Seroprevalence, Distribution Pattern and Control of Crimean Congo Hemorrhagic Fever (CCHF) with its Risk Factors in Pakistan and Neighboring Countries

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Arslan Muhammad Ali Khan, Calvin Ronchen Wei, Sundas Asghar, Zohaib Saeed, Muhammad Subbayyal Akram, Hasnain Idrees, Rameesha Azhar and Maria Sohail

ABSTRACT

Crimean-Congo One of the most significant vector-borne illnesses with the potential to spread to humans after a tick bite is hemorrhagic fever (CCHF). In the Middle East and Asia, the disease is very common. contaminated tick bites, manual tick removal, and contact with contaminated tissue, blood, patients, or cattle during the acute viremic phase are risk factors for this disease. Clinical signs of the illness include fever, muscle discomfort, and increasing hemorrhages. Increased levels of creatinine phosphokinase (CPK), alanine transaminase (ALT), aspartate aminotransferase (AST), and lactate dehydrogenase (LDH) are detected by biochemical testing. Pro-thrombin tests result in longer clotting times, and pathogenesis is mostly associated with epithelial destruction during viral replication and secondary cytotoxic molecule secretion. Endothelial activation is brought on by these substances, which leads to function loss. Infusions of plasma or blood are used in supportive therapy to treat or manage patients. Based on the most recent research, ribavirin, an antiviral medication that effectively prevents the disease, can be used to treat community-onset heart failure. Workers in healthcare are more likely to have infections. A thorough review of the viral epidemiology, zoonotic viewpoints, and important risk factors for community-acquired pneumonia (CCHF) in several Middle Eastern and Asian nations is provided in this book chapter. The pathophysiology and preventative measures of CCHF have also been examined, along with laws and policies pertaining to public education campaigns, research, and development projects that aim to prevent and control infections and are necessary on a worldwide scale.

Keywords: Prevalence, Africa, CCHF, transmission, ticks, Hyalomma.

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[1]Department of Parasitology, Faculty of Veterinary Science, University of Agriculture, Faisalabad, Pakistan
[2]Department of Research and Development, Shing Huei Group, Taipei, Taiwan
[3]Department of Zoology, Institute of Molecular Biology and Biotechnology, The University of Lahore, Sargodha Campus, Pakistan.

[4]Department of Epidemiology and Public Health, Faculty of Veterinary Science, University of Agriculture, Faisalabad.
***Corresponding author:** arslanrajpootkhan374@gmail.com

1. INTRODUCTION

Crimean Congo hemorrhagic fever (CCHF) virus is a lethal agent that is associated with CCHF fever. CCHF virus is present all over the over the world but most commonly it is present in West Africa, Europe, and Asia (Nasirian, 2020). Due to its endemic nature, this zoonotic disease poses a serious hazard to humans and livestock alike. It is a serious health concern since it can cause an acute and potentially fatal disease in humans (Shahhosseini et al. 2021). It has been linked to human severe hemorrhagic syndrome as well as sporadic infections in tourists visiting these regions (Gilbride et al. 2021). The virus that causes Congo hemorrhagic fever (CCHF) is called the Orthonairovirus, and it is a member of the Nairoviridae family and Bunyavirales order (Serretiello et al. 2020).

In nature, CCHFV often possesses a tick-vertebrate life cycle (Gargili et al. 2017a). In the CCHF cycle of distribution, many kinds of animals both domesticated and wild may serve as asymptomatic hosts of CCHFV, which is essential for feeding ticks that support the cycle of transmission to new populations of ticks (Fanelli and Buonavoglia, 2021). Seroepidemiological and serosurveillance have helped identify CCHFV hosts to identify endemic foci of viral transmission (Spengler et al. 2016).

Seroepidemiological investigations can be used to identify CCHF risk areas because the prevalence of antibodies in animals is a reliable predictor of the virus's presence or absence in a specific location (Sas et al. 2017). The main source of data for tracking naturally occurring virus transmission zones and identifying viral-exposed species is also serological surveys. There appears to be little chance of CCHFV infection in humans due to the absence of the virus and the absence of antibodies against people and animals alike (Mendoza et al. 2018). A substantial amount of study has been done on CCHFV hosts and their involvement in the survival and spread of the virus (Mertens et al. 2013). Recently, several kinds of organizations have released reports on in-depth serosurveys. Nonetheless, the majority of the research is local in nature and does not offer a thorough evaluation that spans wide regions or the entire world.

1.1. ABSTRACT

Crimean-Congo One of the most significant vector-borne illnesses with the potential to spread to humans after a tick bite is hemorrhagic fever (CCHF). In the Middle East and Asia, the disease is very common. contaminated tick bites, manual tick removal, and contact with contaminated tissue, blood, patients, or cattle during the acute viremic phase are risk factors for this disease. Clinical signs of the illness include fever, muscle discomfort, and increasing hemorrhages. Increased levels of creatinine phosphokinase (CPK), alanine transaminase (ALT), aspartate aminotransferase (AST), and lactate dehydrogenase (LDH) are detected by biochemical testing. Pro-thrombin tests result in longer clotting times, and pathogenesis is mostly associated with epithelial destruction during viral replication and secondary cytotoxic molecule secretion. Endothelial activation is brought on by these substances, which leads to function loss. Infusions of plasma or blood are used in supportive therapy to treat or manage patients. Based on the most recent research, ribavirin, an antiviral medication that effectively prevents the disease, can be used to treat community-onset heart failure. Workers in healthcare are more likely to have infections. A thorough review of the viral epidemiology, zoonotic viewpoints, and important risk factors for community-acquired pneumonia (CCHF) in several Middle Eastern and Asian nations is provided in this book chapter. The pathophysiology and preventative measures of CCHF have also been examined, along with laws and

policies pertaining to public education campaigns, research, and development projects that aim to prevent and control infections and are necessary on a worldwide scale.

1.2. TRANSMISSION ROUTE OF CCHFV TO HUMANS

Infections with CCHF are enzootic and typically show no symptoms in a variety of animals. Humans are susceptible to the CCHF virus through tick bites, and contact with infected animals or their tissues or plasma (Papa et al. 2017). Hospital nosocomial epidemics are linked to environments with limited resources. For instance, in Al-Fulah, Kordufan, Sudan, a nosocomial outbreak was documented in 2008 following the hospital admission of a 60-year-old male patient who had previously worked as a butcher (Sargianou and Papa, 2013). Nurses who had cared for the index patient were infected with the virus because strict infection control procedures were not followed and personal protective gear, or PPE, was not used. However, those working in the veterinarian profession, abattoir, and livestock business have accounted for the majority of CCHF instances (Msimang et al. 2021). It has been demonstrated that numerous tick genera throughout are carriers of the virus. However, the majority of human illnesses are caused by ticks of the genus *Hyalomma*, possibly as a result of both larval and adult parasites relying on host blood during different stages of their development (Gharbi and Darghouth, 2014). Hyalomma ticks serve as CCHFV vectors as well as hosts. The adult *Hyalomma* ticks maintain CCHFV infection naturally through trans-ovarian and trans-stadial transmission, whereas the larvae and nymphs graze on ungulates, birds, or reptiles (Pascuccia et al. 2009). It is necessary to ascertain the function of reptiles as reservoirs and as capable hosts for the spread of CCHFV. Animals may acquire the CCHFV virus by being bitten by a virus carrier tick. The virus then spreads to ticks that are not affected as they feed on the blood of the afflicted host. Additionally, ticks can get infected directly by blood-feeding on the same host, and viral materials found in tick saliva hasten the spread of infection (Hart and Thangamani, 2021). However, the risk of contracting CCHFV is the same in all mammals. For CCHFV multiplication and transmission, birds are regarded as poor hosts because they frequently exhibit resistance to becoming viremic (Gargili et al. 2017b). Humans are typically thought of as CCHFV's accidental, dead-end hosts (Bente et al. 2013). The main ways that humans become infected are by tick bites, coming into touch with the cells and blood of virulent animals, and through contaminated human tissues, bodily fluids, or blood (Parola and Raoult, 2001). Transmission of CCHFV can also occur when cattle are travelled and migrate from affected regions to uninfected area (Fanelli and Buonavoglia, 2021). Changes in land use and restrictions on the movement and trading of affected livestock can both lessen the risk of CCHFV transmission (Obanda et al. 2021). In the Middle East, contact with contaminated blood from corpses through wounds or mucosal membranes of infected humans and animals was reported to be the most frequent mechanism of CCHFV transmission during several epidemics.

1.4. CLINICAL SYMPTOMS

The CCHFV infection primarily involves four distinct phases: the incubation phase, pre-hemorrhagic, hemorrhagic, and clinical convalescent (Papa, 2019). After infection, the incubation period endures three to seven days. The first 4-5 days of the illness are known as the pre-hemorrhagic phase. Headache, elevated temperature, abdominal discomfort, muscular pain, low blood pressure, and red face are the main symptoms (Fletcher, 2019). Severe symptoms such as skin lesions, ecchymosis, nosebleeds, gum bleeding, and nausea begin to manifest as the condition worsens (Leblebicioglu, 2010). Additional symptoms may include, vomiting, loose stool, mental disorders, and myocardial abnormalities. If the illness is not addressed, individuals may experience multiple organ failure and die. After 10–20 days of illness, survivors start the convalescent phase (Al-Halhouli et al. 2021). It can take a full year for CCHF survivors to fully recover.

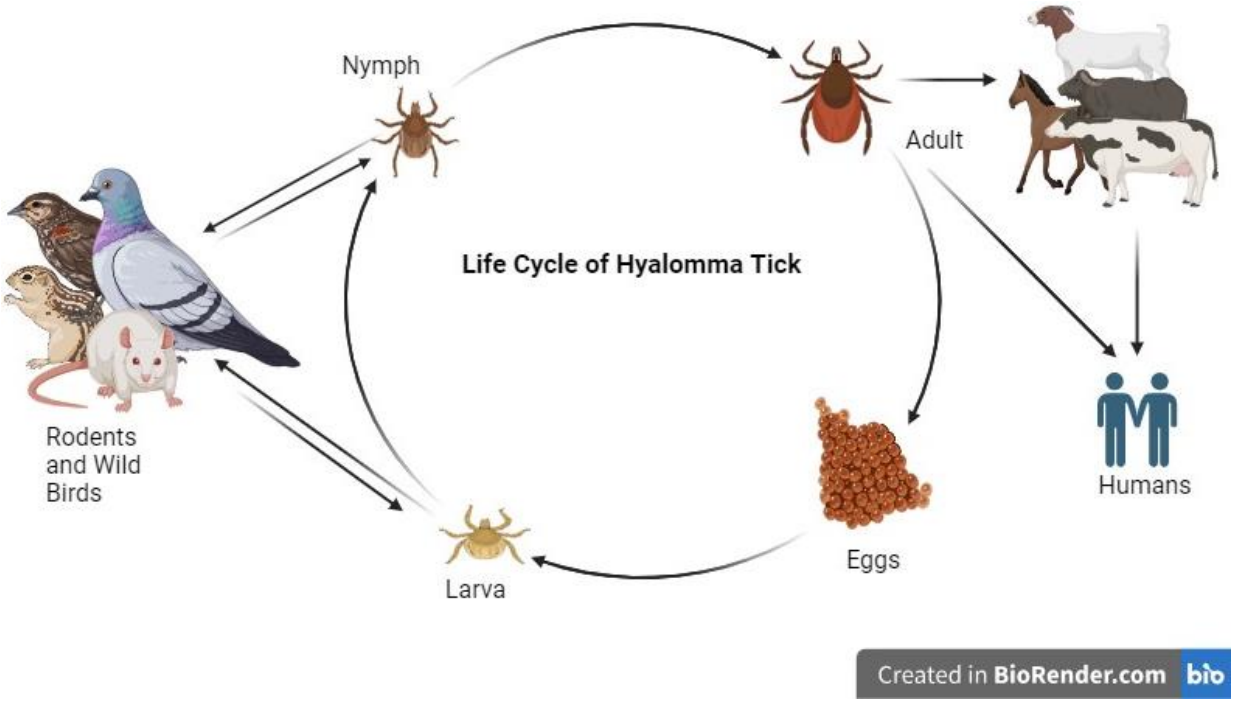

Fig. 1: Lifecycle of *Hyalomma* tick and potential transmission route of CCHFV.

1.5. DISTRIBUTION PATTERN OF CCHF VIRUS

1.5.1. PAKISTAN

With every passing year that goes by, there are more and more cases of CCHF throughout the nation. The virus was initially discovered in ticks infesting nearby cattle in the 1960s. The first recorded human incidence of CCHF was in Pakistan in 1976 (Lea, 2023). There were only 14 cases reported up till 2010. Following 2010, there was a sharp rise in the number of CCHF cases (Chinikar et al. 2012). Over 350 cases of the disease have been identified by the National Institute of Health, Islamabad, between 2014 and 2020 (Nisar et al. 2020). It was suggested that the fatality rate should be higher than 25%. Just 38% of these CCHF instances were recorded from the province of Balochistan, 23% from Punjab, 19% from Khyber Pakhtunkhwa, 14% from Sindh, and 6% from Islamabad, the nation's capital (Karim, 2020). Because people and animals interact closely in rural regions, the sickness was more common there. This disease become much contagious on Eid Ul Adha, occasion, when small and large ruminants are sold and consumed without sufficient examination of animal. Urban areas are more likely to be more affected than rural areas where population is less (Hurrem et al. 2015). In Pakistan, common strains from nearby nations like Iran, Afghanistan and India frequently circulate and propagate, and vice versa. Only 68% of the 248 cases that tested positive for CCHF in 2004 were reported from Sistan of Iran, and Baluchistan, Pakistan (Aslam et al. 2023). Up to 300 more cases each year were reported between 2004 and 2006 (Süss, 2011).

The spread of CCHF is largely being driven by a few risk variables. There are twice-yearly peaks from March to May and August to October due to rapid changes in the climate. The transmission of CCHF is facilitated by a number of factors, including inadequate sanitation, unclean abattoir’s, livestock being moved inside cities, nomadic lifestyles, and a shortage of medical personnel and trained animals (Wallace et al. 2002).

1.5.2. INDIA

The inaugural case of CCHF was found in the Indian state of Gujrat, and it was caused by a nosocomial illness connected to Pakistan on the other side of the border. According to a local livestock survey, tissue and serum samples were examined to determine the presence of *H. anatolicum* (Parihar et al. 2022). Of the 34 cases, eight secondary instances of CCHF were reported. Four Indian states had CCHF instances found in another study (Patil et al. 2022).

1.5.3. CHINA

Hemorrhagic fever cases were reported in western China in 1965 (Papa et al. 2022). Upon diagnosis, samples taken from humans, livestock, and ticks revealed the presence of the CCHF virus (Mourya et al. 2012). 260 individuals were found to have had CCHF infection between 1965 and 1994. Forty was the death rate. In Beijing, China, one imported occurrence was reported in 2013. The Chinese provinces also reported confirmed cases of the CCHF virus (Wang et al. 2019). In China's Inner Mongolia region, the CCHF virus was found in the ticks of camels and sheep. Only 447,848 cases were reported to have been infected by bunyavirales viruses between 1951 and 2021, with CCHFV and three other viruses being the viruses that were identified to generate the greatest illness burden (Teng et al. 2022).

1.5.4. IRAN

Based on the discovery of antibodies against CCHF in the serum of sheep, cattle, and people, the first incidence of CCHF was documented in Iran in the 1970s (Lotfollahzadeh et al. 2011). Viral antigens were discovered to be present in a sheep slaughterhouse in Tehran. The Ixodes genus of ticks was the virus's source. Since 1999, reports of human sickness have been made, and CCHF outbreaks have been documented in several parts of the nation. In 2000, the death rate was 20%; by 2007, it had dropped to 6%. In a study, 203 ticks were examined for the presence of CCHFV; despite being an endemic location, the Kerman province had no positive results (Watts et al. 2019).

1.5.5. AFGHANISTAN

There was a CCHF outbreak in the Afghanistan district of Herat in 2009. There were only 60 positive instances found. Native sheep and cow breeds found in the vicinity were found to have elevated blood IgG levels, suggesting possible pre-exposure (Samadi et al. 2020). In one investigation, ELISA identified 51 positive cases of CCHF; 11 patients of these instances passed away. They were shepherds and butchers (Lea, 2023). In the endemic year, the number of patients with CCHF climbed dramatically from June to September. This demonstrated that environmental variables and lifestyle choices are the main risk factors for the disease's spread. The border between Afghanistan and Iran is home to CCHF vector ticks, which raises the possibility of human CCHF infection (Sahak et al. 2018).

1.6. CONTROL OF CCHFV

The strongest defense against the transmission of CCHF disease is to reduce or prevent exposure to the virus (Mertens et al. 2013). To be more specific, the best human defense against CCHFV is body defense. When visiting or living in an endemic area, individuals should take personal precautions such as avoiding locations where tick vectors are common, especially when they are active, checking their skin and clothing frequently to remove any sticky ticks, and using repellents (Valente et al. 2015). Wearing long sleeves and

shirts with your jeans tucked into your boots is another method of preventing skin tick adhesion (Eisen, 2022). Meat typically undergoes acidification after slaughter or heating at 56 °C for half an hour to destroy or inactivate CCHFV. Consuming unpasteurized milk is not advised. People who work in high-risk fields like veterinary medicine, livestock husbandry, and slaughterhouses, as well as butchers and butlers, should take every measure possible to prevent exposure to CCHFV-infected ticks and infected animal tissues or fluids (Mitchell et al. 2020). These precautions include wearing gloves, gowns, and face shields. Healthcare professionals have a significant risk of contracting infections, especially while caring for patients who have gingivitis, areas of injection, noses, or vaginas (Vaughn, 2013). For the protection of healthcare professionals, safety precautions such as isolation, normal barrier-nursing procedures, and the use of gowns while in contact with healthcare clients or filthy environmental surfaces are advised. Strict biosafety protocols must be followed by laboratory personnel (Schwartz et al. 2022).

It is important to strengthen tactics such as laboratory capacity growth in areas of epidemic and areas at risk of CCHF growth, as well as surveillance utilizing defined case definitions. (Thi, 2015). To lower their chance of contracting CCHFV, both the general public and at-risk groups, such as those in high-risk occupations and the healthcare industry, should be aware of preventative measures. Individuals living in areas where the CCHF is prevalent need to be made aware of the routes of transmission, which include eating raw or undercooked meat right away after slaughter (Kalal, 2019).

It is directed that the aforementioned preventive and control measures be implemented as part of a multidisciplinary effort at the worldwide, national, and regional at particularly in places where CCHF is anticipated to develop. It is essential to develop and put into practice guidelines for early quick response treatments at the hospital, community, and patient levels (Ahmed et al. 2021). There should be an increase in laboratory capacity to enable CCHF to quickly confirm putative clinical cases (Greiner et al. 2016; Jahromi, 2014). It has proven successful in preventing CCHF in at-risk groups by emphasizing education to raise awareness.

Proficient and knowledgeable healthcare workers are vital to avoid, detect and take satisfactory procedures for dangerous transmittable diseases that directed a danger to the universal population. Supportive therapy is also a crucial component of case management. Early detection and analysis of CCHF is crucial for patient recovery as well as for the inhibition of potent nosocomial infections and transmission in the population. Healthcare workers must regularly undergo refresher training to reinforce sound public health practices and understand new developments in the field (Greiner et al. 2016).

Most endemic nations already treat CCHF patients with ribavirin, and new research indicates that this medication may be helpful (Ergonul, 2008). While additional studies have indicated encouraging outcomes, primarily linked to early therapy, the use of ribavirin for the treatment of chronic cardiomyopathy (CCHF) is still controversial because no modification in case casualty rates was observed. The majority of the information regarding the effectiveness of ribavirin is confined to case series and short observational studies, and methodological concerns have been brought up. We conclude that there is not enough information at this time to make a firm determination regarding the effectiveness of ribavirin (Elaldi et al. 2009). A well-designed multi-center, randomised controlled trial that takes severity criteria into account is desperately needed to offer evidence-based data about the efficacy of ribavirin, given the high fatality rates linked to CCHF(Huggins, 1989). Because of the possibility of autoimmune reactions, the use of inactivated suckling mouse brain vaccinations generally raises concerns (Al-Abri et al. 2017). Most cases of CCHF occur in low-resource countries, and the field's research has advanced relatively slowly.

More research may be conducted thanks to the recent genetic characterization of the CCHFV strain used to prepare vaccines. Although long-term field research will be necessary to demonstrate efficacy, a humanized vaccination against CCHF is necessary. Large-scale phylogenetic investigations and strong international collaboration among CCHF researchers are also necessary to produce the best immunogenic vaccine against CCHFV and will help achieve the goals of more effective treatment.

1.7. RISK FACTORS

The virus can be transmitted from one human to another through direct blood contact, body fluids of infected human and during handling of infected ticks (Sarwar, 2017).
There is minimal to no risk of tick exposure in regions outside the tick's geographical range. One of the primary risk factors for CCHFV exposure is either killing the diseased animal or breaking down and pressing the infected tick on the skin (Annex, 2012). Nosocomial infections represent another well-established risk factor. This is more common in healthcare professionals, especially when the condition is hemorrhagic. As mentioned before, this factor was demonstrated in January 1976 at the Central Government Hospital in Rawalpindi, Pakistan, where a nosocomial occurrence took place (Aslam et al 2023b). A shepherd was the source of the illness, which spread to a female doctor, a surgeon, an assistant surgeon, and other medical personnel. Another nosocomial epidemic happened at the Tygerberg Hospital in South Africa (Reddy et al. 2021). There, 33% of the medical staff contracted CCHF as a result of unintentional needle stick contact with the patient, and 8.7% contracted the infection from coming into touch with the patient's blood or other bodily fluids. One of the risk factors for CCHF is the droplet-respiratory route of infection (Whitehouse, 2007). Numerous examples of laboratory-acquired CCHF in Africa attest to this. Numerous instances of CCHF that were obtained from a laboratory in Africa provide evidence that laboratory personnel handling viral samples are also at a significant risk of contracting the illness. The Centers for Disease Control and Prevention have classified CCHFV as a BSL-4 pathogen in the US because to all of these factors.

2. DISCUSSION

This epidemic acutely demonstrated the lack of clear understanding of the fundamental concepts and principles of infection control among both healthcare personnel and hospital administrators. The Pakistani outbreak was eventually contained by a fruitful multidisciplinary association between the hospital's management, clinical microbiologists, and epidemiologists (Sydnor and Perl, 2011). This confirmed the vulnerability and restrictions of the health care system in a resource-poor country that are associated with bloodborne and other occupationally related pathogens.
To summarize, hospital staff who are responsible for patient care experience anxiety, confusion, and fear when a patient is admitted with a highly transmissible or catastrophic viral illness, such as meningococcal meningitis, rabies, or VHF (including that caused by the Ebola and CCHF viruses). With a basic understanding of CCHF and careful adherence to pertinent infection-control and standard barrier procedures, healthcare professionals can be assured that they are adequately safeguarded against this illness (Yousuf et al. 2018).
However, political will is one of the other factors needed to effectively combat CCHF (Sharma et al. 2022). While the medical community sometimes bemoans the sensationalization of some disease events by the media, in the case of the Ebola virus fever, the resulting publicity may have had a significant impact on political visibility and research priorities, ultimately resulting in the development of a new experimental vaccine for this uncommon but deadly infection. Despite being geographically considerably more widespread than the Ebola virus, CCHF has not received the same level of international attention. It would be beneficial to depict it as the "Asian Ebola virus" that it appears to be in order to get additional national, international, and scientific attention that could improve future attempts at prevention and control.

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