Crimean-Congo Hemorrhagic Fever–Distribution, Diagnosis, Treatment and Control Measures

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ABSTRACT: The Crimean Congo Hemorrhagic Fever (CCHF), is a highly pathogenic disease that contributes to high morbidity and mortality. It is due to a tick-borne virus, capable of causing hemorrhagic fever that leads to death, specially affecting the human beings, therefore is of outmost importance in the current decade. The disease is widely distributed covering many continents with 40-60% of mortality. Although it is lethal, but still can be avoided; at both community as well as nosocomial level, by adopting proper strategy for management of the disease. This review is a comprehensive discussion about the Crimean Congo Hemorrhagic fever and covers the preventive and curative measures that can be adopted to prevent the outbreak of CCHF.

Keywords: Crimean Congo Hemorrhagic Fever, Tick borne infection, epidemiology, diagnosis, prevention

INTRODUCTION

Crimean-Congo hemorrhagic fever (CCHF) is a very serious and fatal infection, caused by Crimean-Congo Hemorrhagic Fever virus. The virus belongs to the genus *Nairovirus*, which is one of the five genera of the family *Bunyaviridae*, having approximately 350 species (JCTV, 2014). It causes severe infectious disease in humans (Ergonul, 2006), and the virus has been classified into risk group 4, hence should be handled carefully in Biosafety level 4 (BSL-4) laboratory. The viral hemorrhagic fever associated viral families have resemblance with one another (Geisbert and Jahrling, 2004 but of all hemorrhagic fever associated viruses, Crimean Congo Hemorrhagic virus is of importance due to its wide distribution and extensive epidemics worldwide in the recent decades. Crimean-Congo haemorrhagic fever is characterized by haemorrhagic manifestations with fatality rate ranging from 5% to 30% (Gonzalez et al., 1991). Crimean-Congo haemorrhagic fever is one of the major emerging infectious disease (Lablebicioglu et al., 2015), and It is most widely distributed tick-borne viral infection, geographically widespread with cases reported from different parts of Asia, Africa, the Middle East, Eastern Europe and Greece (Ergonul, 2006). It is the most widely spread tick-borne viral disease with a geographical
distribution following that of Hyalomma spp. of ticks, the main vectors of CCHF virus (Drosten et al., 2003).

**Structure, Nature and Life cycle of virus:**

The CCHF virus (CCHFV) has the evolutionary history of 3100-3500 years (Carroll et al., 2010). It is spherical, uniform sized particle, with diameter of about 100nm (Donets et al., 1977; Zhou et al., 2011; Zivec et al., 2015). The genome consists of single-stranded Negative-sense RNA that is divided into 3 different segments: Small (S), Medium (M) and Large (L). The L, M and S are 11-14.4 kilo bases, 4.4-6.3 and 1.7-2.1 kilo bases in length (Carter et al., 2012). The S segment encodes the nucleo-capsid protein (NP) and a nonstructural protein (NS$_S$), the M segment encodes precursor of the two envelope glycoproteins G$_a$ and G$_c$ while L segment encodes the RNA-dependent RNA polymerase (Mardani and Keshtar-Johromi, 2007). The non-coding complementary regions called as NCRs give the genome its circular appearance, these regions are usually present at 5' and 3' terminal of all the three segments of the virus genome (Hewlet et al., 1977). The genomes were thought to encode a single protein but it was later revealed that, the S segment encodes a non-structural protein (NS$_S$) in the opposite orientation to that of NP protein, making it to be considered as ambi-sense virus (Zivec et al., 2015). The virus is enveloped having bi-lipid layer (Acha and Snzyfres, 2003; Whitehouse, 2004). The proteins on the envelope form protrusions of approximately 5-10 nm long. The membrane receptors on the cell surface for the virus has been identified to be nucleolin and G$_c$ as reported by Xiao et al., (2011). It is classified into the following 7 genotypes: Asia-1, Asia-2, Africa-1, Africa-2, Africa-3, Euro-1 and Euro-2 (Alam et al., 2013). The structure of Crimean Congo Virus has been shown in Fig.1.

![Fig. 1: The internal structure of the Crimean Congo Hemorrhagic Fever with 3 genome segments and lipid envelope (Samreen et al., 2012).](image)

The virus can survive under several conditions and depends on conditions like temperature, pH, humidity and the habitat. CCHFV gets inactivated within 30 minutes at 56°C while gets inactivated for 15 minutes at 60°C. Using chemicals/ disinfectants it can be inactivated usually by the use of 1% hypochlorite and 2% glutaraldehyde. pH also has effect on the virus and can be inactivated at a pH less than 6. The virus has tremendous survival abilities as it can survive in moist conditions for 7 hours at 37°C, for 11 days at 20°C and for 15 days at 4°C. Its survival in dry conditions is reduced for 90 minutes to 24 hours (Public Health Agency of Canada, 2011; OIE, 2014)

The CCHFV binds initially to the cell
surface via receptors that are glycoproteins $G_x$ or $G_z$. The actual details about the attachment, entry and fusion of the virus remain unidentified till date (Zivec et al., 2016). It is suggested that $G_z$ is responsible for the binding as monoclonal antibodies can neutralize CCHFV infection by targeting $G_z$ as reported by Bertolotti-ciarlet et al. (2005). The cell protein nucleolin has also been suspected to contribute in the entry as its functional interaction has been suggested with the protein $G_z$ (Xiao et al., 2011). But no specific receptors have yet been identified that are primarily involved in the CCHFV entry (Zivec et al., 2016). The entry when accomplished is followed by endocytosis (Clathrin-mediated). CCHFV is also dependent on low pH and presence of cholesterol for its entry (Simon et al., 2009; Garrison et al., 2013; Shtanko et al., 2014) Fig.2.

![Fig. 2: The replication cycle of Crimean congo virus (Zivec et al., 2016).](image)

Host

Both wild and domestic animals are susceptible including vertebrates and birds. The preference of tick (Hyalomma spp. majorly), carrying CCHFV varies by its stage of development. Larva and nymphs usually prefer ground birds and small mammals. While adults are found more likely to infect the livestock (WHO, 2013; CABI, 2015). Various animals can serve as host because of wide distribution of *Hyalomma* vector. The incidence rate is influenced by climatic changes and ecological conditions in several European Countries. *Hyalomma* life cycle is more adapted to dry climate and arid type of vegetation (Seif et al., 2017). Environment as well as human activities contribute in the occurrence of endemic outbreak in an area, However, this risk can be minimized by changes in use of land, movement and trading of livestock that is infected (Leblebicioglu, 2010).

### Disease Distribution and Epidemiology:

The first medical incidence of CCHF was reported in 1944, during investigation on epidemic affecting Soviet troops. It revealed that the ‘Crimean hemorrhagic fever’ virus causing this outbreak was exactly similar to the ‘Congo hemorrhagic fever’ virus identified in Africa. These findings gave it the name of ‘Crimean-Congo hemorrhagic fever virus’ (CCHFV) (Talgat et al., 2013). Since its discovery, more than 140 outbreaks in 52 countries has been reported from all over the world (Appannanavar and Mishra, 2011). Outbreaks in the regions of former Soviet Union (Hoogstraal, 1979; Watts et al., 1988), Africa (Saluzzo et al., 1985; Swanepoel et al., 1987), Middle East countries (El-Azazy and Scrimgeour, 1997; Schwarz et al., 1997; Al-Tikriti et al., 1981), Asia including countries like India (Yadav et al., 2014), Afghanistan (Mustafa et al., 2009), Iran (Sharifi et al., 2009; Keshtkar-Jahromi et al., 2013), Pakistan (Sheikh et al., 2005) have been evinced. In the last two decades, random outbreaks have been reported in Bulgaria, India, Pakistan, Turkey, Iran, Sudan, Greece (Ergonul et al., 2004;
Karti et al., 2004; Papa et al., 2004; Bakir et al., 2005; Aradaib et al., 2010; Papa et al., 2011). CCHFV strain (strain AP92) was isolated in 1975 from Rhipicephalus bursa ticks that were collected from goats in Vergina village, northern Greece (Papadopolous et al., 1980). Antibodies against CCHFV were detected in 4 of 64 residents where strain AP92 was isolated but none of them showed any symptoms that resembled CCHF (Antoniadis and Casals, 1982). A sero-survey was conducted that revealed that 1% of a human population had antibodies to CCHFV (Antoniadis et al., 1990).

In Pakistan, CCHF was first reported in Rawalpindi in 1976 and since then number of CCHF cases have been reported in the country (Sheikh et al., 2005). Pakistan is an endemic country and has the fourth highest number of CCHFV infection cases in Asia after Turkey, Russia, and Iran (Ince et al., 2014). A rapid increase in CCHFV positive cases has been observed in Pakistan since 2009 (Leblebiciglu et al., 2015). Cases usually appear between March and May and between August and October. Several outbreaks of the disease have been reported in Pakistan, that spread over a wide geographic area including Baluchistan, Karachi and Rawalpindi that are the most affected regions (Altak et al., 1998).

There is a need for global burden of diseases to be described but due to limited resources there is difficulty in collecting data regarding the disease. ProMED (The Program for Monitoring Emerging Diseases), an internet-based reporting system, designed for emerging infectious diseases, threatening human beings (Madoff, 2004; Madoff and Woodall, 2005; Ince et al., 2014) helps to prevent people from infections through spread of information including early preventive measures, prevention from epidemiologic outbreaks and provide more accurate disease control. The source of information are media reports, official reports, online summaries and local observers (Madoff, 2004). The CCHFV infections were reviewed and reported by ProMED to assess and check the reliability of the data obtained by comparing with other published reports. Table 1 indicates case fatality rate of the disease using ProMed as source with publications from 1988 to 2013 (Ince et al., 2014).

Table 1: The case fatality rate in different countries from 1998 to 2013 (Ince et al., 2014).

<table>
<thead>
<tr>
<th>S.No</th>
<th>Country</th>
<th>Infected patients, n</th>
<th>Fatal cases, n</th>
<th>CFRC (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Turkey</td>
<td>1406</td>
<td>140</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>Russia</td>
<td>891</td>
<td>33</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>Iran</td>
<td>323</td>
<td>38</td>
<td>12</td>
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<tr>
<td>4</td>
<td>Pakistan</td>
<td>230</td>
<td>92</td>
<td>40</td>
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<tr>
<td>5</td>
<td>Afghanistan</td>
<td>61</td>
<td>16</td>
<td>26</td>
</tr>
<tr>
<td>6</td>
<td>Kazakhstan</td>
<td>54</td>
<td>21</td>
<td>39</td>
</tr>
<tr>
<td>7</td>
<td>Kosovo</td>
<td>47</td>
<td>11</td>
<td>23</td>
</tr>
<tr>
<td>8</td>
<td>India</td>
<td>42</td>
<td>25</td>
<td>60</td>
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<tr>
<td>9</td>
<td>Mauritania</td>
<td>35</td>
<td>6</td>
<td>77</td>
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<td>10</td>
<td>Tajikistan</td>
<td>34</td>
<td>28</td>
<td>82</td>
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<tr>
<td>11</td>
<td>South Africa</td>
<td>17</td>
<td>5</td>
<td>29</td>
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<tr>
<td>12</td>
<td>Bulgaria</td>
<td>6</td>
<td>1</td>
<td>17</td>
</tr>
<tr>
<td>13</td>
<td>Greece</td>
<td>5</td>
<td>2</td>
<td>40</td>
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<tr>
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<td>Iraq</td>
<td>2</td>
<td>2</td>
<td>100</td>
</tr>
<tr>
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<td>Namibia</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>16</td>
<td>United Arab Emirates</td>
<td>5</td>
<td>2</td>
<td>40</td>
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<tr>
<td>17</td>
<td>Uganda</td>
<td>5</td>
<td>5</td>
<td>100</td>
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<tr>
<td>18</td>
<td>Georgia</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>19</td>
<td>Oman</td>
<td>1</td>
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<td>100</td>
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<tr>
<td>20</td>
<td>Senegal</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>21</td>
<td>Zimbabwe</td>
<td>1</td>
<td>1</td>
<td>100</td>
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<tr>
<td>Total</td>
<td></td>
<td>3426</td>
<td>451</td>
<td>13</td>
</tr>
</tbody>
</table>
Reservoirs

Reservoirs include animals showing no clinical symptoms. These include cattle, livestock, hares, hedgehogs and vertebrates (CFSPH, 2007; Appannanavar and Mishra, 2011).

Vector

There are both biological and mechanical vectors involved in the transmission of CCHFV.

1. Biological Vector

The virus has been found in the tick of Culicoides spp., Argasidae (also called as soft ticks), Ixodidae (hard ticks), >30 species of ticks has been reported to have CCHFV of which Hyalomma spp are considered as the major vector involved in human infection (Fig.3), but it also varies depending on the region it is existing in, for example; in Kazakhstan Dermacentor nivens ticks are considered as vectors (Onishchenko et al., 2005). The ticks other than genus Hyalomma include a limited number of species of genus Amblyomma, Rhipicephalus and Dermacentor as reported by CABI in 2015.

![Ticks Image](image)

Fig.3: (a) Male tick (b) female tick. The tick from the genus Hyalomma are the principle vectors involved in the transmission of Crimean-congo virus (WHO, 2013)

2. Mechanical Vectors

Migratory birds, Ungulates and livestock act as mechanical vectors. The ticks attached to the body of the birds are introduced into new areas of unaffected populations (CFSPH, 2015). The Livestock has large number of ticks and so has more potential of spreading the virus as a mechanical vector. The presence of ticks in livestock, is not considered unusual, as a single animal can have 100 ticks e.g., Hyalomma marginatum, and thus playing potential role in the transmission of the virus (Estrada-Pena et al., 2012).

Signs and symptoms

CCHFV is characterized by fever and hemorrhage. The infection is difficult to differentiate clinically from other viral hemorrhagic fevers (VHF’s) (Leblebicioglu et al., 2016). The major 4 stages of the infection include incubation, pre-hemorrhagic, hemorrhagic and recovery period (Keshtar-Jahromi, 2011). The incubation period is of 3-7 days. It depends on the route of infection, the viral load that has entered into the body and the source of the infection. The blood is the most infectious source of the virus (Appannanavar and Mishra, 2011). 1- 10 organisms are considered as the minimal viral load for the transmission of the disease (Franz et al., 1997). The overall symptoms of the disease include: High fever, myalgia, pain in the abdominal area, headache followed by nausea, diahorrea (without blood). Symptoms such as cutaneous rash, bradycardia and Hypotension are experienced in the pre hemorrhagic phase (Hoogstraal, 1979; Appannanavar and Mishra, 2011).
The hemorrhagic phase is the most severe stage of the disease, it is usually short but rapid and has visibly complicated symptoms like petechiae, epistaxis, hematemesis, melena, hepato-spleeno-megaly (Ergonul et al., 2004; Bakir et al., 2005; Ozkurt et al., 2006). It usually results in the death of the patient due to multiple organ failure and circulatory shock (Sannikova et al., 2007; Doganei et al., 2008). Death occurs in 40-60% of cases.

**Transmission**

Humans are infected through the bites of ticks, through direct contact with blood or tissues of CCHF patients or viremic livestock (Papa, 2010). The infection can be acquired through the bite of infected tick, by percutaneous and per-mucosal routes, through contact with animal blood or tissues. The aerosol transmission possibility has been under investigation in Russia but up till now, no definite evidence exists (Pshenichnaya and Nanadskaya, 2015).

Transmission via horizontal and vertical ways can occur in case of CCHFV (Masayuki et al., 2004). Person-to-person transmission and nosocomial transmission of CCHFV was confirmed in 2010 and 2011 when such cases were reported in Ahmedabad, India (Yadav et al., 2014). Human cases of CCHFV most frequently occur among agricultural workers or rural inhabitants after bites from infected ticks (Pshenichnaya and Nanadskaya, 2015).

Community level transmission in the form of outbreaks has frequently been reported but its nosocomial infection spread through hospital is also life threatening and has been reported in several countries such as Pakistan, India, South Africa, UAE (van Eden et al., 2010; Ascioglu et al., 2011; Oncu, 2013; Burt and Goedhals, 2015). It can be administered CCHFV, hence supportive therapy is recommended. Antiviral are administered for the best results and other supportive measures like antibiotics are given as required. Recombinant nucleoprotein-based ELISA and Recombinant nucleoprotein ELISA are available which may also be used for early diagnosis of cases. Since Crimean Congo hemorrhagic fever virus strains are specific for CCHFV, but the beneficial effects are seen only on the overall death rate (Pshcnichnaya and Nanadskaya, 2006; Papa et al., 2011). Another study revealed the values 1 x 10^4 per kg and different species of ticks were isolated from the patients with positive serology for CCHFV.

Transmission via biological vectors can occur in case of CCHFV through the bites of ticks. Another study revealed that the quality of marketed fish can be optimized when the microbial quality of the fish is analyzed properly. Various animals can serve as host because of different components and the reservoirs include animals showing no symptoms when infected.Other animals like livestock, hares, hedgehogs and vertebrates are also known to be the source of infection. Migration of insect vectors can also occur in different regions. Various tick species have been associated with the transmission of CCHFV and the epidemic has been caused due to the presence of these vectors in these regions.

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1985; Fisher-Hoch et al., 1995; Mardani, 2001). The CCHF in pregnant patients usually results in abortion or can even cause severe neonatal complications and death. The severity depends on the degree of illness of the mother. The routes of transmission of the virus can be perinatal or intrauterine (Ergonul et al., 2010). Only one study suggests that CCHFV can be transmitted sexually but there is a need for further research on the study of persistence of CCHFV in the body fluids of survivors (Leblebicioglu et al., 2015). Surgical treatment and gastrointestinal bleeding of asymptomatic patients are the most dangerous setups for acquiring CCHFV infection (Shepherd et al., 1985). Fig.4 shows transmission of CCHFV.

Risk Groups

The lack of early diagnosis is a threat for the society and there is a high risk of nosocomial transmission to health care personnel due to splash and needle-stick injuries that may occurred in the absence of adequate personal protective equipment (Seif et al., 2017). Healthcare employees are at risk from occupational infections during patient care The emerging cases of CCHFV in countries lacking CCHFV experience may have problems like infection control challenges, increased risk to healthcare workers and high mortality rate (Pshcnichnaya and Nanadskaya, 2015).

Risk groups include peoples from various walks of life such as Butchers, shepherds, farmers, soldiers, veterinarians, and healthcare workers. CCHFV is a significant public health threat because of high fatality rate, the absence of an FDA-approved vaccine and the potential for human-to-human transmission and nosocomial outbreaks. (Duh et al., 2007).

Diagnosis

Following are some tests that can be conducted to detect the presence of the virus: Enzyme-Linked Immunosorbent assay, Quantitative polymerase chain reaction, (Casals and Tignor, 1974; Swanepoel et al., 1983), Isolation of virus using cell culture and Immuno-histochemical staining. The tests can be conducted by the end of the first day when IgM becomes detectable but produced in a low concentration followed by IgG (Bente et al., 2013).

Other tests that can be used for the detection includes serology are; Complement fixation test, hemagglutination inhibition, Reverse passive hemagglutination inhibition, Indirect Immuno-florescence, IgM antibody captured (MAC) ELISA (Saijo et al., 2002; Charell et al., 2004; Saijo et al., 2005), Recombinant nucleoprotein (rNP)-based IgG ELISA and Recombinant nucleoprotein (rNP)-based IgM ELISA (Shepherd et al., 1989; Vanhromwegen et al., 2012; WHO, 2013).

The virus can be isolated using cell cultures such as MK2, Vero, BHK-21, and SW-13.4. There are little to no cytopathic effects produced hence Immuno-fluorescence can be used in order to detect the presence of virus using specified monoclonal antibodies. The culturing can be done only in the early phase of the infection and usually takes 2-5 days to produce its results. Biosafety level 4 facilities should be available in order to use the cell line culturing method (Appannmanavar and Mishra, 2011). RT-PCR can be used and is considered as a method of choice for rapid diagnosis. It is better than cell culturing

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as it saves time and can diagnose within 8 hours. Real Time PCR has additional advantages as it has low rate of contamination, has high specificity, sensitivity and can provide results within few minutes thus saving a lot of time and effort. One step real time RT-PCR was developed by Drosten et al., (2003) for the detection of CCHFV.

**Prophylaxis/ Preventive measures**

Prevention strategies can help reduce the risk of disease. Some strategies include:

- Prevention should be acquired by everyone at both community as well as nosocomial level.
- Appropriate standard precautions should be used in areas having endemics in order to prevent any sort of secondary transmission (Tarantola et al., 2017).
- Special care must be needed at the time of active season of ticks (Aslam et al., 2016).
- Minimization of vertebrate host infections should be done by proper screening and routine examination for presence of ticks responsible to cause the disease.
- Use of unpasteurized milk and raw or uncooked meat should be avoided (Appanannavar and Mishra et al., 2011).
- Workers in the Lab should follow Strict Biosafety precautions and working with such disease requires Bio Safety level-4 setup. Personal protection should be taken against tick bites. Avoid exposure to infected human or animal/livestock.
- In regions of endemics, people should avoid active tick abundant areas, to avoid any chance of infection. Covering of arms and legs is recommended and advised along with the use of light colored clothing to easily identify the tick.
- Application of tick repellent such as...
permethrin and di-ethyltoluamide are also effective (CDC, 1995; WHO, 2001; Zavitsanou et al., 2009).

- Use of chemicals that can kill the ticks in livestock production area to avoid any livestock production infection. Acarides are used for such purpose.

- People working with livestock can take practical measures such as clothing, use of gloves, goggles to avoid any exposure to the tissue or blood of the livestock (Chin, 2000; WHO, 2001; Zavitsanou et al., 2009).

- The human individual diagnosed or suspected to have infection of CCHFV should be quarantined, and use of gloves, shoe covers, goggles, and other barrier-nursing techniques should be adopted. Only staff specialized for the care and nursing should be allowed to deal with the patient.

- The medical instruments and materials should be autoclaved before incineration (Lloyd and Perry, 1998; NIH, 2002). Liquid bleach should be used to decontaminate the surfaces and the sample collecting jar/bottles should be made decontaminated by applying liquid bleach on the outer surface and use of triple container packing and the sample should be labelled properly. Prevention of transmission in the nosocomial setting can thus be avoided (CDC, 1990; Zavitsanou et al., 2009).

- In case of the death of the patient used of 1:10 bleach solution is recommended and the body should be covered in a plastic bag with an adhesive taping to avoid its contact with the soil (CDC, 1998).

- Use of ribavirin is recommended incase, a person gets exposed to the blood or secretions including bodily fluids of the infected person. For example, it was reported that a health care worker acquired a needle-stick injury and was provided with prophylactic ribavirin did not develop the disease (Smego et al, 2004; Zavitsanou et al., 2009). All these preventive measures can effectively help in avoiding the disease.

**CONCLUSION**

Although Crimean Congo Hemorrhagic fever, a zoonotic tick-borne infection that can affect a large number of animals specially causing lethality in human beings, was discovered in 12th Century, yet it is hard to cure because of its high degree of genetic variation that makes it a potentially lethal virus. Proper vaccine is still not available for the virus. The application of supportive treatment and precautionary measures are the essential tools for the control and prevention of the disease. Awareness is being developed all around the world about the disease but a lot of work still needs to be done to completely understand the nature of virus and it ways of infection, so as to alleviate the burden of the disease and for its complete eradication.

**REFERENCES**


Crimean-Congo Hemorrhagic Fever


