptomatic.

ACKNOWLEDGEMENTS

The authors would want to say thank you to everyone who helped to complete this work and provided support.

CONFLICT OF INTEREST

There are no conflicts of interest, according to the authors.

AUTHORS CONTRIBUTIONS

Together with WMMS, AAD produced the initial text and started the review. WMMS and SSHA looked over the document, provided feedback, and approved the final version.

REFERENCES

Ahmad, S., Hashmi, N., Siddiqui, J.A., Siddiqui, A., Ahmad, S., Hashim, H.T., Essar, M.Y., 2022. The nosebleed fever outbreak in iraq: Challenges, efforts and recommendations. Ann. Med. Surg. 79, 104077.

Akinci, E., Bodur, H., Sunbul, M., Leblebicioglu, H., 2016. Prognostic factors, pathophysiology and novel biomarkers in crimean-congo hemorrhagic fever. Antivir. Res. 132, 233-243.

Akira, S., 1999. Functional roles of stat family proteins: lessons from knockout mice. Stem Cells. 17(3), 138-146.

Al-Rubaye, D., Al-Rubaye, T.S., Shaker, M., Naif, H.M., 2022. Recent outbreaks of crimean–congo hemorrhagic fever (CCHF) in Iraq. Sci. Arch. 3, 109-112.

Al-Shauwreed, A.K.M., Hamadi, S.S., Issa, A.H., Saud, H.A., Alshami, I.J.J., Fares, M.N., 2023. Evolutionary and historical study of crimean-congo hemorrhagic fever virus (cchfv). Med. J. Basrah Univ. 41(1), 12-25.

Al-Tikriti, S., Al-Ani, F., Jurji, F., Tantawi, H., Al-Moslih, M., Al-Janabi, N., Mahmud, M., Al-Bana, A., Habib, H., Al-Munthri, H., 1981. Congo/crimean haemorrhagic fever in iraq. Bull World Health Organ. 59(1), 85.

Alam, M.M., Khurshid, A., Sharif, S., Shaukat, S., Suleman, R.M., Angez, M., Zaidi, S.S.Z., 2013. Crimean-congo hemorrhagic fever asia-2 genotype, pakistan. Emerg. Infect. Dis. 19(6), 1017.

Andersson, I., Karlberg, H., Mousavi-Jazi, M., Martínez-Sobrido, L., Weber, F., Mirazimi, A., 2008. Crimean-congo hemorrhagic fever virus delays activation of the innate immune response. J. Med. Virol. 80(8), 1397-1404.

Appannanavar, S.B., Mishra, B., 2011. An update on crimean congo hemorrhagic fever. J. Glob. Infect. 3(3), 285.

Ascioglu, S., Leblebicioglu, H., Vahaboglu, H., Chan, K.A., 2011. Ribavirin for patients with crimean–congo haemorrhagic fever: A systematic review and meta-analysis. J. Antimicrob. Chemother. 66(6), 1215-1222.

Aslam, S., Latif, M.S., Daud, M., Rahman, Z.U., Tabassum, B., Riaz, M.S., Khan, A., Tariq, M., Husnain, T., 2016. Crimean-congo hemorrhagic fever: risk factors and control measures for the infection abatement. Biomed. Rep. 4(1), 15-20.

Bente, D.A., Alimonti, J.B., Shieh, W.J., Camus, G., Stroher, U., Zaki, S., Jones, S.M., 2010. Pathogenesis and immune response of crimean-congo hemorrhagic fever virus in a stat-1 knockout mouse model. J. Virol. 84(21), 11089-11100.

Bente, D.A., Forrester, N.L., Watts, D.M., Mcauley, A.J., Whitehouse, C.A., Bray, M., 2013. Crimean-congo hemorrhagic fever: history, epidemiology, pathogenesis, clinical syndrome and genetic diversity. Antivir. Res. 100(1), 159-189.

Bereczky, S., Lindegren, G., Karlberg, H., Akerstrom, S., Klingstrom, J., Mirazimi, A., 2010. Crimean–congo hemorrhagic fever virus infection is lethal for adult type I interferon receptor-knockout mice. J. Gen. Virol. 91(6), 1473-1477.

Blacksell, S.D., Dhawan, S., Kusumoto, M., Le, K.K., Summermatter, K., O'keefe, J., Kozlovac, J., Almuhairi, S.S., Sendow, I., Scheel, C.M., 2023. The biosafety research road map: The search for evidence to support practices in the laboratory—crimean congo haemorrhagic fever virus and lassa virus. Appl. Biosaf. 28(4), 216-229.

Bodur, H., Akinci, E., Ascioglu, S., Öngürü, P., Uyar, Y., 2012. Subclinical infections with crimean-congo hemorrhagic fever virus, Turkey. Emerg. Infect. Dis. 18(4), 640.

Bodur, H., Akıncı, E., Öngürü, P., Carhan, A., Uyar, Y., Tanrıcı, A., Cataloluk, O., Kubar, A., 2010. Detection of crimean-congo hemorrhagic fever virus genome in saliva and urine. Int. J. Infect. Dis. 14(3), e247-e249.

Bodur, H., Erbay, A., Akıncı, E., Öngürü, P., Bayazıt, N., Eren, S.S., Kubar, A., 2011. Effect of oral ribavirin treatment on the viral load and disease progression in crimean-congo hemorrhagic fever. Int. J. Infect. Dis. 15(1), e44-e47.

Bonney, L.C., Watson, R.J., Afrough, B., Mullojonova, M., Dzhuraeva, V., Tishkova, F., Hewson, R., 2017. A recombinase polymerase amplification assay for rapid detection of crimean-congo haemorrhagic fever virus infection. PLoS Negl. Trop. Dis. 11(10), e0006013.

Brinkmann, A., Ergünay, K., Radonić, A., Kocak Tufan, Z., Domingo, C., Nitsche, A., 2017. Development and preliminary evaluation of a multiplexed amplification and next generation sequencing method for viral hemorrhagic fever diagnostics. PLoS Negl. Trop. Dis. 11(11), e0006075.

Burt, F., Leman, P., Abbott, J., Swanepoel, R., 1994. Serodiagnosis of crimean-congo haemorrhagic fever. Epidemiol. Infect. 113(3), 551-562.

Burt, F., Leman, P., Smith, J., Swanepoel, R., 1998. The use of a reverse transcription–polymerase chain reaction for the detection of viral nucleic acid in the diagnosis of crimean–congo haemorrhagic fever. J. Virol. Methods. 70(2), 129-137.

Carroll, S.A., Bird, B.H., Rollin, P.E., Nichol, S.T., 2010. Ancient common ancestry of crimean-congo hemorrhagic fever virus. Mol. Phylogenet. Evol. 55(3), 1103-1110.

Carter, S.D., Surtees, R., Walter, C.T., Ariza, A., Bergeron, É., Nichol, S.T., Hiscox, J.A., Edwards, T.A., Barr, J.N., 2012. Structure, function, and evolution of the crimean-congo hemorrhagic fever virus nucleocapsid protein. J. Virol. 86(20), 10914-10923.

Casals, J., 1969. Antigenic similarity between the virus causing crimean hemorrhagic fever and congo virus. Proc. Soc. Exp. Biol. Med. 131(1), 233-236.

Çevik, M.A., Erbay, A., Bodur, H., Eren, S.S., Akinci, E., Şener, K., Öngürü, P., Kubar, A., 2007. Viral load as a predictor of outcome in crimean-congo hemorrhagic fever. Clin. Infect. Dis. 45(7), e96-e100.

Charrel, R.N., Attoui, H., Butenko, A., Clegg, J., Deubel, V., Frolova, T., Gould, E., Gritsun, T., Heinz, F., Labuda, M., 2004. Tick-borne virus diseases of human interest in Europe. Clin. Microbiol. Infect. 10(12), 1040-1055.

Chumankov, M., Butenko, A., Shalunova, N., Mart'ianova, L., Smirnova, S., Bashkiritsev, I., Zavodova, T., Rubin, S., Tkachenko, E., Karmysheva, V., 1968. New data on the viral agent of crime an hemorrhagic fever. Vopr. Virusol. 13, 377.

Crowcroft, N., Morgan, D., Brown, D., 2002. Viral haemorrhagic fevers in europe–effective control requires a co-ordinated response. Euro. Surveill. 7(3), 31-32.

Dakhil, A.A., Saleh, W.M.M., Al-Taher, S.S.H., Alqaisi, K.A.K., Naji, M.M., AbdulRasool, L.M.S., 2024. Seroepidemiological survey of Crimean-Congo Hemorrhagic Fever (CCHF) in small ruminants after a recent human outbreak in Basra governorate, southern Iraq in 2023. Consultant. 64(6):627-634.

De La Calle-Prieto, F., Martín-Quirós, A., Trigo, E., Mora-Rillo, M., Arsuaga, M., Díaz-Menéndez, M., Arribas, J.R., 2018. Therapeutic management of crimean-congo haemorrhagic fever. Enferm. Infecc. Microbiol. Clin. (Engl. Ed.) 36(8), 517-522.

Drosten, C., Gottig, S., Schilling, S., Asper, M., Panning, M., Schmitz, H., GüNther, S., 2002. Rapid detection and quantification of rna of ebola and marburg viruses, lassa virus, crimean-congo hemorrhagic fever virus, rift valley fever virus, dengue virus, and yellow fever virus by real-time reverse transcription-pcr. J. Clin. Microbiol. 40(7), 2323-2330.

Drosten, C., Kümmerer, B.M., Schmitz, H., Günther, S., 2003. Molecular diagnostics of viral hemorrhagic fevers. Antivir. Res. 57(1-2), 61-87.

Duh, D., Saksida, A., Petrovec, M., Ahmeti, S., Dedushaj, I., Panning, M., Drosten, C., Avšič-Županc, T., 2007. Viral load as predictor of crimean-congo hemorrhagic fever outcome. Emerg. Infect. Dis. 13(11), 1769.

Duh, D., Saksida, A., Petrovec, M., Dedushaj, I., Avšič-Županc, T., 2006. Novel one-step real-time rt-pcr assay for rapid and specific diagnosis of crimean-congo

hemorrhagic fever encountered in the balkans. J. Virol. Methods. 133(2), 175-179.
Ergönül, Ö., 2006. Crimean-congo haemorrhagic fever. Lancet. Infect. Dis. 6(4), 203-214.
Ergönül, Ö., 2014. Chapter 10—Crimean-Congo Hemorrhagic Fever. In: Emerg. Infect. Dis. Amsterdam: Academic Press; p:135–148.
Ergönül, Ö., Çelikbaş, A., Dokuzoğuz, B., Eren, Ş., Baykam, N., Esener, H., 2004. Characteristics of patients with crimean-congo hemorrhagic fever in a recent outbreak in turkey and impact of oral ribavirin therapy. Clin. Infect. Dis. 39(2), 284-287.
Ergönül, Ö., Tuncbilek, S., Baykam, N., Celikbas, A., Dokuzoguz, B., 2006. Evaluation of serum levels of interleukin (il)–6, il-10, and tumor necrosis factor–α in patients with crimean-congo hemorrhagic fever. J. Infect. Dis. 193(7), 941-944.
Ergönül, Ö., Whitehouse, C.A., 2007. Clinical and pathological features of Crimean-Congo hemorrhagic fever. In: Ergonul, O., Whitehouse, C.A. (Eds.), Crimean-Congo haemorrhagic fever: global perspective. Springer, Dordrecht, pp. 207-220.
Escadafal, C., Ölschläger, S., Avšič-Županc, T., Papa, A., Vanhomwegen, J., Wölfel, R., Mirazimi, A., Teichmann, A., Donoso-Mantke, O., Niedrig, M., 2012. First international external quality assessment of molecular detection of crimean-congo hemorrhagic fever virus. PLoS Negl. Trop. Dis. 6(6), e1706.
Fagbami, A., Tomori, O., Fabiyi, A., Isoun, T., 1975. Experimantal congo virus (Ib-AN 7620) infection in primates. Virologie. 26(1), 33-37.
Fernandez-Garcia, M.D., Negredo, A., Papa, A., Donoso-Mantke, O., Niedrig, M., Zeller, H., Tenorio, A., Franco, L., The Enivd Members, C., 2014. European survey on laboratory preparedness, response and diagnostic capacity for crimean-congo haemorrhagic fever, 2012. Euro. Surveill. 19(26), 20844.
Filippone, C., Marianneau, P., Murri, S., Mollard, N., Avsic-Zupanc, T., Chinikar, S., Despres, P., Caro, V., Gessain, A., Berthet, N., 2013. Molecular diagnostic and genetic characterization of highly pathogenic viruses: Application during crimean–congo haemorrhagic fever virus outbreaks in eastern europe and the middle east. Clin. Microbiol. Infect. 19(2), E118-E128.
Fillâtre, P., Revest, M., Tattevin, P., 2019. Crimean-congo hemorrhagic fever: an update. Med. Mal. Infect. 49(8), 574-585.
Gargili, A., Estrada-Peña, A., Spengler, J.R., Lukashev, A., Nuttall, P.A., Bente, D.A., 2017. The role of ticks in the maintenance and transmission of crimean-congo hemorrhagic fever virus: a review of published field and laboratory studies. Antivir. Res. 144, 93-119.
Garrison, A.R., Smith, D.R., Golden, J.W., 2019. Animal models for crimean-congo hemorrhagic fever human disease. Viruses. 11(7), 590.
Gonzalez, J.P., Camicas, J.L., Cornet, J.P., Faye, O., Wilson, M., 1992. Sexual and transovarian transmission of crimean-congo haemorrhagic fever virus in hyalomma truncatum ticks. Res. Virol. 143, 23-28.
Gowen, B.B., Holbrook, M.R., 2008. Animal models of highly pathogenic RNA viral infections: hemorrhagic fever viruses. Antivir. Res. 78(1), 79-90.
Guo, Y., Wang, W., Ji, W., Deng, M., Sun, Y., Zhou, H., Yang, C., Deng, F., Wang, H., Hu, Z., 2012. Crimean–congo hemorrhagic fever virus nucleoprotein reveals endonuclease activity in bunyaviruses. Proc. Natl. Acad. Sci. 109(13), 5046-5051.
Hasanoglu, I., Guner, R., Carhan, A.K., Tufan, Z.Y., Caglayik, D., Yilmaz, G.R., Tasyaran, M.A., 2018. Dynamics of viral load in crimean congo hemorrhagic fever. J. Med. Virol. 90(4), 639-643.
Hawman, D.W., Meade-White, K., Haddock, E., Habib, R., Scott, D., Thomas, T., Rosenke, R., Feldmann, H., 2019. Crimean-congo hemorrhagic fever mouse model recapitulating human convalescence. J. Virol. 93(18), e00554-00519.

Hepojoki, J., Strandin, T., Wang, H., Vapalahti, O., Vaheri, A., Lankinen, H., 2010. Cytoplasmic tails of hantavirus glycoproteins interact with the nucleocapsid protein. J. Gen. Virol. 91(9), 2341-2350.

Hoogstraal, H., 1979. The epidemiology of tick-borne crimean-congo hemorrhagic fever in Asia, Europe, and Africa. J. Med. Entomol. 15(4), 307-417.

Jabbari, A., Besharat, S., Abbasi, A., 2008. Some evidences about crimean congo hemorrhagic fever. Pak. J. Med. Sci. 24(1), 187-188.

Jabbari, A., Besharat, S., Abbasi, A., Moradi, A., Kalavi, K., 2006. Crimean-congo hemorrhagic fever: Case series from a medical center in golestan province, northeast of iran (2004-2006). Indian J. Med. Sci. 60(8), 327-329.

Koehler, J.W., Delp, K.L., Hall, A.T., Olschner, S.P., Kearney, B.J., Garrison, A.R., Altamura, L.A., Rossi, C.A., Minogue, T.D., 2018. Sequence optimized real-time reverse transcription polymerase chain reaction assay for detection of crimean-congo hemorrhagic fever virus. Am. J. Trop. Med. Hyg. 98(1), 211.

Leblebicioglu, H., Bodur, H., Dokuzoguz, B., Elaldi, N., Guner, R., Koksal, I., Kurt, H., Senturk, G.C., 2012. Case management and supportive treatment for patients with crimean-congo hemorrhagic fever. Vector Borne Zoonotic. Dis. 12(9), 805-811.

Lindquist, M.E., Zeng, X., Altamura, L.A., Daye, S.P., Delp, K.L., Blancett, C., Coffin, K.M., Koehler, J.W., Coyne, S., Shoemaker, C.J., 2018. Exploring Crimean-Congo hemorrhagic fever virus-induced hepatic injury using antibody-mediated type I interferon blockade in mice. J. Virol. 92(21), e01083-01018.

Maltezou, H.C., Papa, A., 2010. Crimean–congo hemorrhagic fever: risk for emergence of new endemic foci in Europe?. Travel Med. Infect. Dis. 8(3), 139-143.

Mazzola, L.T., Kelly-Cirino, C., 2019. Diagnostic tests for crimean-congo haemorrhagic fever: a widespread tickborne disease. BMJ Glob. Health. 4(Suppl 2), e001114.

Mehravaran, A., Moradi, M., Telmadarraiy, Z., Mostafavi, E., Moradi, A. R., Khakifirouz, S., Shah-Hosseini, N., Varaie, F.S.R., Jalali, T., Hekmat, S., 2013. Molecular detection of crimean-congo haemorrhagic fever (CCHF) virus in ticks from southeastern Iran. Ticks Tick Borne Dis. 4(1-2), 35-38.

Meraz, M.A., White, J.M., Sheehan, K.C., Bach, E.A., Rodig, S.J., Dighe, A.S., Kaplan, D.H., Riley, J.K., Greenlund, A.C., Campbell, D., 1996. Targeted disruption of the stat1 gene in mice reveals unexpected physiologic specificity in the jak–stat signaling pathway. Cell. 84(3), 431-442.

Mertens, M., Schmidt, K., Ozkul, A., Groschup, M.H., 2013. The impact of crimean-congo hemorrhagic fever virus on public health. Antivir. Res. 98(2), 248-260.

Mild, M., Simon, M., Albert, J., Mirazimi, A., 2010. Towards an understanding of the migration of crimean–congo hemorrhagic fever virus. J. Gen. Virol. 91(1), 199-207.

Morrill, J.C., Jennings, G.B., Cosgriff, T.M., Gibbs, P.H., Peters, C., 1989. Prevention of rift valley fever in rhesus monkeys with interferon-α. Rev. Infect. Dis. 11(Supplement_4), S815-S825.

Mukherjee, D., Roy, S., Iturburu, A., Jaiswal, V., 2022. Crimean congo hemorrhagic fever in covid 19 times, an emerging concern in Iraq. Ann. Med. Surg. 80, 104243.

Nubgan, A., Al-Saadi, M., 2023. Crimean-congo hemorrhagic fever favouring factors virus transmission: Special focus on iraq and neighbouring countries. Vet. Integr. Sci. 21(3), 865-877.

Oestereich, L., Rieger, T., Neumann, M., Bernreuther, C., Lehmann, M., Krasemann, S., Wurr, S., Emmerich, P., De Lamballerie, X., Ölschläger, S., 2014. Evaluation of antiviral efficacy of ribavirin, arbidol, and t-705 (favipiravir) in a mouse model for crimean-congo hemorrhagic fever. PLoS Negl. Trop. Dis. 8(5), e2804.

Okorie, T.G., 1991. Comparative studies on the vector capacity of the different stages of amblyomma variegatum fabricius and hyalomma rufipes koch for congo virus, after intracoelomic inoculation. Vet. Parasitol. 38(2-3), 215-223.

Overby, A.K., Pettersson, R.F., Neve, E.P., 2007. The glycoprotein cytoplasmic tail of uukuniemi virus (bunyaviridae) interacts with ribonucleoproteins and is critical for genome packaging. J. Virol. 81(7), 3198-3205.

Papa, A., Papadopoulou, E., Tsioka, K., Kontana, A., Pappa, S., Melidou, A., Giadinis, N.D., 2018. Isolation and whole-genome sequencing of a crimean-congo hemorrhagic fever virus strain, greece. Ticks. Tick. Borne. Dis. 9(4), 788-791.

Papa, A., Sidira, P., Tsatsaris, A., 2016. Spatial cluster analysis of crimean-congo hemorrhagic fever virus seroprevalence in humans, greece. Parasite Epidemiol. Control. 1(3), 211-218.

Pshenichnaya, N.Y., Sydenko, I.S., Klinovaya, E.P., Romanova, E.B., Zhuravlev, A.S., 2016. Possible sexual transmission of crimean-congo hemorrhagic fever. Int. J. Infect. Dis. 45, 109-111.

Ribeiro, D., Borst, J.W., Goldbach, R., Kormelink, R., 2009. Tomato spotted wilt virus nucleocapsid protein interacts with both viral glycoproteins GN and GC in planta. Virol. 383(1), 121-130.

Roberts, T., Bygrave, H., Fajardo, E., Ford, N., 2012. Challenges and opportunities for the implementation of virological testing in resource-limited settings. J. Int. AIDS Soc. 15(2), 17324.

Rodriguez, S.E., Hawman, D.W., Sorvillo, T.E., O'neal, T.J., Bird, B.H., Rodriguez, L.L., Bergeron, É., Nichol, S.T., Montgomery, J.M., Spiropoulou, C.F., 2022. Immunobiology of crimean-congo hemorrhagic fever. Antivir. Res. 105244.

S Al-Yabis, A., Al-Thamery, A.K., Hasony, J.H., 2005. Seroepidemiology of crimean-congo haemorrhagic fever in rural community of basrah. Med. J. Basrah Univ. 23(2), 30-35.

Sah, R., Mohanty, A., Mehta, V., Chakraborty, S., Chakraborty, C., Dhama, K., 2022. Crimean-congo haemorrhagic fever (CCHF) outbreak in iraq: Currently emerging situation and mitigation strategies–correspondence. Int. J. Surg. 106, 106916.

Saleh, W.M.M., Dakhil A.A., Al-Taher, S.S.H., Naji, M.M., AbdulRasool L.M.S., Alqaisi K.A.K., 2025. Seroepidemiological study of crimean-congo hemorrhagic fever (CCHF) in small ruminants in Thi-qar governorate, southern Iraq, 2023. Adv. Anim. Vet. Sci. 13(2):365-371.

Saluzzo, J.F., Le Guenno, B., 1987. Rapid diagnosis of human crimean-congo hemorrhagic fever and detection of the virus in naturally infected ticks. J. Clin. Microbiol. 25(5), 922-924.

Schmaljohn, C., Nichol, S.T., 2007. Bunyaviridae. In: Fields, B.N., Knipe, D.M., Howley, P.M. (Eds.), Fields virology, (5th edition). Lippincott, Williams & Wilkins, Philadelphia, pp. 1741–1789.

Shapiro, S., Barkagan, Z., 1960. On history of hemorrhagic fever in middle Asia. Vopr. Virusol. 5, 245-246.

Shayan, S., Bokaean, M., Shahrivar, M.R., Chinikar, S., 2015. Crimean-Congo hemorrhagic fever. Lab. Med. 46(3), 180-189.

Shepherd, A., Leman, P., Swanepoel, R., 1989. Viremia and antibody response of small african and laboratory animals to crimean-congo hemorrhagic fever virus infection. Am. J. Trop. Med. Hyg. 40(5), 541-547.

Shepherd, A., Swanepoel, R., Gill, D., 1988. Evaluation of enzyme-linked immunosorbent assay and reversed passive hemagglutination for detection of crimean-congo hemorrhagic fever virus antigen. J. Clin. Microbiol. 26(2), 347-353.

Shi, X., Kohl, A., Li, P., Elliott, R.M., 2007. Role of the cytoplasmic tail domains of bunyamwera orthobunyavirus glycoproteins gn and gc in virus assembly and morphogenesis. J. Virol. 81(18), 10151-10160.

Simpson, D.I., Knight, E.M., Courtois, G., Williams, M.C., Weinbren, M.P., Kibukamusoke, J., 1967. Congo virus: a hitherto undescribed virus occurring in africa. Part 1. Human isolations-clinical notes. East. Afr. Med. J. 44(2), 87-92.

Smego Jr, R.A., Sarwari, A.R., Siddiqui, A.R., 2004. Crimean-congo hemorrhagic fever: prevention and control limitations in a resource-poor country. Clin. Infect. Dis. 38(12), 1731-1735.

Smirnova, S., 1979. A comparative study of the crimean hemorrhagic fever-congo group of viruses. Arch. Virol. 62(2), 137-143.

Snippe, M., Borst, J.W., Goldbach, R., Kormelink, R., 2007. Tomato spotted wilt virus Gc and N proteins interact in vivo. Virol. 357(2), 115-123.

Telmadarraiy, Z., Chinikar, S., Vatandoost, H., Faghihi, F., Hosseini-Chegeni, A., 2015. Vectors of crimean congo hemorrhagic fever virus in Iran. J. Arthropod. Borne Dis. 9(2), 137.

Tignor, G.H., Hanham, C.A., 1993. Ribavirin efficacy in an in vivo model of crimean-congo hemorrhagic fever virus (CCHF) infection. Antivir. Res. 22(4), 309-325.

Van Leeuwen, L.P., De Jong, W., Doornekamp, L., Van Gorp, E.C., Wismans, P.J., Goeijenbier, M., 2022. Exotic viral hepatitis; a review on epidemiology, pathogenesis, and treatment. J. Hepatol. 77(5), 1431-1443

Vanhomwegen, J., Alves, M.J., Županc, T.A., Bino, S., Chinikar, S., Karlberg, H., Korukluoğlu, G., Korva, M., Mardani, M., Mirazimi, A., 2012. Diagnostic assays for crimean-congo hemorrhagic fever. Emerg. Infect. Dis. 18(12), 1958.

Vorou, R., Pierroutsakos, I.N., Maltezou, H.C., 2007. Crimean-congo hemorrhagic fever. Curr. Opin. Infect. Dis. 20(5), 495-500.

Wahid, B., Altaf, S., Naeem, N., Ilyas, N., Idrees, M., 2019. Scoping review of crimean-congo hemorrhagic fever (CCHF) literature and implications of future research. J. Coll. Physicians Surg. Pak. 29(6), 563-573.

Wang, S., Lifson, M.A., Inci, F., Liang, L.G., Sheng, Y.F., Demirci, U., 2016. Advances in addressing technical challenges of point-of-care diagnostics in resource-limited settings. Expert Rev. Mol. Diagn. 16(4), 449-459.

Whitehouse, C.A., 2004. Crimean–congo hemorrhagic fever. Antivir. Res. 64(3), 145-160.

Whitehouse, C.A., 2007. Risk groups and control measures for Crimean-Congo hemorrhagic fever. In: Ergonul, O., Whitehouse, C.A. (Eds.), Crimean-Congo hemorrhagic fever. Springer, Dordrecht. Available online: https://doi.org/10.1007/978-1-4020-6106-6_20

WHO, 2013. Crimean congo haemorrhagic fever. Fact sheet no. 208. Available online: http://www.who.int/mediacentre/factsheets/fs208/en/Acces

WHO, 2022a. Crimean-congo haemorrhagic fever. Available online: https://www.who.int/news-room/fact-sheets/detail/crimean-congo-haemorrhagic-fever

WHO, 2022b. Situation report Iraq week 32. Available online: https://iraq.un.org/en/195561
-who-situation-report-iraq-week-32

Wiktorowicz, C.J., Arnold, B., Wiktorowicz, J.E., Murray, M.L., Kurosky, A., 2017. Hemorrhagic fever virus, human blood, and tissues in iron age mortuary vessels. J. Archaeol. Sci. 78, 29-39.

Woodall, J., Williams, M., Simpson, D., 1967. Congo virus: a hitherto undescribed virus occurring in africa. Part 2. Identification studies. East Afr. Med. J. 44(2), 93-98.

Woodall, J.P., 2007. Personal reflections. In: Ergonul, O., Whitehouse, C.A. (Eds.), Crimean-Congo haemorrhagic fever: global perspective. Springer, Dordrecht, pp. 23-32.

Zivcec, M., Safronetz, D., Scott, D., Robertson, S., Ebihara, H., Feldmann, H., 2013. Lethal crimean-congo hemorrhagic fever virus infection in interferon α/β receptor knockout mice is associated with high viral loads, proinflammatory responses, and coagulopathy. J. Infect. Dis. 207(12), 1909-1921.

How to cite this article;
Afrah Ali Dakhil, Wessam Monther Mohammed Saleh and Saad Shaheen Hamadi Al-Tahe. Crimean–Congo Hemorrhagic Fever (CCHF): An integrated overview. Veterinary Integrative Sciences. 2026; 24(1): e2026013-1-20.