



# CRIMEAN-CONGO HEMORRHAGIC FEVER (CCHF): AN EMERGING DISEASE IN AFGHANISTAN

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**Abstract:** Crimean-Congo hemorrhagic fever (CCHF) seems to be a severe viral infection that is spreading throughout Afghanistan. The first case of CCHF was recorded in March 1998 in Takhar province, located in the country's north. And since then, multiple new cases and outbreaks have occurred over the years and continue to do so now. CCHF is a viral disease that is transmitted to humans mostly by hard tick bites or direct contact with the blood of infected animals. In Afghanistan, the prevalence of CCHF outbreaks has grown dramatically around Eid-ul-Adha. The primary symptom of this fatal disease is bleeding. There is no cure for CCHF at the moment, but the antiviral drug Ribavirin is used to treat it. This disease presently lacks a commercially accessible vaccine. The disease is recommended to be controlled through preventative measures such as Avoiding insect bites and coming into touch with the blood of a suspicious animal are just a few of the precautions that can be taken.

**Keywords:** Crimean-Congo Hemorrhagic Fever (CCHF), Viral disease, Afghanistan.

## Introduction

According to Athar et al. (2005), The Crimean-Congo Haemorrhagic Fever Virus causes Congo Hemorrhagic Fever, a viral bite infection (CCHFV), which relates to the Nairovirus genus and the Bunyaviridae family. Ozsoy et al. (2015) indicated that this disease is called zoonotic disease. The disease's most significant vectors are hard ticks (Ixodidae) from the Hyalomma genus. The virus is transferred via ticks, vertebrates, and ticks, but it can also spread horizontally and vertically within a biting population (Zavitsanou et al., 2009; Bente et al., 2013). Cattle, deer, hares, goats, and sheep all have Hyalomma ticks on their bodies. These animals contract the virus after being bitten by infected ticks (Kemp et al., 2014).

Ostriches appear to be prone to CCHF, despite the fact that many birds are immune (OIE, 2014). Viraemia in animals is less severe and lasts for a shorter period of time. These birds play a crucial part in tick life cycles, as well as virus transmission and reproduction. There are no clinical indications in the animals. Humans, unlike animals, show clinical indications of the disease (Peyrefitte et al., 2015; OIE, 2014). The disease is endemic in various parts of Afghanistan, as well as found in many countries like in Asia, Southeastern Europe, the Middle East, and Africa (Saleem et al., 2009).

The pathogenesis of the disease in humans is still unknown. The majority of people become afflicted via tick bites, but the disease can also occur through contact with infected blood and other bodily fluids of infective animals. Because CCHFV can be transmitted directly from person to person, nosocomial outbreaks are possible (Burt et al., 1997; Hasan et al., 2014).

There is currently no approved CCHF vaccine, and most patients are treated with symptomatic and supportive care (Mertens et al., 2013). The most critical steps in preventing this deadly disease are health education and awareness of prevention and control methods. Tick repellents are an effective way to minimize tick populations. Infectious blood samples and other materials containing CCHFV should only be handled at BSL-4 in order to safeguard laboratory personnel and healthcare employees. The medicine ribavirin is commonly used to treat CCHF, either orally or intravenously (Athar et al., 2005). Tick bites can be avoided by using tick repellents, which can help control the disease (Leblebicioglu et al., 2015).

## Historical Background

CCHF is estimated to be one of the world's most commonly spread tick-borne viral infections. The first record of CCHF is estimated to date from the 12th century in Tajikistan, but it was unknown at the time. During the Second World War (1944-45), CCHF was first recognized in Crimea with Soviet military staff when ticks bit a considerable number of Soviet soldiers as a result of sleeping outside and given the name Crimean hemorrhagic fever (Tishkova et al., 2012). Using intra-cerebral inoculation of suckling mice, the virus was first isolated from affected people's blood and tissues. The virus that caused febrile illness in the Belgian Congo in 1956 was found to be the same virus that caused Crimean Hemorrhagic Fever in 1969 (Bente et al., 2013). As a result, the two names for the same virus, CCHFV (Crimean-Congo Hemorrhagic Fever Virus), were integrated to create CCHFV (Crimean-Congo Hemorrhagic Fever Virus) (Appannanavar & Mishra, 2011; Bente et al., 2013).

There was a significant outbreak in Bulgaria between 1954 and 1955, involving 487 cases reported, especially in the Shumen district of North-East Bulgaria. The WHO recorded 1568 CCHF cases throughout Bulgaria between 1953 and 2008, with a 17 percent death rate. An outbreak in Mauritania was reported by Nabeth et al. (2004) in 2003. In 2008, Aradaib et al. (2010) reported

a nosocomial illness in Sudan. The OIE reported multiple cases of CCHF in Georgia, Tajikistan, Kazakhstan, Pakistan, and Iran in 2009. ProMED 2010 reported an epidemic in Pakistan's Khyber Paktunkhwa Province in September 2010. The possibility for the disease to spread across borders is linked to the transfer of ticks and virus during annual bird migrations. Ticks are mostly transported across continents as a result of cattle movement (Hoogstraal, 1979).

It is founded through phylogenetic analysis of CCHF strains that the recent CCHF infection in the Arabian Peninsula was caused by the trade of tick-infested livestock from Africa and Asia (Hoogstraal, 1979). The fact that Hyalomma species ticks favor dry, non-humid temperatures and arid vegetation may explain the high illness prevalence in European countries. Similarly, the Mediterranean region's rising temperatures and decreasing rainfall provide an ideal environment for tick growth and multiplication. Human infection is prevalent in developing and underdeveloped countries as a result of increased contact with livestock (Goodman et al., 2005).

Several cases of CCHF virus have been recorded from Afghanistan since the first incidence of CCHF was recorded in March 1998 in Afghanistan's Takhar province. And confirmed 19 cases with 12 deaths (MOP, 2018). Recent studies indicate an increase in the incidence of CCHF in Afghanistan; however, laboratory diagnostic capabilities and overall public health infrastructure for CCHF management remain insufficient. In Afghanistan, the most common symptoms are fever, headache, and myalgia. Epistaxis is the most common hemorrhagic symptom, and thrombocytopenia is confirmed by a low plasma platelet count that is the most frequently encountered hematologic finding in patients with CCHF in the country. CCHF affected the working-age group in Afghanistan (average age 27–35 years) with a CFR ranging from 11.5 to 33%, with the latest research indicating a CFR of up to 43.3 percent, increasing concerns about the future (Hatami et al., 2019; Mofleh & Ahmad, 2012).

### Clinical Characteristics in Humans

Humans are the only hosts for CCHFV that exhibit clinical symptoms and signs. The clinical course of CCHF appears to be milder in children than in adults (Tezer et al., 2010). Hussain et al., (2016) indicated that CCHF infection typically progresses through four distinct phases as follow:

- The period of Incubation
- The Pre-hemorrhagic stage
- The Hemorrhagic stage
- The recovery stage

**The Incubation period:** This time frame is usually between 3 and 7 days. The incubation period ranges from 1-3 days after a tick bite to 5-6 days after contact with infected blood or tissues, with a maximum of 13 days. The average duration of infection is strongly influenced by the route of infection, the source of infected blood or tissue, and the viral load. The infectious dose (minimum viral load) required for disease transmission is between 1 and 10 organisms. (Mamuchishvili et al., 2015).

**The Pre-hemorrhagic stage:** The disease's pre-hemorrhagic phase is characterized by a number of non-specific prodromal symptoms similar to those of other viral diseases. The most common signs and symptoms are high fever, abdominal pain, headache, myalgia, nausea, and non-bloody diarrhea. A skin rash, relative bradycardia, hypotension, conjunctivitis, tachypnea, pharyngitis, and conjunctivitis are all symptoms (Appannanavar & Mishra, 2011; Vashakidze & Mikadze, 2015).

**The Hemorrhagic stage:** The hemorrhagic stage is usually short. It advances quickly, with signs of bleeding and diathesis. These include conjunctival bleeding, epistaxis, petechiae, hemoptysis, hematemesis, and melena. In addition, some patients may have hepatosplenomegaly. According to Vashakidze & Mikadze (2015), Between 15 and 85 percent of cases end in death. Multiple organ failure, disseminated intravascular coagulation, and circulatory shock all play a role in death under challenging situations. Hemorrhagic symptoms have also been linked to Acute Respiratory Distress Syndrome (ARDS) and disseminated alveolar hemorrhage. Protein, albumin, fibrinogen, and hemoglobin levels are decreased in this disease. However, prothrombin ratio, activated partial thromboplastin time, thrombin time, and fibrin degradation products are higher, indicating the existence of DIC (Swanepoel et al., 1989).

**Convalescent or recovery period:** This stage begins from 15 to 20 days following the commencement of disease in survivors. Patients may experience a weak pulse, tachycardia, memory, and hair loss, as well as hearing loss at this time. These side effects, however, have only been observed in a few outbreaks. CCHFV is found in infected patients' blood, bodily fluids, and tissues; For others, such as family members and healthcare workers, hemorrhages are the most common source of exposure (HCWs). A possible horizontal transfer from a mother to her child has also been documented (Bajpai & Nadkar, 2011).

### Infections and Viruses in Animals

CCHFV is present in various wild and domestic species, particularly tiny mammals that serve as immature tick hosts and giant herbivores that help mature tick hosts. Sheep, Cattle, hares, hedgehogs, goats, dogs, and mice have all been isolated with CCHFV (Kemp et al., 2014). Donkeys, buffalo, horses, pigs, giraffes, rhinoceroses, and other mammalian species have been found to have antibodies. Because the majority of bird species are seronegative, they are believed to be immune to infection; Ostriches, on the other hand, maybe seropositive, and these animals become viremic after experimental inoculation. Moreover, Vorou (2009) discovered weak CCHFV viremia in a lab-infected blue-helmeted guinea fowl (Numidia Meleagris) along with antibodies in a magpie. Turell (2007) reported that a red-beaked Hornbill and a glossy starling became seropositive after experimental infection/vaccination. But did not develop viremia. Because undeveloped Domestic pigs anatomicum ticks occasionally feed on reptiles, anti-CCHFV antibodies have only been found in one mammal, a Tadjikistan tortoise.

Other than deliberately infected neonatal rodents, CCHFV infections are asymptomatic. Laboratory mice, rats, and Syrian hamsters are among the animals involved. The only sign of infection in experimentally infected sheep and calves was a transient and moderate increase in body temperature (Mourya et al., 2014). If animals become infected with CCHFV, they could become viremic and transmit the virus through their blood and tissues. Domestic species such as cattle, sheep, and goats become viraemic for one week after being experimentally infected. CCHFV can be detected in blood for a few days (1-4 days) and in visceral organs for up to five days after experimental infection in ostriches, although most birds appear to be immune to infection. (Goswami et al., 2014).

## Transmission

CCHFV transmits between mammals (asymptomatic) and ticks in such an endemic cycle. This virus has been identified in ticks from seven different genera in the Ixodidae family (hard ticks). Members of the genus *Hyalomma* appear to be the main transmitters of the genus. Transovarial and venereal transmission are all possible for this species. The most prevalent vector in Europe is *Hyalomma marginatum*. However, CCHFV has also been found in *Hyalomma anatolicum* and other species. *Rhipicephalus*, *Dermacentor*, *Boophilus*, and *Ixodes* ticks, as well as other Ixodid ticks, can spread diseases locally (Goswami et al., 2014). CCHFV was discovered in a variety of invertebrate species by Gonzalez et al. (1992); though these animals may not be biological transmitters, the virus could have been eaten in a recent blood meal. Many mammalian species can transmit CCHFV to ticks when they are viremic.

Hedgehogs and hares, for example, are small vertebrates that are likely to be amplifying hosts for young ticks. Birds appear to be immune to infection, yet they may act as mechanical carriers by spreading CCHFV-infected ticks. The virus could be spread across large areas by migrating birds (Leblebicioglu, H., Sunbul, et al., 2015). Humans become infected through both their skin and their meals. Aerosol transmission has been suspected in a few cases in Russia. Infection can be contracted by being bitten by a tick, crushing an infected insect, coming into contact with animal blood or tissues, or drinking unpasteurized milk. Eid-ul-Azha is a time when the risk of CCHFV transmission from animals to humans is higher. Human-to-human transmission occurs when skin or mucous membranes come into touch with blood during hemorrhages or tissues after surgery. CCHFV can live for up to ten days in blood refrigerated at 40°C (104°F). Vertical transmission has also been discussed (from a mother who is infected to her child) (Goswami et al., 2014).

## Pathogenesis

Although the origin of CCHF is unknown, the virus is believed to attack the host immune system and alter immune cells. Glycoproteins (Gn and Gc) from viruses bind to the putative virus receptor on the surface of human cells, allowing the virus to enter the cells via receptor-dependent endocytosis (Appannanavar & Mishra, 2011; Goswami et al., 2014). As a result of immune cell destruction, the virus replicates rapidly, causing overactivity of the vascular system as well as lymphoid organs, which results in the production of pro-inflammatory cytokines (IL-6, IL-10, and TNF) that cause hemodynamic damage. (Appannanavar & Mishra, 2011). The intrinsic coagulation cascade is initiated due to this injury, leading to platelet aggregation and endothelial lining obstruction. Platelet aggregates form as a result of the infection and move throughout the infected host's body, resulting in Disseminated Intravascular Coagulopathy (DIC) and failure of multiple organs, which results in death (WHO, 2014).

## Diagnosis

Blood, tissues, and plasma can all be used to isolate CCHFV. This virus is commonly discovered in the liver, lungs, kidneys, spleen, brain, and bone marrow. Tantawi et al. (1980) isolated CCHFV using the BHK-21 cell line. SW-13 cell line was used for this work. Vero, LLC-MK2, and other cell lines are also employed for this purpose. Only high amounts of the virus can be detected using cell cultures, and this method is much more beneficial during the first five days of infection. Isolation of viruses must be done at the BSL-4 level (Goswami et al., 2014). Inoculation of newborn mice with CCHF can be used to diagnose the disease. It is more responsive than culture-based virus isolation and can identify the virus for more extended periods. This method, however, may cause CCHFV isolation to take a lengthy period. Anti-CCHFV antibodies can be detected using an indirect immunofluorescence technique (Peyrefitte et al., 2015). Burt et al. (1998) performed reverse transcription-polymerase chain reaction (RT-PCR) on serum samples and concluded that this method could be utilized early in the course of CCHF illness. This is a very delicate procedure. Because of the genetic diversity of CCHFV strains, a single set of primers is inadequate to detect all virus variants, and most RT-PCR tests are either customized to detect local variants or do not exist at all. Wasfi et al. (2016) used this method to see the CCHFV in acutely febrile patients, predominantly slaughterhouse workers. An enzyme-linked immunosorbent assay (ELISA) or an immunofluorescence approach are used to detect and quantify IgM (IgM-capture ELISA) and IgG (IgG-sandwich ELISA) antibodies against the CCHFV. Compared to PCR, it is a less sensitive technology. This approach is more sensitive, specific, quick, and reproducible than the complement fixation test and immunofluorescence. Morrill et al. (1990) employed an Agar Gel Diffusion (AGD) approach (IgM-capture ELISA) and IgG (IgG-sandwich ELISA) antibody to discover anti-CCHFV antibodies. Compared to the ELISA, the Indirect Fluorescent Antibody (IFA) method was less sensitive and specific. The Complement Fixation assay was used to demonstrate anti-CCHFV antibodies. Swanepoel et al. (1989) demonstrated anti-CCHFV antibodies using the Reversed Passive Hemagglutination Inhibition method. Immunohistochemistry (IHC) was used by Burt et al. (1997) to diagnose CCHFV in formalin-fixed tissue samples. Reverse Transcription Loop-mediated Isothermal Amplification (RT-LAMP), particularly specific and sensitive, was described by Goswami et al. (2014) as a new approach for fast diagnosis of CCHFV.

## Control and Prevention

CCHFV vaccines are now being developed in two different ways. The first is a formalin-inactivated vaccine manufactured in Bulgaria using contaminated suckling mouse brains. The other is a DNA vaccination that has been tried on mice. Both vaccinations are still under study (Shayan et al., 2015). It is critical to educate the general population regarding tick bites as a transmission route, how to handle ticks, how to handle and slaughter animals, and how to protect themselves. For well-managed animal production facilities, tick management with acaricides is an alternative. It's also a good idea to dip your animal in a solution of insecticide (Leblebicioglu et al., 2015). When possible, human beings should avoid tick-infested areas, particularly during tick season (spring to fall). To minimize tick exposure, wear lightweight clothing that covers your arms and legs, tuck your pants into your socks, frequently check your clothing and skin for ticks, and apply tick repellent such as diethyltoluamide (Deet, Autan) to your skin or Permethrin to your pant legs and sleeves. Individuals who work with livestock or certain other animals from endemic areas should take precautions, including applying repellents to their skin (e.g., diethyltoluamide) and clothing (e.g., Permethrin). as well as wearing gloves or other protective garments to avoid skin contact with infected blood or tissues. CCHFV is highly susceptible to hypochlorite and glutaraldehyde solutions at 1% and 2% concentrations, respectively, and can be killed by heating at 56°C for 30 minutes (Shayan et al., 2015; Appannanavar & Mishra, 2011). According to Zavitsanou et al. (2009), In the event of death, the dead body of a CCHF-infected patient should be sprayed with a 1:10 liquid bleach solution and then wrapped in a winding sheet. On the winding sheet, the bleach solution had to be rushed. Following that, it is sealed in a plastic bag with adhesive tape.

Additionally, the transfer vehicle should be cleaned, and all clothing belonging to the suspect should be burned. Ribavirin, also known in Afghanistan as Ribazole R, is recommended for hospitals to stock (Ali et al., 2011). Biosafety is the most effective way to avoid nosocomial infection. Patients with suspected or confirmed CCHF are isolated and cared for using strict barrier-nursing practices to prevent nosocomial infection. Patients must be treated in a separate room separated from one another by a strict nursing barrier (Shayan et al., 2015). All medical and paramedical professionals and attendants should be required to wear masks, disposable gloves, and gowns. Spills, pricks, injuries, and mishaps should be avoided when managing patients, and needles should be disposed of in an appropriate safety disposal box that is then autoclaved and burned (Zavitsanou et al., 2009). All surfaces should be disinfected with liquid bleach. Patients should be attended to by only authorized paramedical personnel. Personnel and attendants who are not strictly necessary should not enter the patient's room (Aslam et al., 2016; Leblebicioglu et al., 2015). All patient secretions and hospital clothing should be treated as contagious and autoclaved before incineration. All instruments should be decontaminated and autoclaved prior to reuse. After the patient is discharged, the room should be washed down with liquid bleach to kill the virus, and space should be fumigated as quickly as feasible (WHO, 2014).

### Perspectives for the Future

The passive intravenous transfer of anti-CCHFV antibody is expected to be a successful treatment for CCHF. These immunoglobulins, which can be synthesized from survivor sera, are expected to become available shortly, but additional research is required (Keshkar-Jahromia et al., 2011). The European Medicines Agency and the U.S. Food and Drug Administration have not approved a vaccine that has been inactivated with chloroform. And enlarged in the brains of baby mice, crushed with a mortar and pestle, and the resulting solution absorbed into aluminum hydroxide (Al (OH)<sub>3</sub>) before being administered to patients (FDA) (Peyrefitte et al., 2015). A DNA-based vaccination containing the CCHFV component has recently been tested in mice for its capacity to generate neutralizing antibodies. However, it is not yet effective enough for commercial usage. Using transgenic tobacco leaves expressing Gn and Gc glycoproteins, another vaccine candidate was administered to mice that produced IgG and IgA antibodies. Furthermore, prior to commercialization, this vaccine requires further study and development. Smallpox virus vectored vaccines, such as those based on Modified Vaccinia virus Ankara (MVA), can accommodate the M segment of the CCHFV genome, allowing vaccinations against CCHFV to be developed (Buttigieg et al., 2014).

### Conclusion and Recommendations

The tick-borne viral disease known as Crimean-Congo Hemorrhagic Fever (CCHF) has been proven to be transmissible to humans and a new human health risk. In some parts of Afghanistan, including Takhar, the disease has developed into an endemic condition. CCHF infections are most prevalent during the fall and spring seasons. Infecting the immune cells with the CCHFV, the virus induces a hemorrhagic response, resulting in multiple organ failures and death. Most of the time, a diagnosis is made by verifying the patient's symptoms, blood, and DNA. At the moment, there is no licensed CCHF vaccination. Thus therapy is mainly limited to symptom management and supportive care. Prevention and control of this disease primarily rely on avoiding tick bites by using repellents.

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