Crimean-Congo Haemorrhagic Fever Virus: A Silent Widespread Vector-Borne Disease and its Impacts on Public Health

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ABSTRACT

Crimean-Congo Haemorrhagic Fever (CCHF) is a viral disease transmitted to humans through ixodid ticks. This virus can cause severe and sometimes fatal illness in humans. The first documented case of CCHF was recorded in 1944 in the Crimean Peninsula. The disease is now widespread in many developing countries across Asia, the Middle East, Southeast Europe, and Africa. The infection is initially characterized by fever, low blood pressure, erythema, and conjunctival inflammation. Severe cases may exhibit disseminated intravascular coagulation, circulatory shock, hemorrhagic diathesis, and multi-organ failure before leading to death. CCHFV can spread among humans through various routes, including ticks serving as both transmitters and natural reservoirs of the virus. The World Health Organization (WHO) has classified CCHFV as a highly urgent infection due to its diverse range of vectors, the lack of effective medical prophylaxis for prevention and treatment, and a significant mortality rate. Improving international surveillance efforts for CCHF is essential to enhance global health security.

Key words: Crimean-Congo Haemorrhagic Fever, Hyalomma ticks, vector-borne, Pathogenesis, Transmission

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ZOONOSIS

1. INTRODUCTION

Crimean-Congo Haemorrhagic fever (CCHF) is a viral disease that affects humans and is primarily transmitted through *ixodid* ticks around the globe. These ticks are generally found in regions including western China, southern Asia, and the Middle East to southeast Europe and most parts of Africa (Vorou 2009; Tekin et al. 2012). The CCHF virus can be transmitted horizontally and vertically between tick species. Horizontal transmission refers to the spread of the virus between ticks. In contrast, vertical transmission occurs when the virus is passed from an infected female tick to its offspring (Tekin et al. 2012; Bente et al. 2013; Gargili et al. 2017). Infection can be transmitted to humans through various means, including tick bites, crushing of ticks, and exposure to infected blood or tissues. Tick bites lead to transmitting CCHF viral infection in various susceptible hosts, including humans and animals. Though susceptible hosts may experience transient viremia indicating the presence of the virus in the bloodstream for a short period (Tekin et al. 2012; Spengler et al. 2016).

Moreover, transmission can occur through direct contact with infected individuals' blood or other bodily fluids, such as during healthcare procedures or the handling of animal carcasses (Nabeth et al. 2004). It's important to highlight that CCHF can manifest as a severe and occasionally fatal illness in humans. As the disease advances, more severe symptoms, including haemorrhage (bleeding), organ failure, and shock, can occur. Prompt diagnosis and proper medical care are of utmost importance when dealing with CCHF. Implementing stringent infection control measures, which include wearing protective clothing, using tick repellents, and avoiding contact with blood or other bodily fluids, is strongly advised to mitigate the risk of disease transmission (Tezer et al. 2010; Mostafavi et al. 2014). The World Health Organization (WHO) has classified CCHFV as a highly urgent infection, primarily due to its diverse range of vectors, significant mortality rate, and the lack of effective medical prophylaxis for prevention and treatment. The expansion of tick populations has triggered apprehensions about the potential spread of CCHFV to regions that were previously unaffected. This expansion could be influenced by various factors such as human activities, climate change, and the movement of infected animals or imported livestock (Gale et al. 2012; Aslam et al. 2016).

2. DISCOVERY OF CCHF

The first documented case of CCHF was recorded in the summer of 1944 when Soviet troops were reclaiming areas of the Crimean Peninsula that had been under German control. Those affected individuals displayed symptoms of acute febrile illness, characterized by bleeding and shock (Bente et al. 2013). Approximately 200 military soldiers were admitted to medical facilities for treatment, and the observed mortality rate was around 10%. In response to this outbreak, a team of investigators, led by Mikhail Chumakov, was dispatched from Moscow to conduct research. Chumakov, in collaboration with Lev Zilber, had previously identified the pathogen responsible for tick-borne encephalitis in the far eastern region of the Soviet Union in the late 1930s (Kuehnert et al. 2021). Investigators quickly established a connection between the newly observed illness and contact with ticks (Nasirian 2020; Kuehnert et al. 2021). They observed that the abandonment of cultivated land during the German occupation had led to an increase in the populations of hares and other wild hosts of *Hyalomma* ticks. Consequently, soldiers and farm laborers engaged in agricultural restoration were facing a significant number of tick bites. Chumakov and his colleagues demonstrated that the viral infection responsible for the illness, initially named "Crimean hemorrhagic fever," was transmitted through tick bites. They accomplished this by effectively inoculating psychiatric patients and army personnel with serum ultrafiltrates derived from patients or samples of pooled ticks (Watts et al. 2019; Fatima et al. 2023).

3. CAUSATIVE AGENT AND CLASSIFICATION

The *Bunyaviridae* family encompasses several genera, including *Orthobunyavirus*, *Hantavirus*, *Phlebovirus*, *Tospovirus*, and *Nairovirus.* The *nairovirus* genus is responsible for causing CCHFV (Appannanavar and Mishra 2011). The virus has a spike-like glycoprotein embedded in the virion's lipid membrane, which plays a crucial role in the attachment of the virion to cellular receptors. The CCHF virus has a genome consisting of three components: small (S), medium (M), and large (L) genomic segments, which are of negative-sense polarity. Inside the host cell, these genomic components are enveloped by nucleoprotein and RNA-dependent RNA polymerase (RdRp). NP and RdRp play a crucial role in initiating the transcription and replication of the viral genome (Nasirian 2020; Kuehnert et al. 2021). The Nucleoprotein (NP) of the CCHF virus is encoded by the S segment of its genome. The NP consists of a large globular domain that includes both the N-terminal and C-terminal sections of the polypeptide (Fig. 1). To enable the encapsidation of viral RNA, the nucleoprotein undergoes oligomerization, resulting in head-to-tail contacts that form a helical structure. These interactions play a pivotal role in the assembly of the virion and the packaging of viral RNA. The virus produces two types of I transmembrane glycoproteins, N-terminus glycoprotein (GP) and C-terminus glycoprotein (GC), through co-translational cleavage of a single polyprotein encoded by the M segment (Papa et al. 2002a; Nasirian 2020; Kuehnert et al. 2021).
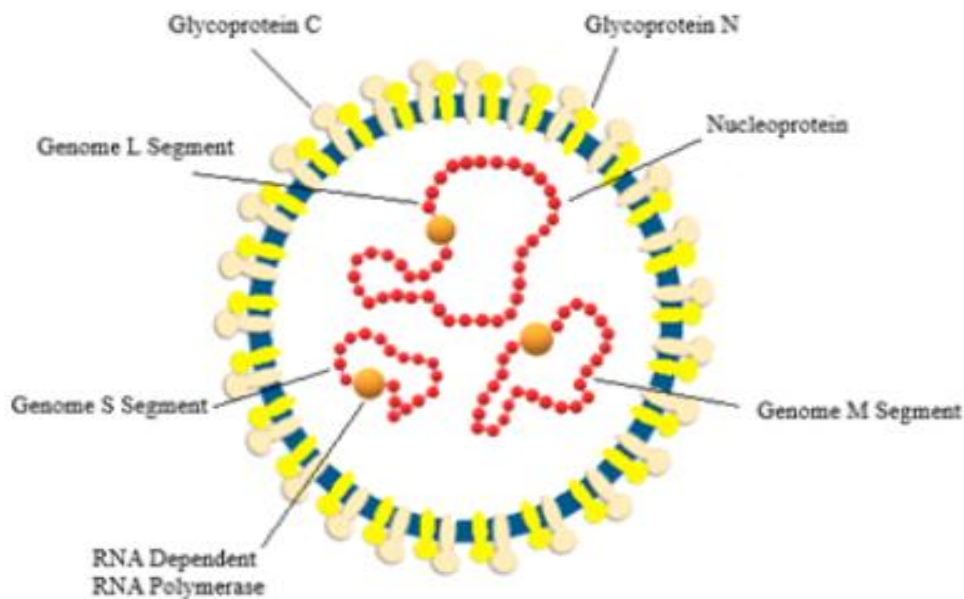

Fig. 1: Graphical presentation of CCHF virus. The virion has a spherical shape with an 80–100 nm diameter. The glycoproteins GP and GC are assembled into spikes scattered throughout the lipid membrane. Specifically, the virus has three single-stranded RNA-dependent RNA polymerase (RdRp), and the nucleoprotein encapsulates RNA genome segments (small, medium, and large).

The glycoproteins of CCHFV stand out due to their abundance of cysteine residues, indicating the presence of numerous disulfide bonds and a complex secondary conformation. The N-terminus of Gn demonstrates features resembling mucin and possesses the potential for substantial O-glycosylation (Papa et al. 2002b; Bertolotti-Ciarlet et al. 2005). The C-terminal cytoplasmic tail of GC is notable for its two zinc fingers, which

can bind to viral RNA. The genetic sequence of the L segment consists of a single reading frame that spans over 12,000 nucleotides (Bertolotti-Ciarlet et al. 2005). An OTU domain is located near the polyprotein's N-terminus, followed by components resembling viral topoisomerase, leucine zipper motifs, and a zinc finger. This sequence encodes a polyprotein of nearly 4,000 amino acids. Towards the C-terminus, the polyprotein contains an RdRp catalytic domain, which exhibits significant sequence homology with the Dugbe virus, another member of the *Nairovirus* genus (Honig et al. 2004a).

4. GEOGRAPHICAL DISTRIBUTION

Human infections with CCHFV have been documented in more than 30 countries spanning Asia, the Middle East, southern Europe, and Africa (Table 1). The first recorded case of CCHF was identified in Bulgaria in 1950, leading to its designation as a recognized infection from 1953 onwards. During the period between 1953 and 1974, a total of 1,105 clinical cases of CCHF was reported. Subsequently, from 1975 to 1996, the number of patients decreased to 279 (Avšic-Zupanc 2008; Papa et al. 2004 and 2011a; Nasirian 2020; Kuehnert et al. 2021). A study carried out in Greece revealed a seroprevalence of 11.6% (34/294) in sheep and 32.9% (139/422) in goats. Similarly, an epidemiological investigation in Novosibirsk, Russia, indicated an antibody prevalence rate of 3.1% among individuals residing in the vicinity (Papa et al. 2010 and 2011b). In 2002, the inaugural case of CCHF emerged in the northern region of Turkey, particularly within the province of Tokat. Subsequently, CCHF was categorized as a notifiable disease in 2003. Subsequently, the annual occurrence of clinical cases has surpassed the cumulative count in all other European countries combined. Numerous instances of human CCHF cases have been documented in the middle and eastern Anatolia regions (Karti et al. 2004; Maltezou et al. 2010; Yilmaz et al. 2008). In 2006, a sero-epidemiological study was undertaken in the endemic regions of Tokat and Sivas. The findings revealed a seroprevalence of 12.8% among rural populations and 2% among urban populations. A study conducted in specific regions found that 79% of the tested domestic livestock had antibodies specific to CCHFV (Gunes et al. 2009). Additionally, a 20% CCHFV positivity rate in Hyalomma ticks was found using an antigen capture ELISA conducted by Vector-Best in Novosibirsk, Russia (Gunes et al. 2011). Furthermore, in 2007, a minor epidemic occurred in the Thrace region of European Turkey, where no prior outbreaks had been documented. An enzyme-linked immunosorbent assay (ELISA) detected CCHFV-specific antibodies in humans, revealing a seroprevalence rate of 5.26% (Midilli et al. 2009).

Within the Eastern Mediterranean Region of the World Health Organization (WHO), which includes 22 countries, there have been documented sporadic human cases and outbreaks of CCHF in several countries. These countries include Iran, Kuwait, Pakistan, Oman, Sudan, Afghanistan, Saudi Arabia, Iraq, and the United Arab Emirates (Malik et al. 2013; Nasirian 2020; Kuehnert et al. 2021). Furthermore, serological investigations conducted on livestock have detected infection in Egypt, Tunisia, and Somalia (Al-Abri et al. 2017; Nasirian 2020; Kuehnert et al. 2021). Outbreaks of infection have been reported in Pakistan, Afghanistan, and Iran, particularly in the border areas of these countries with large populations of nomadic people and their livestock who migrate frequently (Shahhosseini et al. 2021). The exchange of animals and their skins between Iran, Pakistan, and Afghanistan is believed to significantly contribute to the transmission of CCHFV to individuals involved in activities such as handling livestock or their skins, slaughtering infected animals, being close to the tick or patients of CCHF. In 1998, the first documented case of CCHFV was recorded in Afghanistan, and currently, it is prevalent with an average annual incidence of 5–50 cases in humans (Jawad et al. 2019; Ince et al. 2014). Antibodies to CCHFV were initially determined in cattle and sheep in Iran during the early 1970s (Keshtkar-Jahromi et al. 2013). The first confirmed case of CCHF in humans was identified in August 1999 in Iran, when a patient receiving medical

care at a hospital in the southwestern region country died from severe gastrointestinal bleeding (Mardani et al. 2009).

In 1976, the first reported case of CCHFV in Pakistan was documented in Rawalpindi. Since then, there has been a biannual increase in the incidence of CCHF cases in the country (Sheikh et al. 2005). Pakistan is considered an endemic country for CCHF and ranks 4th in terms of prevalence of infection in Asia, following Turkey, Iran, and Russia (Ince et al. 2014). The initial recorded instances of CCHF in Iraq trace back to 1979, with a reported 10 cases and 7 fatalities near Baghdad (WHO 2015). In 1980, several occurrences were documented in Halabja, situated in Iraq's Sulaimani province (Ghareeb and Sultan 2023). In Sudan, the first case of CCHF was recorded in 2008, affecting healthcare personnel in a medical facility in the Kordofan locality. An outbreak in Kordofan resulted in a cumulative count of 10 reported cases. Serosurveys conducted in this region unveiled the existence of CCHF infection in eight individuals who submitted serum samples (Aradaib et al. 2010). In the Gulf region, a study conducted between December 1979 and October 1982 in two hospitals in Kuwait revealed that 4% of serological samples tested positive for CCHFV (Perveen and Khan 2022). A study in Mecca, situated in western Saudi Arabia, during 1989-1990 involved a serological investigation of abattoir workers. This investigation disclosed 40 human cases of CCHFV, resulting in 12 fatalities (El-Azazy and Scrimgeour 1997). A study identified that exposure to animal tissue or blood in abattoirs was a significant risk factor, whereas tick bites did not display a substantial association. In the United Arab Emirates, CCHF was initially documented in 1979, with six instances reported among hospital personnel in Dubai (Baskerville et al. 1981). Table 1 shows the number of cases across different regions of globe.

Table 1: Number of CCHFV cases reported around the globe

Country	Year	Reported Cases	References
Albania	2001-2006	25	Papa et al. 2002a.
Afghanistan	2009	60	Aslam et al. 2023
Afghanistan	1998	19	Sahak et al. 2019
Afghanistan	2000	25	Sahak et al. 2019
Bulgaria	1953-1974	1105	Papa et al. 2004
Bulgaria	1975-1996	279	Papa et al. 2004
Bulgaria	1953-2008	1568	Papa et al. 2004
China	1965-1994	260	Aslam et al. 2023
India	2010-2019	34	Aslam et al. 2023
Iran	2012	870	Keshtkar-Jahromi et al. 2013
Iraq	1989-2009	6	Aslam et al. 2023
Iraq	2010	11	Aslam et al. 2023
Iraq	2021	33	Aslam et al. 2023
Iraq	2022	1085	Aslam et al. 2023
Oman	2014	18	Aslam et al. 2023
Oman	2015	16	Aslam et al. 2023
Pakistan	1976	14	Sahito et al. 2022
Pakistan	2014-2020	356	Sahito et al. 2022
Russia	1999-2020	2361	Volynkina et al. 2022
Russia	2000-2020	385	Volynkina et al. 2022
Turkey	2002	2508	Yilmaz et al. 2008
Turkey	2002-2007	1820	Yilmaz et al. 2008
Turkey	2008	688	Yilmaz et al. 2008

5. VIRUS TRANSMISSION AND CLIMATE CHANGE

The CCHF virus is carried by ixodid ticks and can be transmitted both horizontally and vertically among tick species. Hyalomma ticks, which feed on a variety of hosts throughout their life cycle at different stages of development, play a pivotal role. During their feeding process, infected ticks can transmit CCHFV to susceptible hosts, including humans (Fig. 2). Viruses can spread among ticks through transstadial, transovarial, or venereal routes, making ticks both transmitters and natural reservoirs of the virus (Gunes et al. 2011; Nasirian 2020; Kuehnert et al. 2021; Shahhosseini et al. 2021). Transstadial transmission refers to the passage of viruses from one developmental stage to the next within the tick's life cycle. Transovarial transmission involves the transfer of the virus from infected female ticks to their offspring through eggs. Venereal transmission occurs during mating between infected male and uninfected female ticks. Initial surveys of ticks collected from wild and domestic animals are essential for identifying potential reservoir species (Telmadarraiy et al. 2015).
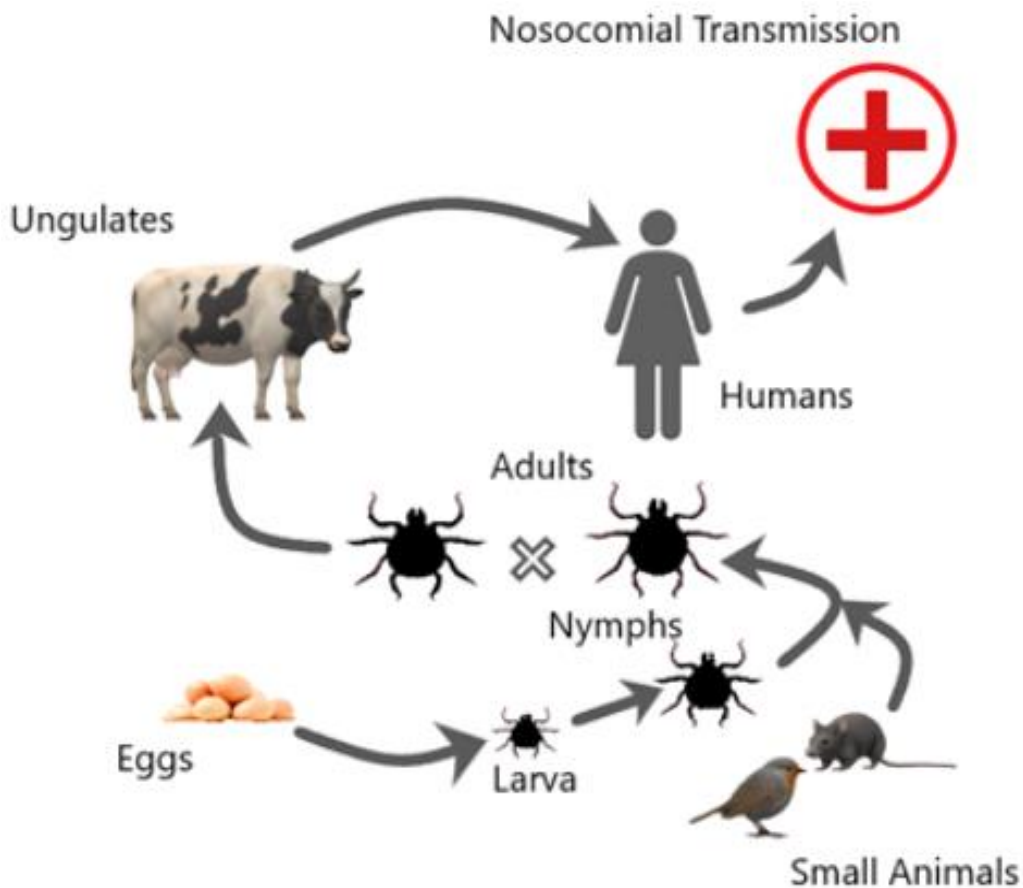

Fig. 2: *Hyalomma spp.* tick life cycle and nosocomial transmission. *Hyalomma* species follow a two-host life cycle, commencing as nymphs on small creatures such as birds and rodents, before transitioning to larger animals and vertebrates, including humans. Notable sources of human infection encompass nosocomial transmission, direct exposure to CCHFV-infected ticks, and contact with infected animals. Factors such as heightened human mobility, the migratory patterns of vertebrate hosts, and the influence of climate change on the migration behaviors of small animals could potentially contribute to an increased prevalence of CCHFV infection within the population.

Competent tick vectors for CCHFV are characterized by their ability to support viral replication in various developmental stages, including larva, nymph, and adult. They can facilitate the transmission of viruses from mature females to their eggs and from adult males to females during copulation (Gargili et al. 2017; Bernard et al. 2022). The virus attains its highest concentrations in the tick's reproductive organs and salivary glands (Valcárcel et al. 2023). When an infected tick bites a mammal, the virus multiplies within the host's tissues, spreading through the bloodstream and potentially infecting other ticks. The risk of virus transmission increases with prolonged attachment of a feeding tick over several weeks, enabling transmission from an infected tick to a host or from an infected host to uninfected feeding ticks (Kuehnert et al. 2021; Shahhosseini et al. 2021).

Hyalomma ticks exhibit a wide geographic distribution, encompassing various habitats such as savannahs, steppes, semi-deserts, farms, foothills, and river floodplains. The acceleration of mean annual temperatures, especially in late fall, could expedite the molting process of ticks, allowing nymphs to mature into adults before winter. This adaptation increases their survival chances during colder months and potentially facilitates their movement to adjacent regions. Consequently, this can enhance the virus's survival and dissemination among ticks (Ergonul 2006; Papa et al. 2002a). Various factors, including rising winter temperatures, reduced winter precipitation, elevated summer evapotranspiration, and the availability of suitable animal hosts, can influence the expansion and migration of tick ecosystems to higher latitudes. Environmental alterations, such as the conversion of floodplains to agricultural lands, changes in grazing patterns, and the conversion of marshy deltas in farming areas, can create more conducive environments for *Hyalomma marginatum* ticks. Research has demonstrated a connection between high infection rates and habitat fragmentation, as well as small agricultural fields in Turkey (EFSA 2010; Estrada-Peña and Venzal 2007; Vorou 2009). Avian migration, which can transport infected ticks, along with the movement of livestock or other species infested with ticks, can potentially aid the spread of CCHFV to new tick habitats. These dynamics underline the intricate interplay between environmental changes, tick populations, and the transmission of CCHFV (Estrada-Peña and Venzal 2007; Vorou 2009).

While the possibility of migratory birds transmitting diseases to previously unaffected European regions is generally considered low, reports from Spain in 2010 indicate the presence of CCHFV-infected ticks (Gale et al. 2012). The spread of CCHFV from endemic to non-endemic areas can result from the convergence of isolated strains with those found in Mauritania and Senegal. However, a lack of fundamental comprehension of interactions between ticks, hosts, and the virus, as well as other factors influencing tick and viral epidemiology, has impeded the development of comprehensive risk assessment models (Estrada-Pena et al. 2012a, b; Vorou 2009).

6. PATHOGENESIS AND CLINICAL PRESENTATION

Following inoculation, the virus undergoes replication within dendritic cells and adjacent tissues, subsequently migrating to local lymph nodes. From there, dissemination occurs in various tissues and organs, including the spleen, liver, and lymph nodes, facilitated by the lymph and blood monocytes. As the infection progresses, tissue macrophages become involved upon infection of receptive parenchymal cells (Peters and Zaki 2002; Geisbert and Jahrling 2004). Notably, a substantial occurrence of apoptosis is observed throughout the disease, resembling patterns seen in other forms of septic shock, even in the absence of lymphocyte infection. The initiation of the extrinsic coagulation pathway is prompted by the production of tissue factors on the cell surface. Within this context, hepatic dysfunction may precipitate intravascular coagulation disruption, leading to reduced levels of coagulation factors, a characteristic

manifestation of CCHFV infections termed diffused intravascular coagulopathy (Geisbert and Jahrling 2004).

In addition to platelet and endothelial cell destruction, CCHFV has demonstrated the capability to induce inflammatory and immunological responses that contribute to hemorrhagic diathesis (Chen and Cosgriff 2000; Peters and Zaki 2002). The release of cytokines, chemokines, and other proinflammatory agents by infected monocytes and macrophages is chiefly responsible for these alterations (Bray 2007; Ergonul et al. 2006). The incubation period for CCHFV typically spans 1 to 9 days, during which the victim typically undergoes a non-specific prodromal phase lasting less than one week. The common manifestations during this phase encompass elevated body temperature, headache, general discomfort, joint and muscle pain, nausea, abdominal discomfort, and occasionally diarrhea (Bray 2007). Initial symptoms often encompass fever, low blood pressure, conjunctival inflammation, and a skin rash or erythema. As the disease advances, patients may develop signs indicative of worsening hemorrhagic diathesis, such as petechiae, bleeding from mucous membranes and conjunctiva, hematuria, emesis of blood, and melena. Complications may include circulatory shock and disseminated intravascular coagulation (Ergonul et al. 2006).

Hemorrhagic diathesis and multi-organ failure are frequently observed prior to death, often occurring within 1-2 weeks after the onset of symptoms. It is important to note that the severity of the disease tends to be milder in pediatric patients (Tezer et al. 2010). Laboratory tests commonly reveal abnormalities such as decreased platelet counts (thrombocytopenia), reduced white blood cell counts (leukopenia), and elevated liver enzymes. Anemia typically does not manifest during the initial stages of the illness but may develop as the condition progresses. Coagulation irregularities present as prolonged bleeding time, prothrombin time, and activated partial thromboplastin time. Furthermore, there may be an elevation in fibrin degradation products and a decline in fibrinogen levels (Mostafavi et al. 2014).

7. EXPANSION OF CCHF CASES

The transmission of CCHFV can occur through contact with the bodily fluids of infected individuals during the initial 7 to 10 days of infection. Health authorities have reported clusters of cases, highlighting the importance of adhering to standard barrier nursing techniques to prevent the spread of the virus (Athar et al. 2005; Maltezou et al. 2009). It's important to note that individuals may travel both before and after the onset of clinical symptoms (Leblebicioglu et al. 2016). Traveling before symptoms emerge can pose diagnostic challenges, as suspicion of the disease may be lower, leading to delayed recognition. Traveling after the onset of symptoms is common among individuals with CCHF. The virus is more prevalent in humans in geographically isolated areas, and the occurrence of the disease is often linked to past tick bites or contact with livestock. Rural areas with high tick activity levels are particularly vulnerable, as ticks are carried by domesticated and wild animals that serve as hosts. This allows for transient viremia and the maintenance of the virus in the natural environment. Measures such as patient isolation and fundamental barriers have been implemented to effectively contain the emergence and spread of diseases like CCHFV, which can result in significant outbreaks (Kuehnert et al. 2021; Shahhosseini et al. 2021).

Hosts, especially migratory birds, and the growth of host populations play a significant role in the dispersal of ticks (Randolph 1998). Changes in tick populations often correspond to the movement of birds or an increase in the number of host animals. The expansion of tick populations across different geographical areas can be attributed to two primary factors. Firstly, ticks carrying the infection can be introduced to separate countries, potentially leading to human-to-human transmission and initiating a chain of disease spread (Shahhosseini et al. 2021). Secondly, non-infected ticks can be introduced to new regions if they

are transported there, where they might establish local populations capable of sustaining the virus transmission. While birds might have a limited role in the transmission cycle of CCHFV, they are still considered important potential vectors for introducing the virus. Cases of *Hyalomma marginatum and Hyalomma rufipes* ticks have been identified in countries like Hungary, Germany, and the U.K., likely brought by migratory birds (Chitimia-Dobler et al. 2016; Hornok and Horvath 2012; Jameson et al. 2012; Shahhosseini et al. 2021). An interesting example is the transportation of *Amblyomma variegatum* ticks to the Caribbean from CCHFV-endemic Senegal through livestock. An anomaly is observed with *Rhipicephalus bursa* ticks, as they seem to propagate a distinct genetic lineage of the CCHFV organized under the Europe 2 clade.

It's important to highlight that *Hyalomma* ticks have also been discovered to carry strains belonging to this clade (Dinç er et al. 2017). The vector competence of *Rhipicephalus* ticks has not been definitively established. The presence of *R. bursa* could indicate either their ability to transmit the virus or the prevalence of R. bursa in regions where strains from the Europe 2 clade are present (Gargili et al. 2017). The movement of domestic and wild animals plays a critical role in the spread of viruses. While certain borders may impose restrictions on the movement of infected animals due to geographical or political reasons, the transportation of animals between regions, particularly livestock, can contribute to the dissemination of diseases (Spengler et al. 2016). In the initial documentation of CCHF in Abbottabad, Pakistan, there was a noticeable influx of livestock migration to the region, potentially involving infected sheep, which led to the identification of the primary case (Saleem et al. 2009). Multiple CCHF outbreaks have been reported in connection with Eid-ul-Adha, a significant religious celebration in the Muslim community, during which many livestock is imported and subsequently slaughtered in urban areas (Mallhi et al. 2016). Moreover, the movement of livestock and other animals, including deer, across hunting estates can serve as a vector for tick transportation. This situation could potentially lead to the establishment of a CCHFV reservoir or the introduction of infected ticks. This concern is underscored by instances such as the discovery of mature *Hyalomma spp*. ticks on a horse that was imported to England (Akuffo et al. 2016). To counter the risk of viral or tick-borne pathogen transmission through animal importation into non-endemic areas, several strategies can be implemented.

8. CCHF RISK ASSESSMENT, OPTIMIZATION, AND REDUCTION

The lack of a comprehensive understanding of virus maintenance in natural habitats, their transmission to human populations, and the intricate interconnections between these processes represent a significant research gap in the context of CCHFV. This holistic framework should guide research efforts toward a health-focused approach to addressing CCHF. In addition to epidemiological, ecological, virological, and vector biology studies, mathematical modeling will play a crucial role in implementing the framework and conducting thorough risk assessments. When incorporated into a framework, modeling techniques can effectively identify critical knowledge gaps, thus aiding in prioritizing epidemiological studies, laboratory-based investigations, and mitigation strategies. The modeling of viruses transmitted by ticks has historically been challenging due to the complex interactions among vectors, hosts, and viruses. Nonetheless, mathematical models have the potential to integrate the biology of hosts, vectors, and viruses, thereby facilitating the identification of key factors that influence disease likelihood.

The tick-host system of CCHF exhibits several characteristics that contribute to non-linear transmission responses, potentially leading to disease outbreaks. Despite the detailed understanding of many processes, it's crucial to comprehend the mechanisms underlying rapidly changing exposure risks. Co-feeding ticks can directly transmit the CCHFV virus to one another through certain hosts, bypassing the

need for the host to experience a viremic response. While feeding, ticks emit pheromones that attract other ticks to the same feeding site, promoting tick-to-tick transmission, a process further facilitated by the presence of tick saliva. The likelihood of co-feeding is positively correlated with the extent of tick infestation. Hosts heavily infested with tick nymphs and larvae are more likely to harbor co-feeding groups. Further research is essential to assess vector competence, which refers to the ability of vectors to acquire and transmit infections. Implementing traditional infection control protocols when handling potentially infected blood or ticks can significantly reduce the risk for individuals in these occupations. Secure tick removal methods involve mechanical techniques and can be performed using readily available tools in most areas (Coleman and Coleman 2017; Akin Belli et al. 2016). Managing diseases transmitted between humans and wildlife demands a multifaceted approach that encompasses various strategies. Preventive measures like translocation control, barriers, and proper husbandry practices play a pivotal role in managing diseases in both domestic and wild animals. Livestock animals, particularly those belonging to the *Bovidae* family, are preferred hosts for mature *Hyalomma* ticks. The interaction between animals, ticks, and humans provides additional opportunities for virus transmission. Understanding the risks associated with emerging and endemic diseases affecting animals and humans is crucial for making informed decisions and implementing preventive health programs for livestock (Booth et al. 1991).

The application of artificial acaricides on domesticated livestock has been a widely adopted approach for managing ectoparasites and ticks globally. Organophosphates are primary chemicals used for ectoparasite and acaricide management, including compounds like pyrethroids, macrocyclic lactones, amidines, and others (Eiden et al. 2017). Acaricides offer a cost-effective means of tick management and can be applied through methods like dips, footbaths, or traditional sprayers (Pavela et al. 2016). However, their effectiveness, cost-efficiency, sustainability, and worker safety can vary among different acaricides (De Meneghi et al. 2016). Unfortunately, the continuous and non-selective use of acaricides has led to the emergence of tick populations resistant to these agents, presenting a global challenge for tick management. Many countries have reported that practically all acaricides have become ineffective in recent times (Abbas et al. 2014; Nandi et al. 2018; Pohl et al. 2014; Li et al. 2004). This underscores the urgent need for alternative and sustainable strategies for tick control to effectively manage the spread of tick-borne diseases like CCHFV.

9. VACCINATION

A drafted roadmap proposed by the World Health Organization outlines alternative vaccination strategies for controlling CCHFV, considering the challenges faced in developing human vaccines. Initial pathway analysis for CCHF was formulated by a WHO working committee on research and development. This analysis includes a timeline for establishing standards and deployment goals for human vaccination. Various vaccine candidates for CCHFV have been developed, incorporating different antigenic variations based on strain and gene combinations (Papa et al. 2011; Tipih and Burt 2020). Establishing clinical markers of protection in this context is vital to facilitate the creation of countermeasures, including vaccines. However, vaccine development encounters several challenges. One major challenge is the diversity of strains, requiring the design of a vaccine that can effectively target the various geographic clades of CCHFV. Another hurdle is the assessment of safety profiles for experimental vaccines (Bente et al. 2013).

Successful wildlife vaccines have been developed and utilized in various scenarios. When designing vaccines for animal use, it's crucial to incorporate the DIVA strategy, which enables the differentiation between vaccinated animals and those previously infected. Immunization with these vaccines triggers the

production of antibodies in the host animal. These antibodies disrupt the biological activity of Bm86, resulting in reduced numbers, mass, and reproductive capacity of pregnant female ticks. The effectiveness of vaccines like TickGARD and Gavac in providing cross-protection against *Hyalomma dromedary* and *Hyalomma anatolicum* ticks in cattle has been demonstrated. However, their efficacy against other tick species, such as *Rhipicephalus appendiculatus* or *Amblyomma variegatum*, remains uncertain (Tipih and Burt 2020).

10. CONCLUSION

Understanding endemic regions and having access to comprehensive data are fundamental for grasping the distribution of disease. Ongoing enhancements in surveillance systems, diagnostic capabilities, and disease-related information mapping are contributing to a more nuanced understanding of CCHFV. The identification of new regions where CCHFV is circulating often hinges on documented cases of human infection. While the increase in disease reporting might be partially attributed to heightened awareness, it's unlikely that awareness alone can explain the observed rise. The potential for more frequent viral circulation within tick and animal populations remains uncertain and necessitates further investigation. Improving international surveillance efforts for CCHF is essential for enhancing global health security. By facilitating early detection and control of potential outbreaks or new introductions, international surveillance initiatives can contribute to mitigating the impact of CCHF and other viral hemorrhagic fever.

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