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CRIMEAN-CONGO HEMORRHAGIC FEVER STATUS IN PAKISTAN, ITS PREVENTION AND CONTROL MEASURES

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Abstract

The Crimean-Congo Hemorrhagic Fever Virus (CCHFV) causes Crimean-Congo Hemorrhagic Fever (CCHF), a zoonotic disease transmitted from animals to humans, primarily through the bite of an infected tick. Human-to-human transmission can also occur through direct contact with the blood or bodily fluids of an infected individual. Diagnosis of CCHF can be achieved using various methods such as enzyme-linked immunosorbent assay (ELISA), immunofluorescence assay (IFA), and polymerase chain reaction (PCR). Since the first reported case in Pakistan in 1976, the country has experienced several outbreaks. Treatment typically involves supportive care and oral administration of ribavirin. While Balochistan is considered an endemic region, numerous cases have been reported from other parts of Pakistan. Currently, no FDA-approved vaccine exists for CCHF. Preventative measures include using acaricides to eliminate ticks, increasing awareness among high-risk populations, and implementing proper precautions when treating patients.

Keywords: *Causing agent, CCHF, Diagnosis, Hemorrhage, Pakistan, Prevention, Transmission, Treatment*

INTRODUCTION

The virus that causes Crimean-Congo hemorrhagic fever (CCHF) is transmitted to humans via the bite of an infected tick. Initially discovered in Crimea in 1944, the disease was first known as Crimean hemorrhagic fever. The term Crimean-Congo hemorrhagic fever was adopted after the disease's principal cause was identified in the Congo in 1969. The viral genome is a single-stranded, negative-sense RNA molecule that is segmented, encoding glycoproteins (Gn and Gc), a nucleocapsid protein, and a viral RNA polymerase in the small, medium, and large RNA segments, respectively (1). As arthropods are the primary vector of CCHFV transmission, the virus is classified as an arbovirus (virus transmitted via arthropods). Ticks of the genus Hyalomma are the most common vectors and carriers, living in soil and feeding on the blood of large and small animals such as cattle, foxes, hedgehogs, hares, and sheep. These ticks play a crucial role in the tick-vertebrate-tick cycle of CCHFV transmission. Although animals may carry viremia for up to two weeks, they show no visible signs of infection (2).

Ixodid ticks, especially those of the Hyalomma genus, can transmit and act as reservoirs for the virus. CCHFV can also be transmitted through direct contact with the blood or tissues of an infected person or animal. In humans, clinical symptoms of CCHF include sudden onset of fever, headache, myalgia, and thrombocytopenia; however, animals do not exhibit symptoms. In 1976, a patient in Rawalpindi, Pakistan, underwent a laparotomy due to symptoms including stomach pain, bloody vomiting, and severe diarrhea. This procedure led to a nosocomial infection that resulted in the deaths of three hospital staff members, including a surgeon. Since 1976, sporadic CCHF outbreaks have occurred in Pakistan. From 2010 to 2014, there were 286 cases with a case fatality rate (CFR) ranging from 20%-29%. In 2016, 86 confirmed cases had a CFR of 41%, indicating a concerning spike in cases. The FE&DSD division of Pakistan's National Institutes of Health (NIH) reported 55 cases in 2017, 63 cases in 2018, and 75 confirmed cases as of December 8, 2019. Endemic areas for CCHFV in Pakistan include Balochistan, which borders Iran and Afghanistan, Sindh, and particularly Karachi, with evidence of the virus's presence in other provinces as well (3).

High-risk individuals can contract the infection through various means, such as consuming raw milk from infected livestock, being bitten by an infected tick, or coming into contact with animal blood or tissues. Aerosol transmission has also been reported from Russia, including a suspected case of horizontal CCHF transmission between a mother and child in the Russian Federation (4). Research has focused on identifying the reservoir species and understanding the virus's persistence and transmission. Most of this research involves sero-epidemiological studies to pinpoint reservoir species and viral circulation. Diagnostic methods for CCHF include indirect immunofluorescence assays (IFA), indirect or sandwich enzyme-linked immunoassays (ELISA), competitive ELISA, virus neutralization assays, reverse passive hemagglutination inhibition (RPHI) assays, immunodiffusion assays like agar gel diffusion precipitation (AGDP), complement fixation (CF) assays, and CELISA (5).

Treatment options for CCHF are limited. Immunotherapy and ribavirin have been used during unusual outbreaks with varying efficacy, but no case-controlled studies have been conducted. Consequently, the Food and Drug Administration has not licensed any antiviral treatments for CCHF. However, future research on CCHFV and a better understanding of its biology could lead to the development of new treatments (6).

HISTORY

It is likely that the first indications of CCHF appeared in Tajikistan around the 12th century, though this was not understood at the time. During World War II, Soviet Union forces stationed in Crimea were the first to exhibit symptoms of Crimean hemorrhagic fever (CCHF) from 1944 to 1955. In 1969, researchers discovered that the same virus, known as the Congo virus, was responsible for both the febrile illness in Belgian Congo in 1956 and the hemorrhagic fever in Crimea. These original names were combined, leading to the current name, Crimean-Congo Hemorrhagic Fever Virus (CCHFV) (7). The first known case of Crimean-Congo hemorrhagic fever occurred in Tajikistan in the 12th century, with symptoms including blood in the belly, rectum, gums, vomit, sputum, and urine. CCHF is also referred to by various names in different regions, such as Asian Ebola, Khungribta (blood taking), Khunymuny (nose bleeding), and Karakhalak (Black Death). Between 1944 and 1945, an outbreak of hemorrhagic fever in the Crimean Peninsula resulted in a 10% fatality rate among those infected. When first detected in 1956 from a patient's blood sample in what was then the Belgian Congo (now the Democratic Republic of the Congo), the virus was nicknamed the Congo virus (8).

AGENT

The CCHF virus (CCHFV) belongs to the Bunyaviridae family and the Nairovirus genus. It is an encapsulated virus with a tripartite or segmented, single-stranded, negative-sense RNA genome. The small (S) segment encodes the nucleocapsid protein (NP), the medium (M) segment encodes the envelope glycoproteins (Gn and Gc), and the large (L) segment encodes the RNA-dependent RNA polymerase (9). CCHFV infects both animals and humans and is classified as an arthropod-borne virus (arbovirus). The Nairovirus genus, a subgenus of the Bunyaviridae family, includes other viruses such as Phlebovirus and hantavirus, which are capable of causing hemorrhagic fever. Nairovirus is divided into seven serogroups. Although both the Hazara virus and the CCHF virus belong to the same serogroup, the Hazara virus has never been associated with human infections (10).

TRANSMISSION

In scientific terms, any hematophagous arthropod that spreads disease while feeding on blood is referred to as a "vector." The ability of an arthropod to acquire, harbor, and transmit microbes is known as its "vector competence." A tick-borne virus can infect a competent vector by having the tick feed on an infected host, even if the viremia is temporary or undetectable. A competent vector not only allows for viral replication within its cells but also transmits the virus when it feeds on a new host. The virus must be resistant enough to survive in eggs and maintain its development in a tick capable of carrying it (transstadial survival). Virus transmission occurs after the tick molts because, unlike hematophagous insects, ticks feed

only after molting. The habitat of tick-borne viruses, particularly CCHFV, during this stage of the tick's life cycle remains unclear. Some tick-borne viruses are transmitted both horizontally from one generation to the next and vertically through transovarial (male to female) or transsexual transmission. The CCHFV virus propagates through both horizontal and vertical transmission. While non-competent ticks may acquire the virus when feeding on an infected host, they cannot harbor the virus in their tissues or transmit it to new hosts (11).

Ixodid ticks, specifically those of the Hyalomma genus, are the primary carriers of CCHFV, serving as both a reservoir and a vector. CCHFV can also be transmitted through direct contact with infected tissues or blood from humans or animals, which show no apparent signs of infection (3). Some scientists believe humans are the final host of CCHFV. In rural areas with a high tick population, humans are most likely to get infected through tick bites. Healthy individuals can contract the virus by coming into contact with contaminated body fluids or blood during the first seven to ten days of infection. Animal blood contaminated through direct or indirect human interaction can also serve as a vector for transmission, which is common in slaughterhouses and meat markets (12).

SIGNS AND SYMPTOMS

Only humans can become sick after being infected with CCHFV (7). There are four main stages that make up the cascade of CCHF: the incubation, the prehemorrhagic, the hemorrhagic, and the convalescent phases. The incubation period may last anywhere from one to five days following a tick bite; however, it most often begins anywhere from five to seven days after the first contact with blood or tissues that carry the virus. Patients have experienced a sudden onset of fever, as well as fatigue, headache, and soreness in their muscles. They may also have vomiting, distinct face and oropharynx hyperemia, a hemorrhagic rash with the formation of ecchymoses, and other symptoms. Additionally, they may bleed from the nasopharynx, the gastrointestinal tract, and other places (13). Laboratory abnormalities such as thrombocytopenia, leukopenia, increased aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), and creatine kinase (CK), as well as delayed prothrombin time and activated partial thromboplastin time (aPTT), are common in patients diagnosed with congestive cardiomyopathy with heart failure. Damage to the endothelium may trigger the coagulation cascade, which can then result in a decreased number of platelets or an impaired ability of platelets to complete their job. In addition, the activation of coagulation may have an effect on the failure of several organs as well as disseminated intravascular coagulation (DIC). Because of viral infection or cytokine-induced vascular injury, CCHF is characterized by the presence of vascular leakage (8). One hundred and twenty patients presented with fever and bleeding as their primary symptoms. Epistaxis was the most frequent symptom of bleeding, whereas less common symptoms included hematemesis, petechiae, melaena, and hematuria (14). CCHF disease or infection may be identified by a number of symptoms, including bloody diarrhea, ecchymosis, petechiae, and epistaxis. Additionally, one or more of the following symptoms could be present: In addition to a strong headache, other symptoms include fever, joint discomfort, chills, and nausea (15).

DIAGNOSIS

The first clinical signals that indicate a CCHFV infection are symptoms such as fatigue, high fever, headache, myalgia, and lack of appetite. These symptoms, when combined with a history of tick bites, contact with ruminant blood or body fluids in a risk area, or direct contact with a CCHF patient, are considered to be the most reliable. Patients diagnosed with CCHF often present with different laboratory findings, such as leukopenia, thrombocytopenia, and elevated levels of transaminases. CCHF cases are identified when viral RNA is confirmed in blood or body fluids by quantitative RT-PCR, or when immunological tests, such as IFA or ELISA, detect CCHFV-specific IgM or IgG antibodies. In addition, CCHF cases are identified when immunological tests, such as IFA or ELISA, detect CCHFV-specific IgM or IgG antibodies (2). There are six different diagnostic procedures eligible for inclusion in the study since they satisfy the requirements. These include a commercial IgG and IgM ELISA from Vector-Best in Novosibirsk, Russia, for precise CCHF sero-diagnosis, and a commercial IgG and IgM IFA from the same company

(Euroimmun, Luebeck, Germany). To find the CCHFV genome, a commercial real-time RT-PCR from Altona-Diagnostics in Hamburg, Germany, as well as a low-cost, low-density microarray designated with the number 26 (#r26) (16). In a collaborative evaluation of CCHF diagnostic tests, it was discovered that commercially available serological assays for detecting CCHFV-specific antibodies in human sera had excellent specificity; however, their reported sensitivities were only 87.8% (range 75.2%-95.3%) for IgM ELISA testing and 80% (range 66.9%-90.2%) for IgG ELISA testing (17).

CCHFV STATUS IN PAKISTAN

In 1960, the virus was discovered for the first time in Pakistan in Hyalomma ticks. Since that time, major witnesses to isolated instances and occasional epidemics have been those who work with animals. There are seven genotypes of CCHFV: Africa 1, Africa 2, Africa 3, Europe 1, Europe 2, Asia 1, and Asia 2. The CCHFV genotypes Asia-1 and Asia-2 are present in Baluchistan, but Asia-1 is more widespread across the rest of Pakistan. In 1976, a patient in Rawalpindi, Pakistan, who was experiencing stomach discomfort and hematemesis (blood vomiting), presented himself to a public hospital as the first reported incidence of CCHF in the nation. Between 1976 and 2000, Pakistan recorded 23 instances of CCHF, with a mortality rate of 39% for those patients. Since 2000, there has been an increase of between 50 and 60 new cases of CCHF every year. Due to ticks having two life cycles in a year, there is often an increase in the number of cases of tick-borne diseases reported throughout the state around June and October. In 2012, there may have been 61 cases of CCHF in the state, and 17 individuals lost their lives as a result. A death rate of 27.8% was found in these cases. Reports indicate the infection being present in Sindh, KPK, and Punjab in addition to Baluchistan, the most affected region. On September 7, 2013, four butchers were found dead after contact with infected sheep meat. It was stated that the virus had once again spread across the city of Haripur. The virus was found in Baluchistan in 2014, highlighting the need for increased measures to manage the infection (12).

Research conducted over five years, from March 1, 1997, to February 28, 2002, comprised 87 male patients (64%) and 48 female patients (36%) out of a total population of 135 patients who had attended the medical professionals. According to viral detection in the blood of 135 hospitalized patients with a high index of suspicion for CCHF, 83 (61%) were confirmed to have CCHF by the Centers for Disease Control and Prevention in Atlanta, Georgia, United States. According to ELISA results, nine patients (10.8%) tested positive for CCHF, 22 cases (26.5%) exhibited IgM positivity, and 52 cases (62.6%) revealed IgM and IgG positivity against CCHF (14). Between 2012 and 2015, there were 161 confirmed cases, with 45 fatalities recorded between 2012 and July 2014. Nineteen fatalities in 2016 indicate that the infection is rapidly spreading across Pakistan (18). Between March 30 and July 20, 2014, there were 42 confirmed cases of Crimean-Congo hemorrhagic fever in the state, resulting in 10 deaths (the case-fatality rate was 24%). Laboratory examinations confirmed the presence of 22 of the infections reported (7). On July 25, 2014, Pakistan's disease early warning system (DEWS) first detected the seasonal rise in human cases of Crimean-Congo hemorrhagic fever. This was the first time the spike had been documented by DEWS. Between March 30 and July 20, 2014, there were 42 confirmed cases of Crimean-Congo hemorrhagic fever recorded across the nation, with 10 fatalities (case-fatality rate of 24%). Lab tests confirmed the presence of 22 of the infections reported (20).

Haider et al. (2016) provided information on CCHF-positive individuals between January and October 2016, using samples from three major cities in Pakistan: Karachi, Rawalpindi, and Quetta. They prospectively analyzed blood samples from 483 patients for CCHFV-specific IgG using ELISA kits. These individuals, displaying possible CCHF symptoms, had been admitted to hospitals across Pakistan. Laboratory tests confirmed that 86 out of the 483 individuals were positive for CCHFV, with the largest number of positive cases found in Balochistan (38 out of 86), making this region the focal point of their investigation. Other regions with confirmed cases included Sindh (17%), Khyber Pakhtunkhwa (17%), Punjab (13%), and Azad Kashmir (8%), while Gilgit Baltistan reported no cases. Among the 86 confirmed cases, 35 individuals (41%) ultimately died, with the highest fatality rate in Balochistan (10 deaths out of 35), followed by Sindh (23%), Khyber Pakhtunkhwa (20%), Punjab (20%), and Azad Kashmir (9%) (30).

In 2017 and 2018, researchers tested 3,710 blood samples from 1,872 people and 1,838 domestic animals (424 sheep, 183 camels, 311 buffaloes, 440 goats, and 480 camels) for CCHFV antibodies using a two-step procedure involving ELISA and confirmatory immunofluorescence assay. They detected 51 positive human samples, representing a 2.7% positivity rate. Among animals, 66 out of 1,838 tested positive, representing a 36.2% positivity rate . In 2019, the National Institute of Health in Islamabad tested 280 blood samples from suspected CCHF cases using RT-PCR, finding 28 samples (10%) positive for CCHFV. The majority of these cases were detected in Quetta, Balochistan (19).

Since the first detection of CCHFV in Rawalpindi, Pakistan has experienced frequent outbreaks (3). Although the virus is enzootic in Balochistan, recent outbreaks have occurred in northern areas such as Abbottabad and Peshawar (KPK), often coinciding with the migration of nomads and livestock during events like Eid ul-Azha and periods of social unrest, such as immigration from Afghanistan and post-2005 earthquake scenarios (21).

A study at Fatima Jinnah General & Chest Hospital in Quetta examined 44 blood samples for CCHF IgM, finding CCHFV-specific IgM in 16 samples (36%) and viral RNA in 6 samples (16%) . In Chakwal, 26 out of 453 human samples (5.7%) tested positive for anti-CCHF IgG antibodies, with seropositivity rates ranging from 1.8% to 9.5% across different human groups. The highest seroprevalence was among those working directly with animals (14/147), followed by slaughterhouse workers (6.57%) and milkmen (1.78%) (25, 27).

Notable historical outbreaks include a case in Rawalpindi in 1994, which led to the deaths of a doctor and members of an operating theater team. Subsequent outbreaks occurred in Quetta in 1994, Peshawar in 2000, and Azad Jammu and Kashmir in 2002, leading to infections among healthcare workers and fatalities. In 2010, Pakistan's National Focal Point Ministry reported 26 new cases to WHO. Pakistan saw 69 confirmed cases in 2014 and 25 cases in Khyber Pakhtunkhwa in 2015, with 11 resulting in death. In 2012, there were 62 recorded cases, with 100 cases reported in 2013, and the number increased to 122. As of mid-August 2016, 20 fatalities were attributed to CCHF in Pakistan (28).

In tick samples collected from various districts, the highest prevalence of CCHF antigen was in Chakwal (33.68%), followed by Mianwali (23.68%), Rawalpindi (23.17%), Attock (20%), Rajanpur (10.39%), and Lahore (8.33%). No CCHFV was found in tick samples from Jehlum, Dera Ghazi Khan, Bahawalpur, or Rahim Yar Khan (31). Of 520 Hyalomma ticks tested, 20 were positive for the CCHFV S segment of DNA. Female ticks were more commonly positive (75%) than male ticks (25%). The highest frequency of CCHFV genomes was in *H. marginatum* (30%), followed by *H. dromedarii* (25%), *H. excavatum* (20%), *H. anatolicum* (20%), and *H. scupense* (5%). The highest rates of CCHFV-positive ticks were in Kalat (60%) and Quetta (30%), with the lowest in Killa Abdullah (10%) (32).

Serological examination showed that 149 (19%) of 800 sheep serum samples and 37 (5%) of 800 goat serum samples had CCHFV-specific IgG antibodies. Conflicting results were found in 11 of 37 positive goat serum samples and 16 of 149 positive sheep serum samples when using different ELISA tests confirmed by IFA. Using real-time RT-qPCR, 8 out of 160 sheep serum pools tested positive for CCHFV genome fragments, while none of the goat serum samples were positive (25).

TREATMENT

The pillar around which the CCHF's healthcare system is built is the provision of general supportive therapy. Close monitoring is required so that progress may be monitored in terms of the restoration of volume and blood component levels. If a patient fits the case description for suspected CCHF, the recommended alternative treatment of ribavirin (oral) should be started as soon as possible, provided that they have the patient's and their relatives' permission to do so and that the attending physician has given it

careful consideration (7). Transfusions or injections of blood substitutes and aminocaproic acid are two treatment options that are recommended by medical specialists in the case of severe blood loss. In certain cases, the administration of fresh frozen plasma, thrombocyte solutions, and erythrocyte preparations may be helpful in the treatment of hematological conditions. In addition to this, it is probable that you may need assistance breathing (2). Ribavirin is an effective antiviral medication, and one of the reasons for this is that it may stop the CCHFV from spreading. In a recent clinical research, the combination of two drugs that are already licensed by the FDA—chloroquine or chlorpromazine and ribavirin—was shown to have a synergistic impact against CCHFV. MxA, a new molecule that is a member of the interferon-induced GTPases and dynamin families, was shown to be effective in inhibiting both the generation and replication of CCHFV (18).

PREVENTION AND CONTROL

- Till now there is no approved vaccine for CCHF but two anti-CCHFV vaccinations being tested in clinical settings. The first method of a vaccine that was created in Bulgaria and made from the brain of an infected suckling mouse that was then inactivated with formaldehyde. The DNA vaccine, which is the second sort of vaccination, has been tested and validated with great effectiveness in mice. The study that is being done right now pertains to both of these vaccinations.
- It is of the utmost importance to educate the general public on the tick bite transmission mechanism, the proper treatment of ticks, animal handling and slaughter, as well as human safety measures.
- Controlling ticks using acaricides is an option worth considering for farms that are well-organized and that raise animals for food. The animals should also be dipped in the insecticide solution. People should make every effort to avoid going into tick-infested regions, especially during the times of day when ticks are most active (spring to fall).
- It is important to protect yourself from tick bites by wearing light clothing that covers your arms and legs, tucking your pants into your socks, frequently inspecting your clothing and skin, and applying a tick repellent such as diethyltoluamide (also known as Deet or Autan) to your skin and/or applying it to your pant legs and sleeves.
- Anyone who works with cattle or other animals in an area where the disease is endemic should take precautions against contracting the disease, such as using insect repellents on their skin (for example, diethyltoluamide) and clothes (for example, permethrin) and wearing gloves or other protective clothing to prevent their skin from coming into contact with infected tissues or blood. It has been shown that solutions containing 1% hypochlorite and 2% glutaraldehyde are capable of killing CCHFV. Additionally, it has been demonstrated that heating the solution to 56 degrees Celsius for thirty minutes is also effective.
- Patients who have died from CCHF should be treated with a liquid bleach solution with a ratio of 1:10, and then they should be wrapped in a winding sheet as recommended. It is necessary to spray a bleach solution onto the sheet that is being twisted. After that, a plastic bag is used to enclose it, and the bag is sealed with tape. It is also advised that the dead person's clothing and the vehicle in which they were transported be cleansed and burned.
- It is highly recommended that hospitals in Pakistan stock up on ribavirin. In order to prevent patients from getting nosocomial infections, biosafety procedures are very necessary.
- Patients suspected of having or confirmed as having CCHF are placed in isolation and undergo extensive barrier nursing care in order to reduce the risk of the transmission of nosocomial infections.
- Patients who are being treated in a separate room are supposed to have a strict nursing barrier between them. Every member of the medical and paramedical staff, as well as every attendant, should be required to wear safety equipment that can only be used once, such as gowns, masks, and gloves.
- After usage, needles should be thrown away in a container that can't be opened, then they should be sterilized in an autoclave and then burned to avoid spreading disease to other individuals. Bleach cleaner in liquid form should be used to clean all surfaces.
- Only qualified paramedics should respond to patients in need of medical attention. Anyone who isn't an essential part of the medical staff shouldn't be allowed in the patient's room under any circumstances.

- Before the incineration can take place, the patient's body fluids and any clothes they wore while they were in the hospital must be handled as potentially contagious materials and sterilized in an autoclave.
- Before any of the instruments may be used again, they must first undergo disinfection and autoclave sterilization. As soon as the patient is moved out of the room, the area should be fumigated, and the surfaces should be cleaned with liquid bleach, in order to eliminate any viruses that may still be present (7).
- Communities, regions, and provinces that are at a higher risk for catching the disease should have health education programs and media campaigns put into place to educate the local people about the hazards and the preventative measures they may take to reduce their likelihood of becoming infected.
- The Provincial Health Directorate need to be involved in efforts pertaining to health education. It is essential that the messages communicated by television, radio, and print media be consistent with one another (35).

CONCLUSION

The virus that causes Crimean-Congo hemorrhagic fever was originally identified in Crimea in 1944 and then in the republic of Congo in 1969; it is a severe enzootic illness with a high mortality rate. The virus has a single stranded, enclosed genome that is divided into three segments—small, medium, and large. Ixodid ticks, especially those of the genus *Hylomma*, serve as both vectors and reservoirs, transmitting the disease to animals and humans via tick bites and contact with blood of infected animal or human. Animals are asymptomatic host while human can show symptoms like fever, headache, fatigue, epistasis, ecchymosis and bleeding from mouth and anus. CCHF may be diagnosed using a variety of techniques, including ELISA, IFA, and RT-PCR. The first incidence of CCHF was recorded in Pakistan in 1976, and since then there have been periodic outbreaks. In years between 1976–2010 Pakistan faced 14 more outbreaks. In recent years, there has been an increase in the number of cases of this infection being recorded in Pakistan. Treatment of the infection is thought to be supportive therapy and use of Ribavirin orally but prevention may overcome the infection by controlling ticks using acaricides to remove ticks from livestock, educating high risk individuals and use of safety precaution among physicians, hospital staff members and caretakers while treating the patient. In order to successfully manage and prevent CCHF, continuous monitoring of the epidemic is required across all provinces of Pakistan.

Conflict of Interest:

The authors have no conflict of interest.

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