Review Article

Crimean-Congo Hemorrhagic Fever (CCHF): An Emerging Disease in Pakistan

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Abstract | Crimean-Congo hemorrhagic fever (CCHF) is an emerging deadly viral disease in Pakistan and is becoming endemic in many regions. The first case of CCHF was reported in 1976 in Rawalpindi and after that, multiple sporadic cases and outbreaks have occurred in subsequent years and till today. CCHF outbreaks have a case fatality rate of up to 40%, which is alarming. It is a zoonotic disease and the virus is transmitted mainly to the humans through hard tick bite and direct contact with blood of the infected animal. The occurrence of CCHF outbreak in Pakistan is increased quite significantly near Eid-ul-Adha. Haemorrhages are the major signs of this fatal disease. No treatment of CCHF is available currently but Ribavirin antiviral drug is used to cure this disease. There is currently no commercially available vaccine for this disease. It is recommended that the disease can be controlled by adopting preventive measures such as avoiding of tick bites and contact with blood of the suspected animal.

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Introduction

Congo Hemorrhagic Fever (CCHF) is a tick-borne viral disease which is caused by Crimean-Congo Haemorrhagic Fever Virus (CCHFV) which belongs to genus Nairovirus and family Bunyaviridae (Donets et al., 1977; Martin et al., 1985; Athar et al., 2002; Ellis et al., 1981). It is a zoonotic disease (Ozsoy et al., 2015; Barthel et al., 2014). The hard ticks (Ixodide) of the genus Hyalomma are the most important vectors of the disease. The virus travels in a tick-vertebrate-tick cycle, but it can also be transmitted vertically and horizontally within the tick population (Bente et al., 2013; Zavitsanou et al., 2009). Hyalomma ticks are present on many animal species for example cattle, deer, hares, goat and sheep. These infected ticks when bite these animals, transfer the virus in them (Kemp et al., 2014).

Many birds are resistant to CCHF, but ostriches seem to be susceptible (Swanepoel and Burt, 2004; OIE, 2014). Viraemia in livestock is of less duration and also of low intensity. These birds play an important role in the life cycle of ticks and in the transmission and replication of the virus (Georgieve, 2009). Animals don't show any clinical signs. As compared to animals, humans show clinical signs of the disease (OIE, 2014; Peyrefitte et al., 2015). The disease is present in many countries including Asia, Africa, the Middle East and Southeastern Europe and endemic in many areas of Pakistan especially Khayber Pakhtunkhwa (KPK) (Saleem et al., 2008).

CCHFV is a spherical, enveloped, negative-sense sin-

gle stranded RNA virus and its genome consists of three segments (i.e. Tri-partite), L-large, M-medium and S-small (Honig et al., 2004; OIE, 2014; Deyde et al., 2006; Goswami et al., 2014). The virus has seven genotypes i.e. Africa-1, Africa-2, Africa-3, Europe-1, Europe-2, Asia-1 and Asia-2. In Pakistan, especially in Balochistan province, genetic analysis of the CCHFV has confirmed the presence of Asia-1 and Asia-2 genotypes (Aslam et al., 2016).

Still pathogenesis of the disease in humans is not well understood (Burt et al., 1997). Most people become infected by tick bites but infection is also possible through contact with infected blood and other body fluids of viraemic animals. As CCHFV has the potential to be transmitted directly from human-to-human, nosocomial outbreaks may also occur (Hasan et al., 2014).

There is no approved CCHF vaccine available yet and usually symptomatic and supportive treatment is done (Jabbari et al., 2012; Mertens et al., 2013; Keshtkar-Jahromi et al., 2013). Health education and awareness on prevention and control measures are the most important steps to prevent this fatal disease. Tick repellents can be used to effectively reduce the ticks' population. To protect laboratory staff and healthcare workers, handling of CCHFV infectious blood samples and other materials should only be carried out at BSL-4 level (Connolly-Andersen et al, 2011). Treatment of CCHF is usually done with oral or intravenous use of drug ribavirin (Athar et al., 2005; Spengler et al., 2016). This disease can be controlled mainly by avoiding tick bites by using tick- repellents (Leblebicioglu et al., 2015).

Historical Background

It is thought that the first evidence of CCHF dates back to the 12th century in Tajikistan but it was not known then (Tishkova et al., 2012). CCHF was first time identified among Soviet Union military personnel in the Crimea during World War- II (1944-45) and was named Crimean Hemorrhagic Fever (Kamboj and Pathak, 2013). The virus was isolated from the blood and tissues of the infected persons using intra-cerebral inoculation of suckling mice. Subsequently, it was shown in 1969 that the virus responsible for Crimea Hemorrhagic Fever was the same as of Congo virus that caused febrile illness in Belgian Congo in 1956 (Bente et al., 2013). Hence, the two names of the same virus were then combined as one name i.e. Crimean- Congo Hemorrhagic Fever Virus- CCHFV (Appannanavar et al., 2011).

In Pakistan, it was initially reported in 1976 in a general hospital of Rawalpindi when a patient was admitted in the hospital with abdominal pain, haematemesis (vomiting of blood), and melena (Alam et al., 2013). Since then, 12 outbreaks mainly in western and northwestern regions of the Pakistan and the western province of Saudi Arabia, the United Arab Emirates, Kuwait, and Iraq had been reported (Zavitsanou et al., 2009). Zavitsanou et al. (2009) reported the case fatality rate up to 50%. Athar et al. (2005) also reported nosocomial outbreaks with a high mortality rate.

Global Scenario

CCHF is thought to be one of the most widely distributed tick-borne viral diseases in the world. This disease is present in Asia, Africa, Southeastern Europe, and the Middle East (Yadav et al., 2015). The first reported outbreak occurred in 1944-45 in Crimea, Russia war when large numbers of the Soviet soldiers were exposed to tick bites due to outdoor sleeping (Hoogstraal, 1979). In 1954-1955, a large outbreak was reported from Bulgaria with 487 cases, mainly in the Shumen area in North-East Bulgaria. WHO, 2008 reported a total of 1568 CCHF cases in Bulgaria from 1953-2008 with case fatality rate of 17 %.

Nabeth et al. (2004) reported an outbreak from Mauritania in 2003. Aradaib (2010) reported a nosocomial outbreak in 2008 from Sudan. OIE (2009) reported many CCHF cases from Georgia, Kazakhstan, Tajikistan, Iran and Pakistan in 2009. ProMED, 2010 reported an outbreak in Pakistan's Khyber Paktunkhwa Province in September 2010.

The trans-boundary transmission potential of the disease is due to dissemination of the ticks and virus through annual bird migrations. Ticks are widely dispersed between continents by movement of livestock also (Hoogstraal, 1979). By phylogenetic analysis of CCHF strains, it is proved that the recent outbreak of CCHF in the Arabian Peninsula was the result of trade of tick-infested livestock from Africa and Asia (Hoogstraal, 1961; Hoogstraal, 1963).

The high prevalence of disease in European countries may be associated with the fact that Hyalomma spe-

cies ticks favour dry, non-humid climates and arid type vegetation. Similarly, the increase in temperature and the decrease in rainfall in the Mediterranean region provide ticks a favourable environment for their growth and multiplication (Maltezou, 2010; Estrada-Pena, 2007). The high incidence of human infection in developing and underdeveloped countries is due to the increased interaction with livestock (Goodman, 2005).

Pakistan Scenario

Crimean-Congo Haemorrhagic Fever is endemic in Pakistan and many number of cases had been reported sporadically since 2000 (WHO, 2014). Numbers of cases of CCHF reported in Pakistan from 2000 to 2012 are shown in the Figure 1.

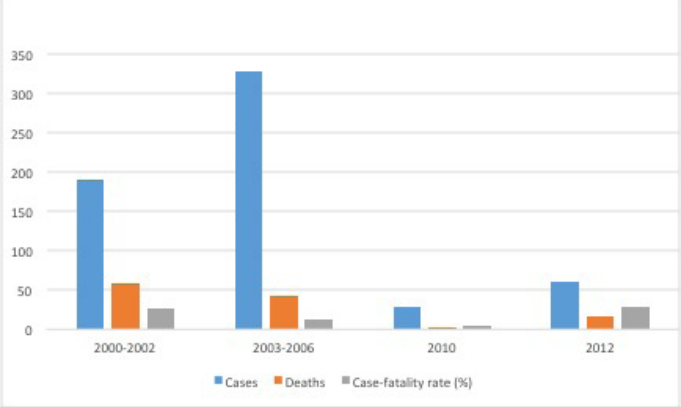

Figure 1: *CCHF status (cases and deaths) in Pakistan from 2000 to 2012*
(Note: Data are taken from WHO, 2014)

Table 1: *No. of cases and deaths due to CCHF (Up to 20 July 2014)*

Province	2012		2013		2014	
	Cases	Death	Cases	Death	Cases	Death
AJK	0	0	1	0	1	0
Sindh	7	3	2	1	0	0
Punjab	8	3	18	5	4	3
Islamabad	0	0	4	1	4	3
Khayber Pakhtunkhwa	9	5	9	4	8	0
Balochistan	38	7	66	9	17	1
Total	62	18	100	20	34	7

Cases include both laboratory-confirmed and suspected cases (WHO, 2014)

The disease early warning system (DEWS) has recently reported a seasonal surge in human infections of Crimean-Congo Haemorrhagic Fever in Pakistan. From 30th March to 20th July, 2014, a total of 42 cases of Crimean-Congo Haemorrhagic Fever, including 10 deaths (case-fatality rate: 24%) have been reported throughout the country. Of these reported infections, 22 cases have been confirmed by laboratory (WHO, 2014). Human infections of Crimean-Congo Haemorrhagic Fever reported from various provinces in Pakistan, 2012-2014 is shown in Table 1.

Clinical Features in Humans

Human beings are the only host of CCHFV in which virus shows clinical signs and symptoms. The clinical course of CCHF among children seems to be milder than in adults (Tezer et al., 2010). The typical course of CCHF infection has following four distinctive phases (Hussain et al., 2016):

- Incubation period
- Pre-hemorrhagic phase
- Hemorrhagic phase
- Convalescent phase

Incubation period: This period is in the range of 3-7 days mostly. Incubation period extends up to 1-3 days after tick-bite and 5-6 days after exposure to infected blood or tissues with a maximum of 13 days. The mean duration is largely influenced by the route of infection, source of infected blood or tissue and viral load (Mamuchishvili et al., 2015). The minimum viral load required for transmission of disease (i.e. the infective dose) is 1-10 organisms (Kaya et al., 2011).

Pre-hemorrhagic phase: The disease begins with the pre-hemorrhagic phase, which is characterized by some non-specific prodromal symptoms during which it resembles those of other viral diseases. The major signs and symptoms include high fever, headache, myalgia, abdominal pain, nausea and non-bloody diarrhea (Appannanavar and Mishra, 2011). This is accompanied by relative bradycardia, hypotension, conjunctivitis, tachypnea, pharyngitis and cutaneous rash (Vashakidze and Mikadze, 2015).

Hemorrhagic phase: Hemorrhagic phase is generally short. It has a rapid course with signs of progressive hemorrhages and diathesis. These include conjunctival hemorrhage, epistaxis, petechiae, hemoptysis, hematemesis and melena. Certain patients may also have hepato-splenomegaly. Vashakidze and Mikadze, (2015) reported the case fatality rate of 15-85%. In severe cases, death occurs as a result of multiple organ

failure, disseminated intravascular coagulation, and circulatory shock. Acute Respiratory Distress Syndrome (ARDS) and diffused alveolar hemorrhage, accompanied by systemic inflammatory reaction, have also been reported during haemorrhagic manifestations (Whitehouse, 2004).

Total protein level, albumin, fibrinogen, and hemoglobin levels are decreased in this disease and the values of prothrombin ratio, activated partial thromboplastin time, thrombin time, and fibrin degradation products are increased which indicate the occurrence of Disseminated Intravascular Coagulopathy-DIC (Swanepoel et al., 1989).

Convalescent period: In the survivors, this period begins 15-20 days after the onset of illness. During this period, patients may have feeble pulse, tachycardia, loss of memory and hair and also the loss of hearing. However, these after effects have been reported only in few outbreaks (Bajpai and Nadkar, 2011).

CCHFV is present in blood, body fluids and tissues from infected patients; haemorrhages are the major source of exposure for other people including family members and healthcare workers (HCWs). Possible horizontal transmission has also been reported from a mother to her child (Saijo et al., 2004).

Infections in Animals

CCHFV can be found in many species of wild and domestic mammals, including small animals that serve as hosts for immature ticks and hosts of mature ticks are the large herbivores. CCHFV has been isolated from a number of species including cattle, sheep, hares, goats, hedgehogs, mice and dogs (Kemp et al., 2014). Antibodies have been reported in horses, donkeys, pigs, buffalo, rhinoceroses, giraffes and other mammalian species. Since most species of birds are sero-negative, hence thought to be resistant to infection; however, ostriches may be sero-positive and these animals become viraemic after experimental inoculation. Vorou (2009) reported low CCHFV viraemia from an experimentally infected blue-helmeted guinea fowl (Numidia meleagris) and also the antibodies in a magpie. Turell (2007) reported that a red-beaked Hornbill and a glossy starling became sero-positive after experimental infection/inoculation but viraemia did not occur in them. As immature Hyalomma anatolicum ticks sometimes feed on reptiles, anti-CCHFV antibodies have only been reported from one reptile, a tortoise from Tadzhikistan (Goswami et al., 2014).

Shayan et al. (2015) reported that CCHFV infections are asymptomatic in animals other than experimentally inoculated newborn rodents including laboratory mice, rats and Syrian hamsters. The only symptom in experimentally infected sheep and cattle was a transient and mild elevation in body temperature (Mourya et al., 2014).

Mammals become viraemic and can transmit CCHFV in their blood and tissues (Messina et al., 2015). Domestic ruminants including cattle, sheep and goats are viraemic for one week after experimental infection. Most birds seem to be resistant to infection, but in ostriches, CCHFV can be found in blood for some days (1-4 days) and in visceral organs for up to five days after experimental infection (Goswami et al., 2014).

Transmission

CCHFV usually circulates between animals (asymptomatic) and ticks in an enzootic cycle. This virus has been found in at least 31 species of ticks, including seven genera of the family Ixodidae (hard ticks). Members of the genus Hyalomma seem to be the principal vectors (Zavitsanou et al., 2009). Transovarial, transstadial and venereal transmission occurs in this genus. The most important vector in Europeis Hyalomma marginatum marginatum but CCHFV can also be found in Hyalomma anatolicum anatolicum and others. Other Ixodid ticks including members of the genera Rhipicephalus, Dermacentor, Boophilusand and Ixodes may also transmit the virus locally (Goswami et al., 2014). Gonzalez et al. (1992) reported CCHFV in many families of invertebrates, although these species may not be the biological vectors; the virus may have been ingested in a recent blood meal.

Many species of mammals can transmit CCHFV to ticks when they are viraemic. Small vertebrates such as hedgehogs and hares, which are infested by immature ticks, may be particularly important as amplifying hosts. With a few exceptions, birds seem to be refractory to infection; however, they may act as mechanical vectors by transporting CCHFV-infected ticks. Migratory birds might spread the virus between distant geographic areas (Howard, 2004; Leblebicio-

glu et al., 2014).

Humans become infected through the skin and by ingestion. Transmission through aerosols was suspected in a few cases in Russia. Sources of exposure include being bitten by a tick, crushing an infected tick, contacting animal blood or tissues and drinking unpasteurized milk (Goswami et al., 2014). Eid-ul-Azha is period of high risk for the transmission of the CCHFV from animals to the humans (Jamil et al., 2005).

Human-to-human transmission occurs especially when skin or mucous membranes are exposed to blood during haemorrhages or tissues during surgery. CCHFV may remain stable for up to 10 days in blood kept at 40°C (104°F). Possible vertical transmission (from an infected mother to her child) has also been reported (Dreshaj et al., 2016; Saijo et al., 2004; Kamboj and Pathak, 2013).

Pathogenesis

The pathogenesis of CCHF is not well understood yet but it is thought that the CCHFV has the ability to attack the host immune system and manipulate the immune cells. The virus enters inside the cells due to receptor-dependent endocytosis using viral glycoproteins (Gn and Gc) which bind the proposed virus receptor human cell surface Nucleolin (Goswami et al., 2014; Appannanavar and Mishra, 2011). Due to the damage of immune cells, the virus replicates very rapidly and causes dysregulation of the vascular system and lymphoid organs which leads to the production of pro-inflammatory cytokines (IL-6, IL-10 and TNF) which induce damage to the endothelial system (Appannanavar and Mishra, 2011). Due to this damage, intrinsic coagulation cascade is activated which leads to platelet aggregation resulting in the blockage of the endothelial lining. The resultant platelet aggregates also travel throughout the body of the infected host and ultimately result in Disseminated Intravascular Coagulopathy (DIC) and multiple organ failure leading to death (Parlak et al., 2015; WHO, 2014).

Diagnosis

The CCHFV can be isolated from blood, plasma or tissues. At autopsy, the virus is most likely to be found in the liver, kidneys, lungs, spleen, bone marrow and brain. Tantawi et al. (1980) used BHK-21 cell line for the isolation of CCHFV. Paragas et al. (2004) used SW-13 cell line for this purpose. Others cell lines including Vero, LLC- MK2 are also used for this purpose (Ali et al., 2011; Goswami et al., 2014). Cell cultures can only detect high concentrations of the virus, and this technique is most useful during the first five days of disease. Virus isolation must be carried out in BSL-4 level (Spickler, 2010; Goswami et al., 2014).

CCHF can be diagnosed by inoculation into newborn mice. It is more sensitive than the isolation of the virus by culture, and can detect the virus for a longer period (Logan et al., 1989). However, this method may result in slow isolation of CCHFV (Shepherd et al., 1986). Peyrefitte et al. (2015) indirect immunofluorescence method to detect anti-CCHFV-antibodies.

Burt et al. (1998) used Reverse Transcription Polymerase Chain Reaction (RT-PCR) on serum samples and stated that this technique can be used early in the course of the CCHF disease. This technique is highly sensitive. However, due to the genetic variability in CCHFV strains, a single set of primers cannot detect all virus variants, and most RT-PCR assays are either designed to detect local variants (Papa et al., 2015). Wasfi et al. (2016) used this method to detect the CCHFV in acute febrile patients mainly slaughterhouse workers.

By using Enzyme-linked Immuno-Sorbent Assay (ELISA) or immunofluorescence assay, IgM (IgM-capture ELISA) and IgG (IgG-sandwich ELISA) antibodies against the CCHFV are detected and quantified. It is less sensitive method than the PCR (Saijo et al., 2002). This assay is more sensitive, specific, rapid and more reproducible than the complement fixation test and immunofluorescence (Donets et al., 1982; Saluzzo and Guenno, 1987). Morrill et al. (1990) used Agar Gel Diffusion (AGD) assay to detect anti-CCHFV-antibodies.

Vanhomwegen et al. (2012) reported that Indirect Fluorescent Antibody (IFA) technique was less sensitive and specific than the ELISA. Shepherd et al. (1989) used Complement Fixation test for demonstrating anti-CCHFV-antibodies. Swanepoel et al. (1987) used Reversed Passive Haemagglutination Inhibition technique to demonstrate anti-CCHFV-antibodies. Burt et al. (1997) reported Immunohistochemistry (IHC) for the diagnosis of CCHFV in formalin-fixed tissue samples. Goswami et al. (2014) and Osman et al. (2013) reported a latest method for quick diagnosis of

CCHFV, which is Reverse Transcription Loop-mediated Isothermal Amplification (RT-LAMP) which is very specific and sensitive method.

Treatment

In CCHF, general supportive therapy is the mainstay of management of patients. Intensive monitoring to guide volume and blood component replacement is recommended (Smego et al., 2004). If the patient meets the case definition for probable CCHF, ribavirin (oral) treatment protocol needs to be initiated immediately with the consent of the patient/ relatives and it should be strictly in consultation with the attending physician (Lania et al., 2014; WHO, 2014). Following is the treatment regimen:

- Oral Ribavirin: 2 gm loading dose
- 4 gm/day in 4 divided doses (8 hourly) for 6 days
- 2 gm/day in 4 divided doses for 6 days

Prevention and Control

There are currently two vaccines against CCHFV which have been developed. The first one is a formalin-inactivated vaccine which was developed in Bulgaria from infected suckling mouse brain. The second is a DNA vaccine which was tested in mice. Both the vaccines are under research (Shayan et al., 2015).

Education of general public about the mode of transmission through tick bites, handling the ticks, and handling and butchering of animals, and the means for personal protection is very necessary (Flusin et al., 2010). Tick control with acaricides is an option for well-managed livestock production facilities. Animal dipping in an insecticide solution is also recommended (Leblebicioglu et al., 2015; Champour et al., 2016). Public are advisedto avoid tick-infested areas when feasible especially when the ticks are active (spring to fall). To minimize exposure, light clothing is to be worn that covers arms and legs, tuck pants into socks, clothing and skin are regularly examined for ticks, and tick repellent such as diethyltoluamide (Deet, Autan) are applied to the skin or permethrin to pant legs and sleeves (Yadav et al., 2015). Persons who work with livestock or other animals in the endemic areas are advised to take practical measures to protect themselves which include the use of repellents on the skin (e.g. diethyltoluamide) and clothing (e.g. Permethrin) and wearing gloves or other protective clothing to prevent skin contact with infected tissues or blood (Öncü, 2013). CCHFV is very sensitive to 1% hypochlorite and 2% glutaraldehyde solutions and can be destroyed by heating at 56˚C for 30 minutes (Appannanavar and Mishra, 2011; Shayan et al., 2015).

According to the recommendations of Zavitsanou et al. (2009), in case of death of the CCHF infected patient, the dead body should be sprayed with 1:10 liquid bleach solution and then wrapped in the winding sheet. The winding sheet needed to spray with bleach solution. It is, then, placed in a plastic bag, which is sealed with adhesive tape. The transport vehicle should also be disinfected and all clothing of the deceased should be burnt.

Hospitals are advised to maintain stock of Ribavirin, in Pakistan it is available in the market as Ribazole® (Ali et al., 2011). Bio-safety is the key to avoiding nosocomial infection. Patients with suspected or confirmed CCHF are isolated and cared for using strict barrier-nursing techniques to prevent nosocomial spread of infection (Shayan et al., 2015). The patients are required to be treated in a separate room under strict nursing barrier (Öncü, 2013). All medical and para-medical staff and attendants should be advised to wear disposable gloves, disposable masks and gowns (Zavitsanou et al., 2009). Any spills, pricks, injury and accidents during the management of patients should be avoided and needles should be discarded in proper safety disposal box which is then autoclaved and incinerated (Tarantola et al., 2007). All surfaces should be decontaminated with liquid bleach (Aslam et al., 2015). The patients should be attended only by designated paramedical staff. Non-essential staff and attendants should not be allowed to enter the room of the patient (Leblebicioglu et al., 2015).

All secretions of the patient and hospital clothing in use of the patient should be treated as infectious and autoclaved before incinerating. All instruments should be de-contaminated and autoclaved before re-use. After the patient is discharged, room surfaces should be wiped down with liquid bleach to kill the virus and fumigation of the room should be done as early as possible (WHO, 2013).

Future Perspectives

The intravenous passive transfer of anti-CCHFV im-

munoglobulin is expected to be an effective treatment for CCHF. These immunoglobulins can be prepared from sera collected from survivors are expected to become available in the near future but further studies are still required (Keshtkar-Jahromi, 2011). A vaccine inactivated by chloroform treatment and amplified in baby mice brain and the brains of those baby mice are subsequently crushed using a mortar and pestle, and the resulting solution is absorbed into aluminium hydroxide ($Al(OH)_3$) before being administered to patients, has been used in Eastern Europe, but is unlicensed by the European Medicines Agency and US Food and Drug Administration (FDA) and not much efficacious (Buttigieg et al., 2014; Peyrefitte et al., 2015).

Recently, a DNA-based vaccine expressing the CCHFV M segment, which induce neutralizing antibodies in some model organism such as mice has been under study but it is not much effective still for commercial use (Buttigieg et al., 2014). Another vaccine candidate using transgenic tobacco leaves expressing Gn and Gc glycopropteins was fed to mice which induced IgG and IgA antibodies. This vaccine also needs advanced research and study for commercial use (Ghiasi et al., 2011). Smallpox virus vectored vaccines such as those based on Modified Vaccinia virus Ankara (MVA), have the capacity to accommodate M segment of the CCHFV genome and can be used to produce vaccine against CCHF (Buttigieg et al., 2014).

Conclusion and Recommendations

Crimean-Congo Haemorrhagic Fever (CCHF) is a tick-borne viral disease which is zoonotic and becoming important for human health prospectus. This disease has become endemic from sporadic in many areas of Pakistan especially Khayber Pakhtunkhwa (KPK). High number of CCHF cases occurs mostly during fall and spring seasons. The CCHFV infects the immune cells and causes haemorrhages leading to multi organ failure and death. Its diagnosis is mainly done by isolation, serological and molecular techniques. There is no approved CCHF vaccine available yet and treatment is usually done symptomatic and supportive. This tick-borne disease can be prevented and controlled mainly by avoiding tick bites by using tick repellents.

Conflict of Interest

The authors declares that there is no conflict of interests regarding the publication of this article.

Authors' Contribution

BH and MA conceived the idea of work. BH and AI reviewed the literature and drafted the manuscript. MA and AI did editing and final write-up. All the authors read and accepted the final manuscript before submission.

References

- Abbas, T., Younus, M., Muhammad, S.A. Spatial cluster analysis of human cases of Crimean Congo hemorrhagic fever reported in Pakistan. Infectious Diseases of Poverty, 2015; 4(1):1. http://dx.doi.org/10.1186/2049-9957-4-9
- Alam, M.M., Khurshid, A., Sharif, S., Shaukat, S., Rana, M.S., Angez, M., Zaidi,S.S.Z. Genetic analysis and epidemiology of Crimean Congo hemorrhagic fever viruses in Baluchistan province of Pakistan. BMC Infectious Diseases, 2013; 13: 201. http://dx.doi.org/10.1186/1471-2334-13-201
- Ali, K.N., Anushree, J., Reenu, C., Mohammad, A., Kamal, K. Crimean Congo Hemorrhagic Fever - An Article Review. International Research Journal of Pharmacy, 2011; 2(5): 33-40.
- Aslam, S., Latif, M. S., Daud, M., Rahman, Z.U., Tabassum, B., Riaz, M. S. Khan, A.,Tariq, M., Husnain,T. Crimean-Congo hemorrhagic fever: Risk factors and control measures for the infection abatement. Biomedical Reports, 2016; 4(1): 15-20.
- Appannanavar SB, Mishra B. An Update on Crimean Congo Hemorrhagic Fever. Journal of Global Infectious Diseases, 2011; 3(3): 285-292. http://dx.doi.org/10.4103/0974-777X.83537
- Alam, M.M., Khurshid, A., Sharif, S., Shaukat, S., Suleman, R.M., Angez, M. Crimean-Congo hemorrhagic fever Asia-2 genotype, Pakistan. Emerging Infectious Diseases, 2013; 19(6): 1017-1018. http://dx.doi.org/10.3201/eid1906.120771
- Athar, M.N., Baqai, H.Z., Ahmad, M., Khalid, M.A., Bashir, N., Ahmad, A.M., Balouch, A.H., Bashir, K.Crimean-Congo Hemorrhagic Fever Outbreak in Rawalpindi, Pakistan, Contact Tracing and Risk Assessment. American Journal of Tropical Medicine and Hygiene, 2005; 72(4): 471-473.

- Aslam,S., Latif, M.S., Daud, M., Rahman,Z.U., Tabassum,B., Riaz, M.S., Khan, A., Tariq, Husnain,T. Crimean-Congo hemorrhagic fever: Risk factors and control measures for the infection abatement (Review). Biomedical Reports, 2016; 4: 15-20.
- Aradaib, I.E., Erickson, B.R., Mustafa, M.E., Khristova, M.L., Saeed, N.S., Elageb, R.M. Nichol, S.T. Nosocomial outbreak of Congo Haemorrhagic Fever in Sudan. Emerging Infectious Diseases, 2010; 16: 837-839. http://dx.doi.org/10.3201/eid1605.091815
- Badole,S.L.,Yadav,P.D.,Patil,D.R.,Mourya,D.T., Animal models for some important RNA viruses of public health concern in SEARO countries: Viral hemorrhagic fever. Journal of vector borne diseases, 2015; 52(1): 1-10.
- Bajpai, S.,Nadkar, M.Y. Crimean Congo Hemorrhagic Fever: Requires Vigilance and Not Panic. Journal of the Association of Physicians of India, 2011; 59: 164-167.
- Bente, D.A., Forrester, N.L., Watts, D.M., McAuley, A.J., Whitehouse, C.A., Bray, M. Crimean-Congo Hemorrhagic Fever: History, epidemiology, pathogenesis, clinical syndrome and genetic diversity. Antiviral Research, 2013; 100(1): 159-189. http://dx.doi.org/10.1016/j.antiviral.2013.07.006
- Buttigieg, K.R., Dowall, S.D., Findlay-Wilson, S., Miloszewska, A., Rayner, E., Hewson, R., Carroll,M.W.A Novel Vaccine against Crimean-Congo Haemorrhagic Fever Protects 100% of Animals against Lethal Challenge in a Mouse Model. PLoS One, 2014; 9(3): 91516. http://dx.doi.org/10.1371/journal.pone.0091516
- Burt, F.J., Swanepoel, R., Shieh, W.J., Smith, J.F., Leman, P.A., Greer, P.W., Coffield, L.M., Rollin, P.E., Ksiazek, T.G., Peters, C.J., Zaki, S.R. Immunohistochemical and in situ localization of Crimean-Congo hemorrhagic fever (CCHF) virus in human tissues and implications for CCHF pathogenesis. Archives of Pathology and Laboratory Medicine, 1997; 121(8): 839-46.
- Burt, F.J.,Leman, P.A.,Smith, J.F.,Swanepoel, R. The use of a reverse transcription-polymerase chain reaction for the detection of viral nucleic acid in the diagnosis of Crimean-Congo Haemorrhagic Fever. Journal of Virological Methods, 1998; 70(2): 129-137. http://dx.doi.org/10.1016/S0166-0934(97)00182-1
- Barthel, R., Mohareb, E., Younan, R., Gladnishka, T., Kalvatchev, N., Moemen, A., Mansour, S.S., Rossi, C., Schoepp, R., Christova, I.Seroprevalance of Crimean-Congo Haemorrhagic Fever in Bulgarian livestock. Biotechnology, biotechnological equipment, 2014; 28(3): 540-542. http://dx.doi.org/10.1080/13102818.2014.931685
- Connolly-Andersen, A.M., Moll, G., Andersson, C., Åkerstrom, S., Karlberg, H., Douagi, I., Mirazimi, A. Crimean-Congo Hemorrhagic Fever Virus Activates Endothelial Cells. Journal of Virology, 2011; 85(15): 7766-7774. http://dx.doi.org/10.1128/JVI.02469-10
- Champour, M., Chinikar, S., Mohammadi, G., Razmi, G., Shah-Hosseini, N., Khakifirouz, S., Mostafavi, E., Jalali, T.Molecular epidemiology of Crimean-Congo hemorrhagic fever virus detected from ticks of one humped camels (Camelus dromedarius) population in northeastern Iran. Journal of Parasitic Diseases, 2016; 40(1):110-5. http://dx.doi.org/10.1007/s12639-014-0458-y
- Dreshaja, S., Ahmetia, S., Ramadanib, N., Dreshajc, G., Humollib, I., Dedushaj, I. Current situation of Crimean-Congo hemorrhagic fever in Southeastern Europe and neighboring countries: a public health risk for the European Union?Travel Medicine and Infectious Disease, 2016; 14(2): 81-91. http://dx.doi.org/10.1016/j.tmaid.2016.03.012
- Deyde,V.M., Khristova,M.L., Rollin,P.E., Ksiazek,T.G., Nichol,S.T.Crimean-Congo Hemorrhagic Fever Virus Genomics and Global Diversity. Journal of Virology, 2006; 80(17): 8834-8842. http://dx.doi.org/10.1128/JVI.00752-06
- Donets, M.A., Chumakov, M.P., Korolev, M.B., Rubin, S.G. Physicochemical characteristics, morphology and morphogenesis of virions of the causative agent of Crimean Hemorrhagic Fever. Intervirology, 1977; 8: 294-308. http://dx.doi.org/10.1159/000148904
- Donets, M.A., Rezapkin, G.V., Ivanov, A.P., Tkachenko, E.A. Immunosorbent assays for diagnosis of Crimean-Congo hemorrhagic fever (CCHF).The American Journal of Tropical Medicine and Hygiene, 1982; 31(1): 156-162.
- Estrada-Pena, A.,Venzal, J.M. Climate niches of tick species in the Mediterranean region: modeling of occurrence data, distributional constraints, and impact of climate change. Journal of Medical Entomology, 2007; 33: 1130-1138. http://dx.doi.org/10.1093/jmedent/44.6.1130
- Ellis, D.S., Southee, G., Lloyd, G.S., Platt, N.,

Jones, S., Stamford, E.T., Bowen, D., Simpson, D.I. Congo/Crimean Hemorrhagic Fever virus from Iraq 1979: I. morphology in BHK 21 cells. Archives of Virology, 1981; 70(3): 189-98. http://dx.doi.org/10.1007/BF01315125

- Flusin, O., Iseni, F., Rodrigues, R., Paranhos-Baccalà, G., Crance, J.M., Marianneau, P., Bouloy, M., Peyrefitte, C.N. Crimean-Congo hemorrhagic fever: basics for general practitioners. Medecine Tropicale, 2010; 70(6): 429-38.
- Gonzalez, J.P., Camicas, J.L., Cornet, J.P., Faye, O., Wilson, M.L.Sexual and transovarian transmission of Crimean-Congo Haemorrhagic Fever Virus in Hyalomma truncatum ticks.Research in Virology, 1992; 143(1): 23-8. http://dx.doi.org/10.1016/S0923-2516(06)80073-7
- Grard, G., Drexler, J.F., Fair, J., Muyembe, J.J., Wolfe, N.D., Drosten, C., Leroy, E.M. Re-Emergence of Crimean- Congo Hemorrhagic Fever Virus in Central Africa. PLOS Neglected Tropical Diseases, 2011; 5(10): 1350. http://dx.doi.org/10.1371/journal.pntd.0001350
- Ghiasi, S.M., Salmanian, A.H., Chinikar, S. Mice Orally Immunized with a Transgenic Plant Expressing the Glycoprotein of Crimean-Congo Hemorrhagic Fever Virus. ResearchGate, 2011; 18(12): 2031-7. http://dx.doi.org/10.1128/cvi.05352-11
- Goswami,T.K., Singh,D.K., Saminathan,M., Verma, A.K., Dhama, K. An Emerging Threat of Crimean Congo Hemorrhagic Fever: Call for Preparedness. Advances in Animal and Veterinary Sciences, 2014; 2(1): 8-14. http://dx.doi.org/10.14737/journal.aavs/2014.2.1.8.14
- Hasan,Z., Atkinson, B., Jamil, B., Samreen, A., Altaf, L., Hewson, R. Diagnostic Testing for Hemorrhagic Fevers in Pakistan: 2007-2013. The American Journal of Tropical Medicine and Hygiene, 2014; 91(6): 1243-1246. http://dx.doi.org/10.4269/ajtmh.14-0383
- Hussain, Q., Shaikh, B. H., Bhutto, A. R., Sohaib, M. An Unusual Case of Crimean Congo Hemorrhagic Fever: Prolonged Bleeding with Successful Recovery.Journal of the College of Physicians and Surgeons Pakistan, 2016; 26(2): 151-153.
- Honig, J.E., Osborne, J.C., Nichol,S.T. Crimean-Congo hemorrhagic fever virus genome L RNA segment and encoded protein. Virology, 2004; 321(1): 29-35. http://dx.doi.org/10.1016/j.virol.2003.09.042
- Hoogstraal, H. The Epidemiology of Tick-Borne Crimean-Congo Hemorrhagic Fever in Asia, Europe, and Africa. Journal of Medical Entomology, 1979; 15(4): 307-417. http://dx.doi.org/10.1093/jmedent/15.4.307
- Hoogstraal, H., Kaiser, M.N., Traylor, M.A., Gaber, S., Guindy, E. Ticks (Ixodidae) on bird's migration from Africa to Euroupe and Asia. Bulletin of the World Health Organization, 1961; 24: 197-212.
- Hoogstral, H., Kaiser, M.N., Traylor, M.A., Guindy, E., Gaber, S. Ticks (Ixodidae) on bird's migrating from Europe and Asia to Africa 1959-1961. Bulletin of the World Health Organization, 1963; 28: 235-262.
- Jabbari, A., Tabasi,S., Abbasi, A., Alijanpour,E. Crimean-Congo Hemorrhagic Fever: treatment and control strategy in admitted patients. Caspian Journal of Internal Medicine, 2012; 3(2): 443-444.
- Jamil, B., Hasan, R.S., Sarwari, A.R., Burton, J., Hewson, R., Clegg, C. Crimean-Congo Hemorrhagic Fever: experience at a tertiary care hospital in Karachi, Pakistan. Transactions of the Royal Society of Tropical Medicine and Hygiene, 2005; 99(8): 577-84. http://dx.doi.org/10.1016/j.trstmh.2005.03.002
- Kaya,A., Engin,A., Guven,A.S., Icagasıoglu,F.D., Cevit,O., Elaldı,N., Gulturk,A. Crimean-Congo hemorrhagic fever disease due to tick bite with very long incubation periods. International Journal of Infectious Diseases, 2011; 15: 449-452. http://dx.doi.org/10.1016/j.ijid.2011.03.007
- Kamboj,A., Pathak,H. Crimean-Congo hemorrhagic fever: a comprehensive review. Veterinary World, 2013; 6(10): 812-817. http://dx.doi.org/10.14202/vetworld.2013.812-817
- Keshtkar-Jahromia, M., Kuhnb, J.H., Christovac, I., Bradfuted, S.B., Jahrlingb, P.B., Bavari, S. Crimean-Congo hemorrhagic fever: Current and future prospects of vaccines and therapies. Antiviral Research, 2011; 90(2): 85-92. http://dx.doi.org/10.1016/j.antiviral.2011.02.010
- Kemp, A., Msimang, V., Weyer, J., Paweska, J.T. Crimean-Congo Haemorrhagic Fever and Tick bite Fever in South Africa, 2012-2014. National Institute for Communicable Diseases, Infectious Diseases Bulletin, 2014; 12(3): 59-62.
- Keshtkar-Jahromia, M., Kuhnb, J.H., Christovac, I., Bradfuted, S.B., Jahrlingb, P.B., Bavarid, S. Crimean-Congo Hemorrhagic Fever: Current and future prospects of vaccines and therapies. Antiviral Research, 2011; 90(2): 85-92.

- Leblebicioglu, H., Eroglu, C., Yavuz, K.E., Hokelek, M., Acici, M., Yilmaz,H. Role of Migratory Birds in Spreading Crimean-Congo Hemorrhagic Fever, Turkey. Emerging Infectious Diseases, 2014; 20(8): 1331-1334. http://dx.doi.org/10.3201/eid2008.131547
- Leblebicioglu,H.,Sunbul,M.,Memish,Z.A.,Tawfiq, J.A.A., Bodur,H., Ozkul,A., Gucukoglu, A., Chinikar, S., Hasan,Z. Consensus report: Preventive measures for Crimean-Congo Hemorrhagic Fever during Eid-al-Adha festival. International Journal of Infectious Diseases, 2015; 38: 9-15. http://dx.doi.org/10.1016/j.ijid.2015.06.029
- Logan, T.M., Linthicum, K.J., Bailey, C.L., Watts, D.M., Moulton, J.R.Experimental transmission of Crimean-Congo hemorrhagic fever virus by Hyalomma truncatum Koch. The American Journal of Tropical Medicine and Hygiene, 1989; 40(2): 207-12.
- Lania, R., Moghaddam, E., Haghani, A., Chang, L.Y., AbuBakar, S., Zandi,K. Tick-borne viruses: A review from the perspective of therapeutic approaches. Ticks and Tick-borne Diseases, 2014; 5(5): 457-465. http://dx.doi.org/10.1016/j.ttbdis.2014.04.001
- Mourya,D.T., Yadav,P.D., Shete,A., Majumdar,T.D., Kanani,A., Kapadia,D., Chandra,V., Kachhiapatel,A.J., Joshi,P.T., Upadhyay,K.J., Dave, P., Raval,D. Serosurvey of Crimean-Congo Hemorrhagic Fever Virus in Domestic Animals, Gujarat, India, 2013. Vector-Borne and Zoonotic Diseases, 2014; 14(9): 690-692. http://dx.doi.org/10.1089/vbz.2014.1586
- Maltezou, H.C. Papa, A. Crimean-Congo Hemorrhagic Fever: risk for emergence of new endemic foci in Europe? Travel Medicine and Infectious Disease, 2010; 8: 139-143. http://dx.doi.org/10.1016/j.tmaid.2010.04.008
- Mertens, M., Schmidt,K., Ozkul,A., Groschup,M.H. The impact of Crimean-Congo Hemorrhagic Fever Virus on public health. Antiviral Research, 2013; 98(2): 248-260. http://dx.doi.org/10.1016/j.antiviral.2013.02.007
- Morrill, J.C., Soliman, A.K., Imam, I.Z., Botros, B.A., Moussa, M.I., Watts, D.M. Serological evidence of Crimean-Congo Haemorrhagic Fever viral infection among camels imported into Egypt. The Journal of Tropical Medicine and Hygiene, 1990; 93(3): 201-204.
- Mamuchishvili, N., Salyer, S.J., Stauffer, K., Geleishvili, M., Zakhashvili, K., Morgan, J. Notes from the field: Increase in reported Crimean-Congo hemorrhagic fever cases--country of Georgia, 2014. Morbidity and mortality weekly report, 2015; 64(8): 228-9.
- Martin, M.L., Lindsey-Regnery, H., Sasso, D.R., McCormick, J.B., Palmer, E. Distinction between Bunyaviridae genera by surface structure and comparison with Hantaan virus using negative strain electron microscopy. Archives of Virology, 1985; 86(1): 17-28. http://dx.doi.org/10.1007/BF01314110
- Messina, J.P., Pigott, D.M., Golding,N., Duda, K.A., Brownstein, J.S., Weiss, D.J., Gibson, H., Robinson, T.P., Gilbert, M., William Wint, G.R., Nuttall, P.A., Gething, P.W., Myers, M.F., George, D.B., Hay, S.I.The global distribution of Crimean-Congo hemorrhagic fever.Transactions of the Royal Society of Tropical Medicine and Hygiene, 2015; 109(8): 503-13. http://dx.doi.org/10.1093/trstmh/trv050
- Nabeth, P., Cheikh, D.O., Lo, B., Faye, O., Vall, I.O., Niang, M., Wague, B., Diop, D., Diallo, M., Diallo, B., Diop, O.M. Simon, F. Crimean-Congo hemorrhagic fever, Mauritania. Emerging Infectious Diseases, 2004; 10: 2143-2149. http://dx.doi.org/10.3201/eid1010.040586
- Öncü, S. Crimean-Congo Hemorrhagic Fever: An Overview. Virologica Sinica, 2013; 28 (4): 193-201. http://dx.doi.org/10.1007/s12250-013-3327-4
- Office International Epizootics (OIE), World Health Organization (WHO), Food and Agriculture Organization of the United Nations (FAO), 2009: Partners Available at: http://www.glews.net/index.php (accessed 5 March 2016).
- Ozsoy, S., Gokmen, A., Ozdemir, M., Akduman, B., Korkusuz, I., Javan, G.T. Medical examiners and Crimean-Congo hemorrhagic fever contamination risk. Journal of Forensic and Legal Medicine, 2015; 36: 32-36. http://dx.doi.org/10.1016/j.jflm.2015.08.010
- Osman,H.A.M., Eltom, K.H., Musa, N.O., Bilal,N.M., Elbashir, M.I., Aradaib, I.E.Development and evaluation of loop-mediated isothermal amplification assay fordetection of Crimean Congo hemorrhagic fever virus in Sudan. Journal of Virological Methods, 2013; 190: 4-10. http://dx.doi.org/10.1016/j.jviromet.2013.03.004
- Peyrefitte, C., Marianneau, P., Tordo, N., Bouloy, M.Crimean-Congo Haemorrhagic Fever.Revue scientifique et technique (International Office of

Epizootics), 2015;34(2): 391-401. http://dx.doi.org/10.20506/rst.34.2.2365
- Papa, A., Mirazimi, A., Köksal, I., Pena, A. E., Feldmann, H. Recent advances in research on Crimean-Congo hemorrhagic fever. Journal of Clinical Virology, 2015; 64: 137-143. http://dx.doi.org/10.1016/j.jcv.2014.08.029
- Parlak,E., Ertürk,A., Çağ,Y., Sebin,E., Gümüşdere, M. The effect of inflammatory cytokines and the level of vitamin D on prognosis in Crimean-Congo hemorrhagic fever. International Journal of Clinical and Expermental Medicine, 2015; 8(10): 18302-18310.
- Paragas,J., Whitehouse,C.A., Endy,T.P., Bray,M. A simple assay for determining antiviral activity against Crimean-Congo hemorrhagic fever virus. Antiviral Research, 2004; 62(1): 21-25. http://dx.doi.org/10.1016/j.antiviral.2003.11.006
- Saleem, J., Usman, M., Nadeem, A., Sethi, S.A., Salman, M. Crimean-Congo hemorrhagic fever: a first case from Abbottabad, Pakistan. International Journal of Infectious Diseases, 2009; 13: 121-123. http://dx.doi.org/10.1016/j.ijid.2008.07.023
- Spengler,J.R.Bergeron, É. Rollin, P.E.Seroepidemiological Studies of Crimean-Congo Hemorrhagic Fever Virus in Domestic and Wild Animals. PLOS Neglected Tropical Diseases, 2016; 10(1): 1-14. http://dx.doi.org/10.1371/journal.pntd.0004210
- Saijo,M., Qing,T., Niikura,M., Maeda,A., Ikegami,T., Prehaud,C., Kurane,I., Morikawa, S. Recombinant Nucleoprotein-Based Enzyme-Linked Immunosorbent Assay for Detection of Immunoglobulin G Antibodies to Crimean-Congo Hemorrhagic Fever Virus. Journal of Clinical Microbiology, 2002; 40(5): 1587-1591. http://dx.doi.org/10.1128/JCM.40.5.1587-1591.2002
- Saijo, M., Tang,Q., Shimayi,B., Han,L., Zhang,Y., Asiguma,M., Tianshu, D., Maeda, A., Kurane,I., Morikawa,S. Possible Horizontal Transmission of Crimean-Congo Hemorrhagic Fever Virus from a Mother to Her Child. Japanese Journal of Infectious Diseases, 2004; 57: 55-57.
- Spickler., A.R. 2010: Emerging and Exotic Diseases of Animals, Communicable diseases in animals: Crimean-Congo Hemorrhagic Fever: 4th edn. CFSPH Iowa State University.
- Smego, R.A., Jr., Sarwari, A.R., Siddiqui,A.R. Crimean-Congo Hemorrhagic Fever: Prevention and Control Limitations in a Resource-Poor Country. Clinical Infectious Diseases, 2004; 38(12): 1731-1735. http://dx.doi.org/10.1086/421093
- Shayan, S., Bokaean, M., Shahrivar, M.R., Chinikar, S. Crimean-Congo Hemorrhagic Fever. Laboratory Medicine, 2015; 46(3): 180-9. http://dx.doi.org/10.1309/LMN1P2FRZ7BKZSCO
- Swanepoel, R., Shepherd, A.J., Leman, P.A., Shepherd, S.P., McGillivray, GM., Erasmus, M.J., Searle, L.A., Gill, D.E. Epidemiologic and clinical features of Crimean-Congo hemorrhagic fever in southern Africa.The American Journal of Tropical Medicine and Hygiene, 1987; 36(1): 120-132.
- Saluzzo, J.F., Guenno,B.L. Rapid diagnosis of human Crimean-Congo hemorrhagic fever and detection of the virus in naturally infected ticks. Journal of Clinical Microbiology, 1987; 25(5): 922-924.
- Shepherd, A.J., Swanepoel, R., Leman,P.A.Antibody Response in Crimean-Congo Hemorrhagic Fever. Clinical Infectious Diseases, 1989; 11(4): 801-806. http://dx.doi.org/10.1093/clinids/11.Supplement_4.S801
- Shepherd, A.J., Swanepoel, R.Leman, P.A., Shepherd,S.P.Comparison of Methods for Isolation and Titration of Crimean-Congo Hemorrhagic Fever Virus. Journal of Clinical Microbiology, 1986; 24(4): 654-656.
- Swanepoel, R., Gill, D.E., Shepherd, A.J., Leman,P.A., Mynhardt,J.H., Harvey, S.The Clinical Pathology of Crimean-Congo Hemorrhagic Fever. Clinical Infectious Diseases, 1989; 11(4): 794-800. http://dx.doi.org/10.1093/clinids/11.Supplement_4.S794
- Tezer, H., Sucaklı, I.A., Saylı, T. R., Celikel, E., Yakut, I., Kara, A., Tunc, B., Ergonul, O. Crimean-Congo hemorrhagic fever in children. Journal of Clinical Virology, 2010; 48(3): 184-186. http://dx.doi.org/10.1016/j.jcv.2010.04.001
- Tishkova, F.H., Belobrova,E.A., Valikhodzhaeva,M., Atkinson,B., Hewson,R., Mullojonova, M. Crimean-Congo Hemorrhagic Fever in Tajikistan. Vector-Borne and Zoonotic Diseases, 2012; 12(9): 722-726. http://dx.doi.org/10.1089/vbz.2011.0769
- Tantawi, H.H., Al-Moslih, M.I., Al-Janabi, N.Y., Al-Bana, A.S., Mahmud, M.I., Jurji, F., Yonan, M.S., Al-Ani, F., Al-Tikriti, S.K. Crimean-Congo Haemorrhagic Fever virus in Iraq: isolation, identification and electron microscopy. Acta Virologica, 1980, 24(6): 464-467.
- Vorou, R.M. Crimean-Congo Hemorrhagic Fe-

ver in Southeastern Europe. International Journal of Infectious Diseases, 2009; 13: 659-662. http://dx.doi.org/10.1016/j.ijid.2009.03.028

- Vashakidze, E., Mikadze, I. Epidemiology, Clinical and Laboratory Features of Crimean-Congo Hemorrhagic Fever in Georgia. Georgian Medical News, 2015; 247: 54-8.
- Vanhomwegen, J., Alves, M.J., Županc, T.A., Bino, S., Chinikar, S., Karlberg, H., Korukluoğlu, G., Korva, M., Mardani, M., Mirazimi, A.,Mousavi, M., Papa, A., Saksida, A., Sharifi -Mood, B., Sidira, P., Tsergouli,K., Wölfel,R., Zeller, H., Dubois, P. Diagnostic Assays for Crimean-Congo Hemorrhagic Fever. Emerging Infectious Diseases, 2012; 18(12): 1958-1965. http://dx.doi.org/10.3201/eid1812.120710
- Whitehouse,C.A. Crimean–Congo Hemorrhagic Fever. Antiviral Research, 2004; 64(3): 145-160. http://dx.doi.org/10.1016/S0166-3542(04)00163-9
- Wasfi, F., Dowall, S., Ghabbari, T., Bosworth, A., Chakroun, M., Varghese, A., Tiouiri, H., Ben Jemaa, M., Znazen, A., Hewson, R., Zhioua, E., Letaief, A. Sero-epidemiological survey of Crimean-Congo hemorrhagic fever virus in Tunisia. Parasite (Paris, France.), 2016; 23: 10. http://dx.doi.org/10.1051/parasite/2016010
- Yadav,J.P., Dhaka,P., Vijay,D., R,G.M., Dhanze,H., Kumar,ACrimean Congo Hemorrhagic Fever: Present Scenario, Prevention and Control. Journal of Foodborne and Zoonotic Diseases, 2015; 3(3): 27-33.
- Zavitsanou,A., Babatsikou, F., Koutis, C. Crimean Congo Hemorrhagic Fever: An Emerging Tick-Borne Disease. Health Science Journal, 2009; 3(1): 10-18.
- Howard., C.R. 2004: Perspectives in Medical Virology, Volume II. Viral Haemorrhagic Fevers: ELSVIER, B.V.
- Georgiev,V.S. 2009: National Institute of Allergy and Infectious Diseases, NIH. Volume II: Impact on Global Health. Humana Press, USA.
- Goodman, L.J., David, T.D. Sonen, S.E. 2005: "Tick-Borne Disease of Humans". ASM Press, Washington, D.C. http://dx.doi.org/10.1128/9781555816490
- Swanepoel, R., Burt, F.J. 2004: Crimean-Congo Haemorrhagic Fever. In: Coetzer, J.A.W., Tustin R.C (eds), Infectious diseases of livestock with special reference to South Africa, 2nd edn. pp. 1077-1085. Oxford University Press Southern Africa, Cape Town.
- Tarantola, A., Ergonul, O., Tattevin, P., 2007: Estimates and Prevention of Crimean-Congo Hemorrhagic Fever Risks for Health-Care Workers. In: Ergonul, O., Whitehouse,C. A (eds), Crimean-Congo Hemorrhagic Fever: A Global Perspective, 1st edn. pp. 281-294. Springer Link. http://dx.doi.org/10.1007/978-1-4020-6106-6_21
- Turell,M.J., 2007: Role of Ticks in the Transmission of Crimean-Congo Hemorrhagic Fever Virus. In: Ergonul, O., Whitehouse,C. A (eds), Crimean-Congo Hemorrhagic Fever: A Global Perspective, 1st edn. pp. 143-154. Springer Link.
- ProMED-mail, 2016: Partners Available at: https://www.iamat.org/ (accessed 23 March 2016).
- World Health Organization Regional Office for Europe, 2008: Partners Available at: www.euro.who.int/surveillance (accessed 2 March 2016).
- World Organisation for Animal Health (OIE), World Health Organization (WHO), Food, Agriculture Organization of the United Nations (FAO), 2009: Partners Available at: http://www.glews.net/index.php (accessed 5 March 2016).
- World Organisation for Animal Health, 2014: Partners Available at: http://www.oie.int/ (accessed 14 March 2016).
- World Health Organization (WHO), 2014: Partners Available at: http://www.emro.who.int/ (accessed 19 March 2016).