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Crimean-Congo hemorrhagic fever, transfer patterns, vectors and history in Iran and neighboring countries

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Abstract

Crimean-Congo hemorrhagic fever (CCHF) is indeed to be considered as one of the most significant vector-borne diseases globally. The virus responsible for CCHF can persist in various animals and lead to severe infections in humans. Ticks of the *Ixodidae* family are the acknowledged vectors of CCHF virus (CCHFV) transmission to humans. In this review, different tick species from Iran and its neighbors and their roles in the transmission of CCHFV were evaluated. However, the transmission patterns of CCHF to humans primarily involve tick bites, direct contact with the blood, organs, or tissues of contaminated animals, and exposure to CCHF patients are important in virus transmission. The results of this review confirm that the tick vectors in Iran and its neighbors are very common. Even though tick bite is one of the most important risk factors for CCHF, it cannot explain all cases, and there are other important risk factors, such as high-risk occupations and having contact with livestock. Ticks that have been proven to transmit the disease, especially *Hyalomma marginatum*, are scattered in Iran and neighboring countries. Transporting passengers and livestock and sometimes smuggling livestock are the means of transmitting the virus between neighboring countries. Therefore, there is a need for joint preparedness and response programs to prevent and manage CCHF between Iran and its neighbors.

Introduction

Ticks are obligate blood feeders infesting a wide variety of terrestrial and flying vertebrates and a few marine snakes and lizards. These hematophagous arthropods, with about 900 species, are divided into three families, including *Argasidae* (soft ticks), *Ixodidae* (hard ticks), and *Nuttalidae*. In addition to transmitting different diseases through biological or mechanical ways, ticks also can have a negative impact on host health through serious annoyance, dermatitis, fatigue, malnutrition, and tick paralysis in humans and animals.[1]

The ecology and physiology of ticks make them second only to mosquitoes in the number of pathogens they vector, while ticks are the most important disease vector of moderate climates. However, climate change may alter the diversity and composition of tick species in ecological niches, which can cause virus expansion to previously native areas for Crimean-Congo hemorrhagic fever virus (CCHFV) in the near future.[2,3]

The role of ticks in CCHFV transmission was first confirmed by the development of human disease following the inoculation of tick extracts.[4] The biology of hard ticks is especially suited to support their role as vectors and reservoirs of CCHFV.[5] The CCHFV is an enveloped negative-sense RNA virus belonging to the *Orthonairovirus* genus in the *Nairoviridae* family of the *Bunyavirales* order. Phylogenetic analysis of the CCHFV S-segment suggests the strains cluster into seven major clades, including clade I (Africa 2), clade II (Africa 1), clade III (Europe 2), clade IV (Africa 3), clade V (Europe 1), clade VI (Asia 1), and clade VII (Asia 2). It is the most important cause of severe and fatal human hemorrhagic disease and CCHF has a variable case fatality rate of 3.00% to over 50.00%.[6]

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No evidence of disease has been detected in animals naturally infected with CCHFV. The range of clinical cases and reports of CCHFV in ticks extends over large regions of Africa and Eurasia, including Mediterranean region, and from Middle East to India.[7] Ticks of the *Ixodidae* family are the acknowledged vectors of CCHFV transmission to humans. *Hyalomma marginatum* has the most prominent role globally in the natural history of CCHF in the Mediterranean basin and Middle Asia. Dramatic increases in CCHFV circulation occur when *Hy. marginatum* populations dramatically increase as a result of optimal weather conditions and anthropogenic ecological changes.[8] Besides transmission through tick bites, CCHFV infection can also occur through contact with patients during the acute phase of illness, or with blood or tissues of viremic animals. Similar to other tick-borne diseases, human cases are seasonal. A higher risk of CCHFV infection is widely associated with tick exposure (tick bite or handling tick with bare hands) or animal exposure (herders, agricultural workers, abattoirs, and veterinarians).[6,9] That is why transmission patterns related to certain occupations, such as agricultural occupations, health-care workers, and abattoir workers are associated with higher exposure risk and higher case fatality rates.[10] Additionally, religious holidays in countries where CCHFV is endemic, such as Eid-al-Adha, pose an increased risk for human exposure as cattle and sheep, known vertebrate hosts of CCHFV, are sacrificed. Nosocomial infections, where there is a human-to-human transmission, can occur in a healthcare setting.[11,12] The incidence of CCHF has increased over the past decade, especially in Iran, Türkiye, and Central Asia.[13]

To date, the maintenance of CCHFV has been shown in eight species of unfed ticks, including *Rhipicephalus bursa*, *Hy. scupense*, *Hy. anatolicum*, *Hy. marginatum*, *Hy. turanicum*, *Hy. rufipes*, *Ixodes ricinus*, and *Haemaphysalis* spp.. Unfed specimens result from the molt of a previously fed stage or are newly hatched from eggs. Finding the virus in unfed ticks unequivocally demonstrated that the virus survived tick molting or was passed transovarially from the engorged female to the larvae via the eggs. The virus was also detected in the eggs of *Dermacentor* spp. and *Hyalomma* spp. These species of ticks are the only ones so far reported to acquire the virus in nature and pass the virus to the eggs or the next life cycle stage. Most studies reporting CCHFV in ticks have relied on collecting ticks feeding on vertebrate hosts and then detecting the virus. Thus, CCHFV has been reported so far in 28 tick species collected from hosts; these include one species of *Amblyomma*, one of *Dermacentor*, 15 species of *Hyalomma*, three of *Haemaphysalis*, one of *Ixodes*, 10 of *Rhipicephalus*, and three species of *Argasidae* (in the *Argas* and *Ornithodoros* genera). As mentioned above, ticks of the *Ixodidae* family are considered the main vectors of CCHFV.[8,14]

In this comprehensive review, we delve into the intricate aspects of CCHF by examining its vectors, transmission patterns, and epidemiological trends, specifically within the geographical region encompassing Iran and its neighboring countries.

Materials and Methods

The authors conducted a comprehensive literature review by examining all available papers, including newly identified taxa from Iran and its neighboring regions, and new reports on genera and species. This review encompassed the investigation of tick-borne diseases, with a particular focus on CCHF and its associated vectors. The authors also conducted focused searches for keywords, such as CCHF, vector-borne disease, CCHF in Iran, CCHF transmission, and CCHF vectors and CCHF in all neighboring countries by the name.

To facilitate this extensive literature search, the authors utilized a range of reputable databases, including Google Scholar, ScienceDirect, Mary Ann Liebert, Scopus, Web of Science, SpringerLink, Taylor & Francis Online, Wiley Online Library, BioMed Central, MEDLINE, PubMed, TR Dizin, and SID. In addition, the authors assessed the reliability of the identified papers based on factors, such as citation frequency, journal reputation, and credibility of the researchers involved.

Ticks species in Iran and neighboring countries. Crimean-Congo hemorrhagic fever virus vectors are mainly *Hyalomma* ticks; however, CCHFV was isolated from different tick species, including soft tick species (*Argasidae* family*)*. Up to the present date, it has been documented that Iran hosts a diverse range of tick species, with 50 species identified. These species are distributed across 11 *Argasidae* and 39 *Ixodidae* in 11 genera occurring in Iran, including two *Alveonasus* spp., one *Carious* spp., three *Argas* spp., one *Otobious* spp., and four *Ornithodoros* spp. in soft ticks, and three *Dermacentor* spp., nine *Heamaphisalys* spp., eleven *Hyalomma* spp., six *Ixodes* spp., eight *Rhipicephalus* spp., and two *Amblyomma* spp. in hard ticks.[15-18] The reported diversity of tick species in Iran's neighboring countries, such as Türkiye, has indeed encountered some variations and disagreements among different researchers. Aydin and Bakirci's report indicated 28 species in the family of *Ixodidae* and four species in the family of *Argasidae.*[19] Subsequently, Chavshin and Seyyed-Zadeh reported 55 species in *Ixodidae* and eight species in *Argasidae* for the same region. However, the number of tick species in Türkiye averages between 40 and 60.[20]

Ticks infestations and the diseases they transmit present a substantial challenge to the health and productivity of approximately 10 million livestock in Iraq. Hoogstraal and Kaiser identified 21 species from various genera, like *Argas* spp., *Ornithodoros* spp., *Haemaphysalis* spp., *Hyalomma* spp., *Ixodes* spp., and *Rhipicephalus* spp. these findings are dated, and there haven't been any recent reports on tick species in the region. Hoogstraal and Kaiser

suggested that it's highly likely that there are more tick species currently inhabiting the region.[21] The examination of existing literature unveiled that *Rhipicephalus*, *Hyalomma*, and *Haemaphysalis* are the primary genera responsible for infesting livestock in Iraq.[22]

The tick fauna is relatively well known in the Saudi Arabia. Various tick species are indigenous to Saudi Arabia. According to Perveen *et al*. reported 37 tick species and subspecies infesting livestock and wild animals were documented and identified various tick-host relationships.[23] Literature review revealed that *Amblyomma* spp., *Haemaphysalis* spp., *Hyalomma* spp., and *Rhipicephalus* spp. are the major genera comprising of 17 species infesting livestock in Saudi Arabia.[24]

Very little work has been carried out on ticks infesting in Kuwait. Only seven tick species, including *R. annulatus*, *Hy. dromedarii*, *Hy. impeltatum*, *Hy. schulzei*, *Hy. anatolicum*, *Hy. marginatum*, and *R. sanguineus* have been documented from Kuwait.[25]

Oman has a relatively high diversity of flora and fauna, especially certain arthropod parasites involved in disease transmission. Twelve tick species have been reported from Oman, including *A. variegatum*, *R. annulatus*, *Hy. anatolicum*, *Hy. dromedarii*, *Hy. impeltatu*m, *Hy. rufipes*, *R. sanguineus*, *O. foleyi*, *O. savignyi*, *H. indica*, *I. hoogstraali*, and *Hy. Turanicus.*[23]

Tick fauna and tick-borne diseases are poorly studied in Qatar. Six species of ticks, including *Hy. dromedarii*, *Hy. impeltatum*, *Hy. aegyptium*, *Hy. marginatum*, *Hy. rufipes*, and *Hy. anatolicum* have been reported on camels, cattle, humans, and birds from Qatar.[26]

The identification and survey study on livestock ticks in the United Arab Emirates showed that the main ticks include *Hy. dromedarii*, *Hy. anatolicum*, *R. sanguineus*, and *A. lepidum* in region.[27]

Pakistan alone presents a huge diversity of ticks due to its geographical location in the sub-tropical region. More than 53 tick species were reported in the country, and the most commonly distributed genera are *Rhipicephalus* spp., *Dermacentor* spp., *Amblyomma* spp., *Hyalomma* spp., *Haemaphysalis* spp., *Argas* spp., and *Ornithodoros* spp.[28]

Afghanistan has various species of ticks in terms of tick fauna. The country's generally mountainous and arid climate has led to the settlement of ticks adapted to these climatic conditions. Livestock farming is one of the major professions in the country, and consequently, the tick population is actively present. However, due to the country's exposure to various wars over the past 40 years, there is a lack of scientific publications and fauna studies. Hoogstraal reported 39 species of ticks in Afghanistan, but in recent years, new species have been discovered through limited research. Various ticks belonging to the genera of *Ixodes* spp., *Hyalomma* spp., *Haemaphysalis* spp., *Rhipicephalus* spp., *Argas* spp., *Ornithodoros* spp., and *Aponomma* spp., have been reported in published papers.[29]

In a report published in the Soviet Union in 1984, it was documented that the tick species in Turkmenistan constituted a total of 38 species and subspecies. These species comprised 12 species of *Hyalomma* spp., 10 species of *Ixodes* spp., eight species of *Rhipicephalus* spp., five species of *Haemaphysalis* spp., and three species of *Dermacentor* spp. Notably, all *Hyalomma* species that had been reported within the Soviet Union were found to be present in Turkmenistan. In recent years, there has been a lack of updated research conducted in the region, and the reported tick species have not been updated since the Soviet Union era. Additionally, alongside the ixodid ticks in Turkmenistan, a tick belonging to the *Ornithodoros* genus, which is an *Argasid* tick reported from the region, has also been documented.[30]

There is limited information available regarding the tick species found in both Azerbaijan and Armenia. However, the most concrete report dates back to 1957 when the Soviet Union reported 26 species in the Azerbaijan region and 23 species in *Dermacentor* spp., *Haemaphysalis* spp., *Ixodes* spp., *Rhipicephalus* spp., *Argas* spp., and *Ornithodoros* spp. In recent years, studies conducted in the region have identified six tick species on mammals, and a report published in Azerbaijan emphasized the significance of 14 tick species of medical importance. In studies conducted in Armenia, the most dominant species reported was *Dermacentor marginatus*. Furthermore, recent research in Armenia has revealed the emergence of new tick species, particularly in high-altitude regions.[31,32]

History of CCHF and vectors of CCHF in Iran and neighbors. The history of CCHF in Iran dates to 1970 when the disease was first detected in 45.00% of sheep's sera in the country. Between 1970 and 1978, scientists conducted research on the serology and epidemiology of CCHF in both humans and livestock in Iran. Then, in 1978, CCHFV was isolated from engorged *Ornithodoros lahorensis* soft ticks (*Argasidae*) in northeastern Iran. Since 1999, Iran has been actively detecting CCHF cases every year (mainly in southeastern Iran), with some CCHF cases being nosocomial.[33] Many epidemiological studies have been conducted throughout Iran, and each year, the disease is reported from endemic regions of the country. However, in recent years, there have also been reports of disease from new regions. In one of these studies, a total of 1027 cases were examined between 2000 and 2014, and the endemic regions for CCHF disease were identified as the southeast and central parts of the country.[34] The CCHF in Iran is primarily associated with two tick species, including *Hy. marginatum* and *Hy. anatolicum*, being particularly prevalent in the central region. Interestingly, aside from these primary vectors, there are other tick species, such as *Hy. dromedarii*, *Hy. detritum*, and *Hy. asiaticum* that have been identified as positives for the virus genome.[35,36]

The first report of CCHF in Türkiye dates back to the 1970s when the report demonstrated serum positivity in human cases. The first clinical cases of CCHF appeared in 2002 in the Eastern Anatolia province. Following these initial cases, the disease rapidly spread in the region. Subsequently, the Anatolian region of Türkiye transitioned into an endemic area for CCHF. It is noteworthy that *Hy. marginatum* is recognized as a main vector of CCHF in Türkiye.[37,38] Between the years 2002 and 2007, a total of 1820 cases of CCHF were reported from various regions in the Anatolian region of Türkiye. As of the last available statistics in 2018, there were more than 11,000 confirmed clinical cases of CCHF reported in Türkiye from 2002. The mortality rate associated with these cases was approximately 5.00%. These figures highlight the significance of ongoing surveillance and public health efforts to manage and control CCHF in the country.[38]

The history of CCHF in Iraq reveals interesting results spanning from the first reported case until the present. The initial report of CCHF in Iraq dates back to 1979. After that, the reported cases remained sporadic in the region until 2020. However, a notable shift occurred thereafter, as CCHF started to spread in various regions of the country. Between 1990 and 2010, more than 300 cases of CCHF were confirmed in Iraq. However, in the year 2022 alone, there were 219 confirmed cases of CCHF, indicating a significant increase. The results further revealed that the disease has spread notably in the southern region of the country more than in other regions, and the only vector represented was *Hy. marginatum*. This observation suggests a rising trend of CCHF across all regions of Iraq.[39]

Limited information is available regarding CCHF cases in Saudi Arabia. The first report of CCHF in the country dates to 1990 in Mecca. Recently, a few new reports about seropositivity in humans and livestock have been published. Studies suggested that the main source of CCHF in Saudi Arabia is imported livestock through Jeddah port. This highlights the importance of monitoring and controlling the movement of livestock to prevent the spread of CCHF in the region. Recent reports have indicated the detection of virus genome in *Hy. schulzei*, *Hy. anatolicum*, and *Hy. dromedarii*. However, it appears that the source of infection might be infected livestock blood and tissue.[40]

There are few reports about CCHF in Kuwait in the last decades. The only report available is from the early 1980s, indicating seropositivity in 18 samples. Surprisingly, there haven't been any recent epidemiological surveys to accurately assess the occurrence of the disease in the region, despite the persistence of the vectors.[9,41]

In Oman, the first reported cases of CCHF occurred in 1995 and involved two farmers who had direct contact with livestock. Subsequent studies revealed the presence of ticks in the same area. During the early 2000s, reports in Oman indicated seropositivity for CCHF in humans, as well as sheep, goats, and camels. However, clinical cases witnessed a notable surge after 2011, with recent years witnessing reports of severe manifestations. Importantly, a majority of patients with clinical symptoms had a documented history of contact with livestock. The primary vector identified in these reports was *Hy. anatolicum*.[40,42]

The first reported case of CCHF in the United Arab Emirates was in 1979 when an individual was admitted to the hospital. Unfortunately, nosocomial transmission occurred, leading to more than five additional cases, resulting in three deaths. In the mid-1990s, there was a high prevalence of CCHF among workers in close contact with livestock in the United Arab Emirates. This outbreak was characterized by a significant occurrence of the disease, particularly among those involved in handling livestock (35 cases). Unfortunately, the outbreak was associated with a high fatality rate (62.00%), indicating the severity of the disease in affected individuals.[43] As of the last decade, there have been no reported cases or occurrences of CCHF in humans in the United Arab Emirates. This period of absence of reported cases and main vector could be attributed to various factors, including effective public health measures, enhanced surveillance, and perhaps a reduction in the prevalence of the virus in the local environment.

Since the first case report in 1976, Pakistan has been recognized as an endemic area of CCHF. Pakistan faces several challenges in achieving comprehensive epidemiological statistics, primarily related to its healthcare system and socio-cultural conditions. Despite these challenges, various reports consistently show the occurrence of CCHF every year, and there is evidence of increasing trends. For instance, one report documented 2834 cases of CCHF in Pakistan between 1960 and 2019. Between 2016 and 2023, the reported statistics indicate more than 45 deaths and hundreds of cases of CCHF in Pakistan, and Baluchistan province has been known as a high-risk area. However, it is acknowledged that these numbers may be an underestimate due to the challenges associated with data collection, reporting, and health-care infrastructure. Literature reviews on the main vector of CCHF in Pakistan have not definitively identified a specific tick species as a primary vector. However, molecular detection methods have revealed high positivity for the CCHF virus in *Hyalomma* ticks, particularly *Hy. anatolicum* and *Hy. marginatum*.[44,45]

Afghanistan has been acknowledged as an endemic country for CCHF since 1998, marked by the first confirmed cases in Takhar province. Subsequently, the disease has spread throughout the entire country, reaching 33 out of 34 provinces. Due to limitations in healthcare systems and the challenging conditions brought about by conflict and war, Afghanistan has faced significant hurdles in managing CCHF. Surveillance studies in Afghanistan commenced in 2007 and the reports from

these studies, spanning until 2018, documented a total of 1284 cases. These findings reveal a notable and consistent increase in cases each year. Recently, there have been several reports indicating the occurrence of CCHF in various provinces of Afghanistan. Additionally, these reports have highlighted high mortality rates associated with the disease. The main vector for CCHF in Afghanistan has been reported to be *Hyalomma* spp., with the dominant species being *Hy. marginatum*.[46]

The last report about CCHF in Turkmenistan dates to 1946. According to the available information, a total of 14 cases were reported until 1968. Following that period, there is no documented information about CCHF in Turkmenistan up to the present time.[47]

Despite the presence of vectors in Qatar, the Republic of Azerbaijan, and Armenia, there have been no reported human cases of CCHF in these regions until now.

Crimean-Congo hemorrhagic fever transmission patterns and mortality in Iran and neighbors. The CCHF infection cycle depends on several variables, illustrating its complex ecology. Ticks serve as vectors crucial for maintaining and transmitting the virus. Livestock and wild animals, including rodents and birds, act as reservoirs, harboring the virus and contributing to its persistence in nature. Humans, in turn, become hosts.[8,14] The transmission patterns of CCHF to humans primarily involve tick bites, direct contact with the blood, organs, or tissues of contaminated animals, handling of slaughtered animals, exposure to CCHF patients, and the risk of nosocomial transmission within health-care settings.[2,6,8] The CCHF transmission patterns and mortality rates exhibit variations in Iran and neighboring countries, influenced by geographic conditions, tick fauna, livestock populations, industrial practices, and socio-economic and socio-cultural factors, as well as the level of knowledge about the disease among the population. The adequacy of the health system further contributes to these differences. The complex interplay of these factors underscores the need for region-specific approaches in disease management, surveillance, and public health interventions to effectively address the distinct dynamics of CCHF in this geographical context.

The primary transmission patterns in Iran revolve around direct contact with infected animals, specifically involving exposure to their organs, blood, and tissues. Tick bites and nosocomial infection are other modes of transmission. Reported mortality rates for CCHF in Iran have shown variations over time. One of the initial reports indicated a mortality rate exceeding 17.00%. Subsequent data, spanning from 2009 to 2015, reflected an average mortality rate of 21.00%, with rates exceeding 11.00% in children. However, the overall average mortality rates in Iran have been reported to range between 10.00 and 40.00%, with specific reports citing both higher and lower rates.[48,49]

A literature review on the transmission patterns of CCHF in Türkiye reveals that the main modes of transmission are tick bites and direct contact with infected animals. Additionally, nosocomial contamination has been identified as another route of transmission. Notably, despite the prevalence of tick-borne and animal-related transmissions, the highest reported mortality rate is associated with nosocomial infections, reaching 16.00%. The last report about the incidence of CCHF in Türkiye returns to 2018 with 5.00% mortality.[38,50]

In response to the rising number of CCHF cases in Iraq, researchers have directed their focus toward investigating the infection roots in the region. The findings highlight that the primary transmission pattern is closely tied to relationships and direct contact with animals. This is attributed to the widespread practice of livestock husbandry in the region. In the first CCHF report in Iraq, the presence of nosocomial transmission was noted. The CCHF poses a high risk during religious gatherings, including events like Eid al-Adha and Ashura day. These occasions were marked by increased interaction and potential exposure to animals. Mortality rates in Iraq have consistently been higher than 10.00%, with the latest reports indicating a notable increase to over 16.00%.[11,39]

The incidence of CCHF has witnessed an increase in Oman in recent years, marking a shift from sporadic cases to an emerging disease in the region. The associated mortality rate is reported to be around 30.00%. The primary transmission pattern identified involves contact with infected animals, particularly through butchering practices during Eid al-Adha.[42]

Transmission patterns in Pakistan and Afghanistan, based on lifestyle and socio-economic factors, exhibit similarities. The infection roots (animal contact, tick bite, and nosocomial infection) are widespread in both countries, characterized by a traditional farming culture and weak healthcare system adequacy. The combination of these variables contributes to a high mortality rate in the region. The average mortality rates in Pakistan have been reported to range from 4.00 to 30.00%. However, specific reports indicate higher mortality rates exceeding 40.00% in the region. Reports from Afghanistan suggest no significant differences in mortality compared to Pakistan, with mortality rates falling within the range of 15.00 to 45.00%.[45,46]

Surveillance of CCHF in Saudi Arabia, Kuwait, United Arab Emirates, Qatar, Turkmenistan, Azerbaijan, and Armenia has been limited in recent years, primarily relying on sporadic case reports and seroepidemiological research. Consequently, transmission patterns and accurate mortality rates have not been comprehensively reported in these countries. There is a need for enhanced monitoring and screening of cases, reservoirs, and vectors in the regions.

In conclusion, the ecology and epidemiology of CCHF in Iran are only beginning to be understood. Türkiye, Iran's neighbor to the northwest, has seen a dramatic increase in the number of human infections since 2002, but the causes of this increase may be due to both the climatic and geographic characteristics providing the appropriate environment for ticks to reproduce and these vectors spread to rural areas involved with agriculture *via* cattle, sheep, goats and small mammals, like hedgehogs, hares, and rodents. While there is a cumulative temperature requirement for the molting of *Hyalomma* ticks, climate change appears to be only one of many factors. Alterations in habitat and populations of small mammals and migratory birds, as well as other factors, are also being investigated in studies focusing on the potential for CCHF to spread within Europe, Africa, and Asia. It is noteworthy that the increase in CCHF cases in Türkiye in 2008, followed by a leveling out of case numbers, mirrored what occurred in Iran during the same period. It should also be noted that cases in Iran were first identified in 1999 and increased through 2002 when the first patient was recognized in Türkiye. Although Iran has not been included in studies of the ecology and epidemiology of CCHF, the apparently simultaneous increase in cases across such distant and different geographic areas raises questions about CCHFV transmission and the conclusions of epidemiological studies that have focused only on Türkiye.[3,7] Surprisingly, regions of northwestern Iran that most closely resemble Türkiye do not have the highest rates of infection in the country. Sistan and Baluchestan province, the region with the largest numbers of CCHF cases in Iran, borders Pakistan in the southeast and is sparsely populated. Its desert terrain has a completely different ecosystem than northern Iran or Türkiye, but *Hyalomma* ticks harboring CCHFV are present.[33] Unfortunately, until now there have been no comprehensive studies of the ecological cycle of CCHFV in that province. Further investigation of factors, including changes in ecological factors, such as rainfall, humidity, and temperature across a wide range of areas, may still be useful, despite the lack of findings from previous studies focusing on Africa and Europe. Studies of the unique ecological niche of Sistan and Baluchestan could provide new information about the establishment, persistence, and transmission of CCHFV.

As mentioned earlier, the neighboring countries of Iran, including Pakistan and Afghanistan to the east, and Türkiye and Iraq to the west, are endemic regions for CCHF. This poses a significant threat to Iran, given its proximity to these endemic areas. In non-endemic neighboring countries, the risk of acquiring human infection is mostly related to the imported livestock carrying infected ticks. The risk seems to be the greatest during Hajj season when hundreds of thousands of cattle are imported to the region for ceremonial sacrifice.

Based on reports on primary transmission patterns, it is evident that countries where the primary mode of transmission involves contact with infected animals and nosocomial transmission, tend to exhibit higher mortality rates compared to the cases associated with tick bites. It appears that the observed variation in mortality rates, influenced by transmission routes, may be related to the viral load in cases. Different transmission routes could potentially impact the viral load, subsequently influencing the severity of the disease and associated mortality, but this has not been proved yet. Certainly, numerous factors could contribute to the variations in mortality rates, including host immune response, pathogenicity of virus, and health system of the country. The interplay of these factors adds complexity to the understanding of CCHF outcomes.[13] From seven genotypes of CCHF, four different geno-types are circulating in Iran, including Asia-1, Asia-2, Europe-1, and Europe-2. The broad genetic diversity of CCHFV in Iran reflects the variety of viruses found in neighboring countries. Iran shares the Asia 1 strain with Pakistan and Afghanistan, Asia 2 with Central Asia, Europe 2 with Greece, and Europe 1 with Türkiye.[6,14,33] Ticks that have been proven to transmit the disease, especially *Hyalomma* spp., are scattered in Iran and neighboring countries. Transporting passengers and livestock and sometimes smuggling livestock are the means of transmitting the virus between neighboring countries. Therefore, there is a need for joint preparedness and response programs to prevent and manage CCHF between Iran and its neighbors.

This review confirms that the tick vectors in Iran and its neighbors are very common, and *Hy. marginatum* is the main vector of CCHFV in the region, and the scheme of risk factors and risk groups for CCHF in Iran does not differ substantially from the neighbors. Even though tick bite is one of the most important risk factors for CCHF, it cannot explain all cases, and there are other important risk factors, such as high-risk occupations and having contact with livestock.

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Conflict of interest

The authors declare that there are no conflicts of interest in disclosing this work.

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