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Prevalence of Crimean-Congo hemorrhagic fever in Pakistan and its new research progress

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ABSTRACT

Crimean-Congo hemorrhagic fever is a deadly and life-threatening viral sickness spreading throughout the world with high mortality rate of 10%–40%. The causative agents are ticks which show diversity in their strains and thus it is difficult to make vaccine, however some strains are conserved which is the positive point in vaccines development. From 2012 to 2015, a total of 161 cases were confirmed for Crimean-Congo hemorrhagic fever virus in Pakistan. And from 2012 to July 2014, 45 deaths were reported in the country. It is spreading sporadically in Pakistan. Mapping of endemic areas and cross-border veterinary surveillance should be developed in high risk areas and workshops should be arranged to increase public awareness about the disease. Control measures must be taken to avoid spreading of the disease to new areas.

1. Introduction

Crimean-Congo hemorrhagic fever (CCHF) is caused by Crimean-Congo hemorrhagic fever virus (CCHFV) which belongs to the family of Bunyaviridae, genus *Nairovirus*[1].

The second most widespread arbovirus of medical importance after Dengue is CCHFV. CCHF is a viral fatal disease that has been explained and clinically determined in almost 30 countries all over the globe with the fatality rate of 10%–40%[2,3]. This virus has been causing substantial and progressive morbidity and fatality in several regions of the planet. In 1944 it was categorized as a viral infection by Soviet scientists[4].

CCHF really is a deadly viral sickness brought on by household as well as wild animals. And the causative agents are called ticks which are the external blood sucking parasites of these livestock mammals. The most notable vectors for CCHFV are the *Hyalomma* species of tick. Other ticks species acting as vectors of CCHFV include *Ornithodoros*, *Ixodes*, *Dermatocentor*, *Boophilus* and *Rhipicephalus* species[5,6]. Ticks are considered as one of the most common human ectoparasites. Bites of these ticks are usually painless because many people don't even notice their bites. They are responsible for the transmission of bacterial, viral, rickettsial and protozoan disease agents[7]. These causative agents are found in Asia, the Middle East, Eastern Europe, the belt across central Africa and South Africa, Eurasia and Madagascar[8]. About 700 different species of hard ticks have been described throughout the world. Two hundred and sixty-nine among them are found to cause health-related problems for humans[9-11]. CCHFV is an enveloped negative-sense single stranded RNA virus. The virions are spherical, pleomorphic ranging from 85 to 105 nm in diameter, with a 5 to 7 nm thick bilayered lipid envelope[6,12,13]. The RNA has 3 negative strands that encode the heredity information *i.e.* small, middle and large respectively. The large segment codes for the RNA polymerase; the middle segment encodes the envelope proteins (Gc and Gn); and the small segment codes for the nucleocapsid protein[14].

In order to cause infection the CCHFV must have to replicate its heredity material and this purpose is achieved first by adsorption to the host cell by its protruding glycoprotein recognizing receptors.

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Then by means of clathrin-dependent endocytosis, it gets a way to enter the cell and results in membrane fusion. The RNA polymerase is then dumped into the host cytoplasm. The viral proteins are produced by transcription and translation and in the meanwhile RNA is also replicated. The newly formed CCHFV then buds off through the plasma membrane of the host and becomes ready to get entered in the other cell[12].

This virus is transmitted to humans through the bite of an infective adult tick of the genus *Hyalomma*. Crushing an infected tick also causes infection by skin lesions. Contact with infected blood and tissues of animals and humans also leads to infection. However, person to person transmission occurs by coming in contact with bloody vomit, body fluids or aerosols from the advanced stage patients[15]. The injections and surgical procedures in hospitals may also play role in spreading the disease. Therefore, those professions which deal with infected animals and humans such as livestock breeders, abattoir workers and healthcare workers are at risk to this disease[16].

CCHF has an unexpected attack with excessive fever, vertigo, chills, vertigo, malaise, diffuse myalgia, irritability, photophobia, and limb, head and back aches. This fever can last between 5 and 12 days and may be biphasic or continuous. Some other recurrent symptoms include diarrhea, abdominal pain, bradycardia, anorexia, hyperemia and edema of the neck and face, nausea and vomiting and conjunctival congestion. Thrombocytopenia and leucopenia are mostly present, as is proteinuria[13].

On the 4th day, the signs of hemorrhagic phase begin with epistaxis, petechia, bleeding from the vagina, hemorrhaging of the gums and gastric mucosa. The liver becomes swollen and painful. Death occurs due to blood loss, pulmonary hemorrhages, neurological complications and incurrent infections, characterized by weakness, weak pulse, and sometimes complete loss of hair with the estimated fatality rate of 30% and 50%. The recovery period starts after 15 to 20 days of disease[13,15,17]. The intensity of illness is related with the virus quantity in the blood (up to 109 genome equivalents/mL of blood)[18,19].

2. Epidemiology

CCHF was first reported in Crimean Peninsula during 1944–1945. It was a large outbreak of severe CCHF with a case fatality rate of 10%[6]. The disease was called as Crimean hemorrhagic fever and was later reported in central Asian republics of the former Soviet Union and all over the Europe and other countries[5]. Later on, this virus was found to be antigenically identical to CCHFV, which was isolated in 1956 from a febrile patient of Democratic Republic of Congo, and was then named as CCHFV[20].

Among the tick-borne viruses, CCHFV has the most extensive geographical range[2]. Infection of CCHFV is reported in 30 different countries, until now with some major outbreaks in Africa, Southeast Europe, Middle East, and Asia[2,21]. The mortality rate among South African cases ranges from 5% to 30%[22].

In Asia, outbreaks were recorded in Kazakhstan (1948–1968), China (1965–1994, 1994–1995), Tajikistan (1943–1970), and Pakistan (1976, 1994, 2000)[2].

3. CCHFV in Pakistan

In Pakistan, CCHFV was first isolated in 1960s from ticks in Changa-Manga forest near Lahore[21]. CCHF is endemic in Baluchistan from where 9 human cases have been reported, and also from Kashmir and Peshawar[21,23,24].

The first case was reported in Pakistan in 1976 in Rawalpindi when Dr. Mateen died when he was treating a patient with abdominal pain, melena and hematemesis at the Central General Hospital (now Benazir Bhutto Hospital)[24,25]. Three deaths occurred including a surgeon (Dr. Mateen) and an operation theatre's attendant while eleven patients were found infected with the virus[23].

Another outbreak of CCHF was reported in December 1994 in Quetta, Baluchistan. This resulted in death of a patient. Two surgeons who operated upon him were also found infected with the virus along with a health care personnel at Agha Khan University Hospital, Karachi, where these surgeons were being treated[26].

A 30 years old male from Peshawar was taken to the emergency room of Shifa International Hospital, Islamabad in December 2000. He was suffering from fever associated with chills, sore throat and rigors seven days before admission. After 5 days his gums started bleeding accompanied with melena and hematemesis. His father died two weeks ago with the same symptoms when he slaughtered a sheep. Serum samples of index patient and his attendant were positive for CCHF virus[27].

On the evening of 7th December 2005, a 32 years old previously healthy man was admitted to the Combined Military Hospital, Abbottabad. He belonged to a family which owned butchery and barbeque shop. Within 24 h of hospital admission he died because of multi-organ failure. His blood PCR was positive for CCHF virus[28].

On 12nd February, 2002, a 25-year-old Kashmiri woman from Bagh in Azad Jammu and Kashmir, 100 km northwest of Rawalpindi/Islamabad became the victim. The index patient died shortly after admission to hospital. Two health care workers became the secondary cases, one died after 13 days of coming in contact with the index patient. The other got recovered with oral ribavirin[24].

As of 15th October 2010, World Health Organization was reported with 26 cases by the National Focal Point, Ministry of Health, Pakistan. From 1st January to 9th June 2013, 16 suspected cases of CCHF, including six deaths were reported from Pakistan with a case fatality rate of 37.5%. Seven of these reported cases have been laboratory-confirmed. In 2012, Pakistan faced a similar outbreak of CCHF, during which 61 suspected cases, including 17 deaths were reported (case fatality rate 27.8%).

CCHF continues to spread in Pakistan and cases are reported sporadically since 2000 in areas that are not known as foci for the disease[3].

In Pakistan, 69 cases were confirmed last year up till November and there were 183 confirmed cases between 2011 and 2013. In 2015, at least 25 CCHFV positive patients in critical condition from Peshawar, Dir, Kohat and Swabi were brought to Hayatabad Medical Complex. Out of them, 11 died[29]. In the past 4 years, CCHF resulted in 35 deaths with a fatality rate up to 50%. As shown in Figure 1, according to the epidemiological analysis, 62% of the cases were

traced back to animals in Quetta, Killa Saifullah, Killa Abdullah and Ziarat districts of Balochistan. Similarly a number of patients diagnosed in Rawalpindi, Peshawar, Banu, Multan and Chakwal also possessed history of contact with animals[29]. Monthly reported CCHF cases from January 2012 to date show varied trends as shown in Figure 2. However mass scale animal movements anticipated prior to Eid-ul-Azha could serve as a source of propagation for sticks infested with CCHF virus thereby increasing the risk of disease transmission. Whereas Figure 3 illustrates that maximum number of confirmed CCHF cases eported in 2014.

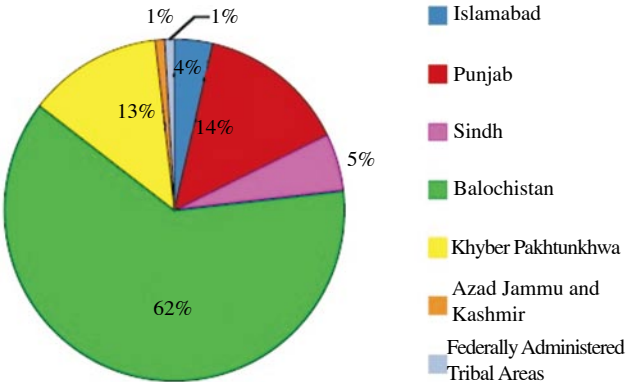

Figure 1. Reported CCHF cases by province/area in Pakistan, 2012–2014 (n = 190).

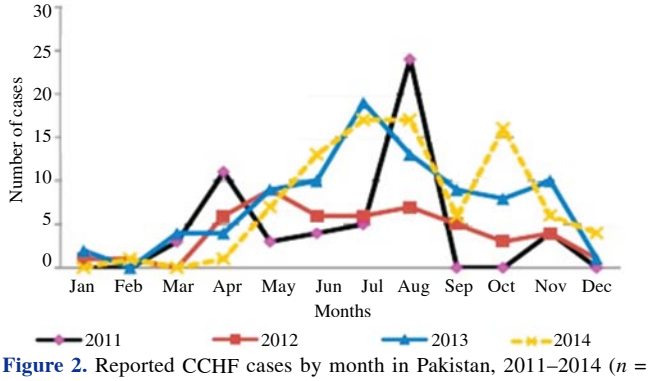

Figure 2. Reported CCHF cases by month in Pakistan, 2011–2014 (n = 280).

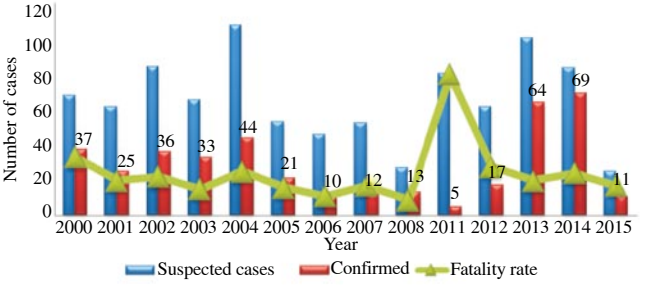

Figure 3. Reported CCHF cases in Pakistan along with fatality rate from 2000–2014.

4. New researches related to CCHF

According to the new research on CCHFV, new cellular factors were identified which are essential for CCHFV infection. A discovery can lead us to the novel targets for therapeutic interventions against the pathogen and can help us to identify new treatments[30]. In this new research, the first step was to identify the pathway of infection and to know the entry of virus into the cell, a critical step in virus replication cycle. Next step is the identification of drugs that can prevent virus' interactions with the multivesicular bodies. These identified drugs have the potential to be developed into broad spectrum antiviral treatments. This is the first research of its kind which indicates that where the virus penetrates into the cell to infect it and thus revealing a target site at which a drug therapy need to act.

Moreover, the great genetic variations in different strains of CCHFV is a big hurdle in the development of vaccine against CCHF virus. Despite this genetic variability, some epitopes are conserved and CCHFV vaccines may have to be either immunogens derived from several CCHFV strains, or can target the immune response on conserved neutralizing epitopes[31]. Bulgaria and former Soviet Union used inactivated vaccine which was derived from mouse brain[32]. However, vaccine is not available in most of the countries.

5. Prevention and control

The lack of care and reasonable facilities to accommodate quality care for livestock animals is one of the foremost reasons for the extensive spread of this disease. Proper monitoring of animals, especially sacrificial animals which are imported from other countries for Eid ul Adha, should be done in order to control the spread of this disease. Preventive measures are not often very easy or useful as the spread of ticks cannot be controlled with ease. Another way to reduce the spreading of the causative agent is to use acaricides, as they minimize the chances of infection of ticks. It's best to wear gloves and other protective clothing in order to reduce the risk of transmission of virus from animals to humans. Close physical contact with CCHF-infected persons should be avoided. Ribavirin along with hematological support is the main stay of treatment with good prognosis. It also lies upon the shoulders of the law enforcement and healthcare authorities to make certain that only healthy animals enter the country.

6. Conclusions

CCHFV is highly contagious with increased mortality rate, so there is a need to increase awareness among public, specially, among people who work with livestock and health care workers regarding the mode of spread of illness. Environmental and climatic factors which play role in the spreading of disease need to be studied further. There should be mapping of endemic areas and cross-border veterinary surveillance should be developed in high risk areas. The involvement of both animal and health sector will be important to control the current wave of this outbreak. Contract tracing should be ensured and health care authorities should be informed at time. Much needs to be done in Pakistan for re-enforcing control measures to prevent spread of the disease to new areas.

Conflict of interest statement

We declare that we have no conflict of interest.

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