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Review Article

Crimean-Congo Hemorrhagic Fever: A Systematic Review

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Abstract

Crimean-Congo hemorrhagic fever is an predominatingly lethal viral contagion qualified in around thirty countries, and it has the roughly inclusive geographic allocation of the medically significant tick borne viral infections. Human become infected by tick bites, through pulverize infected ticks, next to contact with a case of Crimean-Congo hemorrhagic fever pending the acute stage of infection, or through handle with tissues or blood from viremic kine. Clinical features mostly display a spectacular progression recognized by myalgia, fever and bleeding. The best method used for diagnosis of Crimean-Congo hemorrhagic fever virus by real time polymerase chain reaction.

Keywords: CCHF, CCHFV, Classification of CCHFV.

INTRODUCTION

Crimean–Congo hemorrhagic fever is a viral zoonotic illness lead to increase in the patient temperature combined with bleeding from each site of the body, the causative agent of this disease usually transmitted by ticks to animal vertebrate host by sylvatic cycle. The biological vectors that responsible of transmission of this virus are tikes, these tikes considered the reservoirs for Crimean-Congo virus [1].

Because they can spread CCHFV to other ticks and keep the virus alive for months or even years. Animals may not show any symptoms, but some of them have the capacity to multiply the virus to the point that they can infect ticks and people directly by coming into touch with contaminated bodily fluids. The recent appearance of CCHF in Spain shows that rates of tick-human interaction that promote viral transmission are changing and cause CCHF to appear [2]. Other European nations, like France, may be experiencing a quiet CCHFV outbreak due to the presence of one of the virus' primary tick vectors, the discovery of Crimean-Congo hemorrhagic fever viruses targeting antibodies in animals, at least in Corsica, and the lack of human cases [1]. In this research, we examine the CCHFV epidemiological cycle as it has been postulated to occur in the local French setting and we identify the elements that are most likely to have an impact on how the virus spreads between tick vectors and nonhuman vertebrate hosts. For this, 1,035 publications from 1957 to 2021 in total were chosen for data extraction.

The results of this study not only allowed for the identification of the tick species that appear to be the most promising CCHFV candidates in France, but they also served to emphasize the significance of local host community abundance and composition on the occurrence of vector-borne infections. Regarding the alleged Hyalomma marginatum transmission cycle, which is thought to exist in France, at least in Corsica, it is presumable that tick vectors are still only marginally infected and that the likelihood of disease onset in people is still low. It is discussed how likely it is that certain elements will change this equilibrium. The introduction or reemergence of zoonotic illnesses spread by vectors around the world demonstrate the relationship between viruses, vectors, animals, and people, which can result in health issues and monetary losses [1, 2]. Additionally, the spread of competent vectors, the movement of hosts, and conducive environmental factors for vector-borne pathogens are all important for the transmission and persistence of vector-borne diseases [3].

The ticks are the major carrier of viral infections and ectoparasites of people, animals, and livestock. In North Africa and Middle East region, as the management of the vectors still considered a challenge, a number of viral infections by tikes have been recorded, including Tick-Borne Encephalitis (TBE) and Crimean-Congo

hemorrhagic fever [4]. Crimean-Congo hemorrhagic fever virus is the cause of the serious tick-borne zoonosis known as CCHF [5]. It is a pathogen with a level 4 biosafety rating and dead cases as high as fifty percent [6].

Crimean-Congo hemorrhagic fever was found in several countries in the Middle east region [7, 8] and is endemic in some of these nations [9, 10]. In fact, there seems to have been an increase in the incidence of CCHF during the past ten years [8]. However, there is a dearth of precise data, which is most likely caused by the absence of thorough monitoring systems and a lack of knowledge about the epidemiology of viruses and transmission risk factors. Many animals, including camels, cattle, goats, and sheep, exhibit little or no symptoms of CCHF [11, 12].

Ticks, mostly of genus hyalomma, serve as vectors and reservoirs for diseases. Man can become infected through tick bites, coming into touch with CCHF patients, or coming into contact with the bodily fluids, tissues, or blood of animals or people who have the virus [7, 13]. The high death rate of the Crimean-Congo hemorrhagic fever infection in the UAE, Saudi Arabia and Oman [14, 15] was thought to be related to the tick which consider the vector of the virus. Additionally, most cases occurred in people who deals with animal industries [7, 13]. This fever/the causative virus has been recorded in the Arabian region, however there is still a lack of information regarding the prevalence of the disease, death rate, and clinical characteristics [10].

CCHFV classification and genome structure:

In the family Bunyaviridae, which consist of the genera Hantavirus, Phlebovirus, and Tospovirus, the CCHFV is a Nairovirus [16]. With the exception of Tospovirus, which affects plants, all of these genera are known to contain human diseases [17]. Nairoviruses are transmitted by ticks [18], and their long genomic L segments set them apart from other bunya viruses. The diameter of the RNA-enveloped CCHFV virus is between 80 and 100 nm [19].

The virus's lipid coat is covered in spikes made of the (Gn) and (Gc) glycoproteins, which enable it to attach to cellular receptors. The enzyme RNA polymerase necessary for genome replication and transcription in the reservoir cell, is contained within the nucleoprotein (NP). The genome is composed of negative polarity single-stranded RNA and is divided into 3 pieces: short [S], middle [M], and great or large (L) [20].

A genetically diversified arbovirus is Crimean-Congo hemorrhagic fever virus. The genetic lineages of the virus were revealed through test of total and part of the segment S sequences. Concurrent infection of viral strains with vector from several pedigree may result in segment reassortment and recombination, which may result in the formation of novel CCHFV genetic variants. [21].

Ticks catch CCHFV when feeding on the blood of cases of an infected animal. This virion grow in the midgut of the tick before moving on to the hemocoel and salivary glands, and then by saliva to the following host. Compared to mosquitoes, ticks take more blood per unit of time and do so for longer. Vectors obtain the blood by the acidic intracellular compartments of the gut epithelium [22]. The virus does not need to bind to a receptor in the midgut of the tick in order to infect and replicate in the midgut cells and spread to numerous body locations including the salivary glands and reproductive organs [23].

While replicating and spreading, the virus navigates a number of obstacles inside ticks. The tick's adhesion to the host during the feeding period promotes viral multiplication. Through chronic infection and trans-ovarial and trans-stadial transmission to the following life stages, CCHFV can remain linked to the vector for an extended period of time [6].

Further research is necessary, though, to determine the frequency of both of these transmission methods. For instance, ticks may go for extended periods of time without eating, which allows them to act as Crimean-Congo hemorrhagic fever virus infection reservoirs even in the absence of the host. For instance, CCHFV was detectable in H. marginatum up to 700 days following an infected blood meal. Furthermore, even after being stored at 4 °C for up to 10 months, ticks have been reported to still bite vertebrates and pass the virus [24].

Route via which CCHFV infects humans The majority of animals with Enzootic and asymptomatic CCHF infections exist [25]. Human infection by the CCHF virus, tick bites, or contact with contaminated human or animal tissues or blood are all possible [26]. Hospital nosocomial epidemics are linked to under-resourced environments [27]. As an illustration, a nosocomial epidemic was documented in AlFulah, Kordufan, Sudan in 2008 when a patient, a 60-year-old man who had previously a butcher by trade who was admitted to the hospital. As a result of a lack of stringent infection control protocols and personal protective equipment, the virus spread among cases of nurses cared for the index patient [27].

However, the bulk of CCHF occurrences have affected people who work in the veterinary field, the slaughterhouse/abattoir, and the cattle business [28]. The virus has been observed to spread throughout the Arab world in a variety of tick taxa. Hyalomma-genus ticks, however, are the primary vector for human diseases, possibly as a result of both immature and adult ticks feeding on host blood, which is necessary for each stage

of tick development [29]. For CCHFV, Hyalomma ticks serve as both reservoirs and vectors [30].

While the larvae and nymphs of the Hyalomma tick graze on small animals, the adults of birds or reptiles consume ungulates, maintaining CCHFV in the environment through transovarial and transracial transmission [31]. It is necessary to determine the function of reptiles as reservoirs and as capable hosts for the transmission of CCHFV. Through the bite of an infected tick, the CCHFV virus is passed from animals to humans. The virus then spreads to unaffected ticks as they feed on the infected host's blood. Tick infection can also occur when infected and uninfected ticks co-feed on the same host. and viral agents found in tick saliva speed up viral transmission [32]. However, the risk of CCHFV infection exists in all mammals. The birds are frequently resistant to becoming viremic, hence they are regarded as CCHFV replication and transmission on unreliable hosts [33]. The majority of experts agree that humans are the CCHFV's unintentional, terminal host. bites from ticks, coming into contact with animal tissues and blood, and contact with infected human tissues and bodily fluids/blood are the three main ways that people become infected [34]. Transmission of the CCHFV can also result from cattle commerce and travel from affected areas to new ones [35].

Differences in the restrictions on the movement and trading of affected livestock can lessen the threat of CCHFV spread. The most frequent method of the virus transmission. In the Arab world, it was determined that sick people and animals' wounds or mucous membranes could have exposed them to tainted blood from carcasses [36].

Crimean-Congo hemorrhagic fever virus molecular biology considered as enveloped virus negative sense one of RNA viruses from the Bunyavirales family. Moreover, to this virus, the family Nairoviridae includes arthropod-borne viruses such the Hazara virus, Dugbe virus number 11 and Nairobi sheep disease. Despite this, humans appear to experience little to no illness from these viruses11. The segmented genome of the is bound by the L protein and coated with viral nucleoprotein, just like in other bunya viruses [37].

Three genomic parts encode the viral proteins, and this virus has a very sophisticated genomic organization than other elements that can lead to infections. These proteins use the viral RNA which is negative sense act as a template to create the positive-sense viral RNA upon entry, which then starts viral protein synthesis and replication. The receptor binding and viral entry processes are carried out by the glycoproteins Gc and Gn, which are present on the surface of the virus [12].

The small genomic segment that called S segment, also known as the small non-structural protein, and the viral non-structural protein (NP) are both encoded in an opposite-sense reading frame. In the Crimean-Congo virus life cycle, nonstructural protein not only interacts with the viral RNA to form ribonucleoprotein complexes abut also exhibits endonuclease activity, interacts with host heat shock proteins during intracellular viral replication and in infectious particles, and promotes translation of viral mRNAs type thirteen to type sixteen. Also, the NP and NS may influence host cell apoptosis [19]. Indicating that this virus life cycle depends on control of host cell apoptosis. In vitro and in vivo, Crimean-Congo hemorrhagic fever virus infection causes host cell death, and indicators of apoptosis have been reported to be increased in this virus infected individuals [21]. Host apoptosis may be pro- or antiviral, but this is unknown. Increased viral titers in response to host apoptosis inhibition in vitro are indicative of an antiviral effect. It ais unknown where in the intrinsic apoptosis pathway the Crimean-Congo hemorrhagic fever virus non- structural protein prevents activation of caspase three and caspase nine, as well as the induction of apoptosis driven aby BAX and the release of cytochrome c from mitochondria.

These findings collectively show that Crimean-Congo hemorrhagic fever virus is suppressed by its non –structural protein and that host apoptosis may have antiviral activity on the virus. As well as, the virus NSs have been shown to disrupt mitochondrial membrane potential, inducing apoptosis [19]. Later on during infection, Crimean-Congo hemorrhagic fever virus also stimulates activation of BID, a protein that is pro-apoptotic, most likely through extrinsic apoptotic signals [18]. These findings raise the possibility that this virus may also promote apoptosis [24].

Although it has been proposed that caspase 3's cleavage of NP may constitute aa host defense against Crimean-Congo hemorrhagic fever virus type seventeen, structural investigations have demonstrated that this motif is protected from the host caspase 3 by oligomeric conformations of non- structural protein [25]. Thus, host caspase number three can only cleave non – structural protein when it is present in particular conformations [25]. Increased viral RNA polymerase activity was seen when viral non- structural protein was mutated to remove caspase type three cleavage twenty five, indicating that cleavage of non- structural protein may control viral RNA synthesis.

In a CCHFV mini-replicon system, non-structural protein with a wild-type DEVD motif and NP with a modified DEVD motif both displayed equivalent reporter activity, providing that host caspase cleavage of this motif in orthomairo viruses is not necessary for viral replication.

The CCHFV containing the uncleavable AEVA motif did not, however, grow in tick cell culture. M

segment codes for the virus's glycoprotein precursor [GPC]. When compared to other Bunyavirales, the M segment of the CCHFV is complex. The GPC goes through proteolytic processing to produce the distinct viral glycoproteins Gn and Gc. Additionally, the aGP160/85 protein goes through additional proteolytic processing to produce the GP38 protein and aa heavily glycosylated mucin-alike domain a[MLD] [38].

The GPC is proteolytically degraded by host furin-like and SKI-1 proteases as the proteins pass through the endoplasmica reticulum and Golgi apparatus [39]. Crimean-Congo hemorrhagic fever virus undergoes fusion and entry that is clathrin- and pH-dependent, and the Gn and Gc participate in receptor binding and entry. The roles of the other GPC-encoded proteins are less well understood. Although MLD and GP38 might also influence how the GPC is processed properly, localization signals that direct developing proteins to the Golgi apparatus seem to be restricted to Gn. It is unknown if the GP160/85 protein, which has been found in the supernatants of infected cells [39] and ais released from the pre-Gn protein in the Golgi apparatus by host proteases35, has any biological significance in this context [40].

The MLD protein is heavily glycosylated and exhibits little sequence conservation across several Crimean-Congo hemorrhagic fever virus isolates, even though its role in the Crimean-Congo hemorrhagic fever virus life cycle is unknown. This implies that it is sensitive to demand for selected diversity. The deletion of the MLD protein gene had no effect on the virus-like particle (VLP) infectivity, but it did cause aa reduction in the incorporation of CCHFV glycoproteins [41]. The Ebola virus (EBOV) causes endothelial membrane rupture and vascular permeability [38], which limits T cell activation by down regulating the major histocompatibility complex (MHC)-I on the surface of infected cells.

If the CCHFV MLD performs similar functions, it is unknown. As a part of the GP160/85 protein, GP38 may be released separately or along with the MLD and it aids in proper virion assembly. Limited information from the study of VLPs indicates that GP38 may be present on the viral envelope and plasma membrane, but other studies have not found GP38 in true CCHFV virion. What it does in these circumstances is not apparent, though. Given that Ifnar// mice were infected with recombinant CCHFV that was missing NSm, NSm appears to be not necessary for CCHFV infection of mammalian hosts [30].

The virus's adaptation to either altered the non-structural protein, but it's likely that non-structural protein still functions in the tick or another interferon (IFN)-competent host [42, 43]. However, it is unclear what the non-structural protein does in these hosts. L Section The length of the long (L) segments of the orthonairoviruses linked to Crimean-Congo hemorrhagic fever virus and other members of the Bunyavirales group surpasses 12,000 nucleotides [44]. The viral RNA polymerase and cap-snatching actions are present in the encoded L protein [45, 46].

It's intriguing to note that the OTU protease, which, is located precisely at the amino ends of the L protein of the virus. Crimean-Congo hemorrhagic fever virus has been found to stimulate group one interferon stimulate by RIG-I [47], and the OTU part inhibits RIG-I-mediated host non specific immune response through the deubiquitylation function [48]. Because ISG15 changes to the protein of the virus and this protein can act as antiviral, the de-IS Gylating procedure can be regulated the host immunity [49, 50]. Some data suggest that the OTU domain can control the viral RNA polymerase in the host aISG15 [51], other data suggest that the OTU-inactive virus defect is brought on by ubiquitin's persistent occupancy of the OTU catalytic domain, which reduces RNA polymerase activity [48]. In the OTU domains of CCHFV and related viruses, it has been postulated that species-specific preferences for either ubiquitin or ISG15 govern host specificity to the infection [52, 53].

Surprisingly, human pathogenic viruses in the Bunyavirales order typically contain nonspecific immunity antagonists in their NSm and NS [54]. However, equivalent roles for the Crimean-Congo hemorrhagic fever virus NSs or NSm proteins have not been demonstrated, and the OTU part ais the only recognized immediate antagonist of the group one interferon stimulate to Crimean-Congo hemorrhagic fever virus [54].

Genetic Diversity:

Crimean-Congo hemorrhagic fever virus is a genetically heterogeneous virus, which corresponds to its vast geographical spread. Although Crimean-Congo hemorrhagic fever virus strains' The Crimean-Congo hemorrhagic fever virus GPC is significantly less conserved than the NP and L proteins, with different types that express less than seventy five percent a.a conservation [37]. In contrast, the L and NP proteins are highly stable. Geographic location affects the genetic diversity of the Crimean-Congo hemorrhagic fever virus in a considerable way, and Crimean-Congo hemorrhagic fever virus clades segregate accordingly [55].

It is uncertain what is the important mechanisms encourage the sequence variation of the Crimean-Congo hemorrhagic fever virus in the geographic area. This means the human is the only accidental steward for the Crimean-Congo hemorrhagic fever virus, the tick reservoir or animal amplifying hosts are where the selective forces acting on the virus are likely to originate. It's interesting to note that Crimean-Congo Hemorrhagic Fever virus strains obtained from comparable locations decades apart display significant

sequence conservation [56, 57]. Suggesting that the historical evolution of the crimean-congo hemorrhagic fever virus is restricted by geographic boundaries. On the other side, long-distance migration might produce genetic diversity. Crimean-Congo hemorrhagic fever virus isolates from different geographical lineages have been used to establish historical Crimean-Congo hemorrhagic fever virus mobility and co-circulation. Varieties cluster with African isolates of the virus rather than eastern European isolates, suggesting aa long-distance introduction of the Crimean-Congo hemorrhagic fever virus to Europe from Africa. The segmented genome of the virus that causes Crimean-Congo hemorrhagic fever also goes through reassortment [58].

Individual transmission and danger signs in tight correlation with the endemicity of is the geographic transmission of the main arthropod vector and reservoir, Hyalomma ticks4. virus causing crimean-congo hemorrhagic fever Crimean-Congo hemorrhagic fever virus is an arthropod-borne virus that primarily infects people by biting or handling an infected tick. Tick bites may be common in endemic areas but are not considered a risk factor for infection [59]. The virus that causes Crimean-Congo hemorrhagic fever, on the other hand, direct contact with the blood or tissues of viremic animals, typically livestock, can cause the virus to be transmitted to humans. As a result, those who engage in outdoor activities, such as soldiers, farmers, forest workers, and hikers, as well as people who deal closely with livestock, such as shepherds, farmers, butchers, slaughterhouse personnel, and veterinarians, are at a high risk of contracting the disease [60].

Medical care employee undergoing inpatient treatment are at infection due to reports of nosocomial and interfamily transmission caused by needle sticks or dealing with patient secretions and blood [61]. Sexual contact or medical treatments that create aerosols can both result in the transmission of the Crimean-Congo hemorrhagic fever virus [62]. Although massive outbreaks continuous by transmission from human to another, like those found with EBOV, have not been recorded for the Crimean-Congo hemorrhagic fever virus, human-to-human transmission of the virus looks ineffective [63].

Epidemiology of CCHF in the Arab world:

When 200 Soviet soldiers fell ill in 1944 while assisting farmers in Crimea, the disease became known as Crimean-Congo hemorrhagic fever. The virus' current name was given to it when it causes infection to thirteen-year-old male in the Congo in nineteen fifty-six [27]. It was given the name arbovirus in 1962 [64]. In the MENA region, the Crimean-Congo hemorrhagic fever virus has the widest geographic distribution of any tick-borne virus.

Several Arab countries have reported a large number of CCHF cases. Similar geographical ranges are shared by Crimean-Congo hemorrhagic fever and Hyalomma ticks. In endemic areas, the livestock and wildlife that these ticks feed on may function as asymptomatic reservoirs of CCHFV in the transmission cycle [65]. Several types of hosts and favorable climatic and ecological circumstances in many Arab countries that cross borders could contribute to future increases in Crimean-Congo hemorrhagic fever incidence. Ecological conditions and human activity can also have a substantial impact on the persistence and recurrence of Crimean-Congo hemorrhagic fever virus within a region [66].

Variations that used, transportation, urbanization and trade of invalid cattle and domestic animal can all affect the risk of Crimean-Congo hemorrhagic fever virus transmission. The estimate of the burden of crimean-congo hemorrhagic fever has major challenges in many countries because to deficiencies in surveillance and diagnostic capacity [67]. In the section that follows, we will delve into the epidemiology of the Crimean-Congo hemorrhagic fever virus in distinct Arab countries.

Iraq Crimean-Congo hemorrhagic fever was first discovered in the country in 1979, when a twenty four year-old female was demonstrated at Al-Yarmouk Hospital in Baghdad with the illness. Two close friends, one doctor, and one healthcare worker later succumbed to the disease and pass away [22]. After that, sporadic patients of Crimean-Congo hemorrhagic fever were reported in Iraq between 1980 and 2014 [68], and the majority of these individuals had a history of animal contact. Other incidents involved physicians or other medical specialists. The majority of the animals appear positive with a high incidence for the Crimean-Congo hemorrhagic fever virus in a 1980 study by Tantawi et al. to determine the prevalence of the virus in animals [69].

Clinical picture of CCHFV in the Arab world:

Crimean-Congo hemorrhagic fever virus infection can be broadly classified into four types based on the incubation time, pre-hemorrhagic, bleeding, and convalescent stages [70]. The incubation period is the 3–7 day period after infection during which there are no symptoms. The pre-hemorrhagic phase, which is the second stage and lasts for several days, is characterized by symptoms such a high body temperature, headache, nausea, myalgia and hypertension [27]. The next phase which considered the third phase is characterized by several symptoms such as hemoptysis, diarrhea, ecchymosis, epistaxis and changes in the cardiovascular neuropsychiatric and systems [7].

Critically ill patients may experience multi-organ failure and pass away. Healing starts 10–20 days after the illness first appears for those who survive it. It may take up to a year for survivors of Crimean-Congo

hemorrhagic fever to fully recover [13]. However, several people allegedly recovered significantly in a lot less time [14]. A devastating sickness with a high mortality risk of up to 50% in people infected with the Crimean-Congo hemorrhagic fever virus affects humans [71], and in cases of nosocomial transmission, the risk can reach up to 80% [72]. In Arab countries, the mortality rate fluctuated between 26% and 61% throughout various outbreaks. The prevention of well-documented human-to-human infection transmission depends on early detection [73].

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