Socio-economic Impact, Zoonotic Transmission and Transboundary Health Protection for CCHF

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Abstract

Crimean Congo Hemorrhagic fever (CCHF) is a sever tick-borne illness with a fatality rates of 30% or higher. The causative agent, Crimean Congo Hemorrhagic fever virus (CCHFV), is classified as a biosafety level-4 virus, highlighting the urgent research need for research and development efforts. CCHF is endemic and has wide geographic distribution in Asia, Africa and Middle East and Eastern Europe. The primary vector for CCHF is the *Hyalomma* genus of ticks which plays a central role in spreading this disease. High-risk groups for CCHF include healthcare workers, agricultural and animal related workers and household and service workers. While many species can carry CCHFV asymptomatically, only humans develop severe illness. Three primary pathways for tick's entry are considered: infected tick vectors, livestock and wildlife. In under-developed regions, illegal cross-border movement of ticks and hosts contributes CCHF spread into new endemic areas. The survival of the infected ticks in these emerging regions depends on abiotic and biotic factors, exposure of residents, and the presence of the livestock and wildlife. Stakeholders, including government authorities, farmer communities, veterinary professionals, meat industry workers, public health offices, wildlife conservationists and educators can play crucial role in crafting and implementing strategic policies to educate the general people, reduce transmission risks and strengthen preventive measures against CCHF.

Keywords: Crimean Congo hemorrhagic, tick-borne illness, zoonotic disease, high-risk groups, stakeholders

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Introduction

1. Overview of Crimean-Congo Hemorrhagic Fever

Crimean-Congo hemorrhagic fever (CCHF) is a zoonotic disease with high fatality rate caused by Crimean Congo hemorrhagic virus (CCHFV) (Kouhpayeh 2019; Nasirian 2020). Historical records indicate that a physician in Tajikistan observed hemorrhagic manifestations of CCHF in a patient in 1100 AD (Hoogstraal 1979; Maltezou & Papa 2011). This disease was formally recognized in 1944 on an outbreak among military personal stationed situated on the Crimean Peninsula during 1944 (Hoogstraal 1979) affecting 200 soldiers, who presented with hemorrhagic syndrome and shock resulting in 10% mortality rate. Early investigations aimed to determine whether the ticks were vectors responsible for disease transmission (Ergönül 2006) and trials were conducted to transfer the disease to volunteer soldiers and psychiatric patients in an efforts to understand the virus ethology (Whitehouse 2004; Bente et al., 2013). Later, after 1967, Soviet scientist Chumakov successfully isolated the virus from a patient in Uzbekistan (Papa et al., 2015).

CCHF is generally asymptomatic in domestic and wild animals, which often act as reservoirs of the virus (Fanelli & Buonavoglia 2021). Many domestic animals can experience viremia without displaying any visible symptoms (Temur et al., 2021) complicating efforts to identify infected animals. CCHFV can infect a different animal species, including livestock and wild animals; however, only humans develop a severe illness, resulting in higher morbidity and mortality. The virus incubation period within ticks typically lasts around nine days, whereas transmission through infected blood or tissues requires five to six days. Patients experiencing hemorrhagic symptoms can transmit the disease through bodily fluids, including from the gums, nose, mouth and injection sites (Ergönül 2006). Clinical symptoms include hemorrhage, fever, myalgia with potential for rapid and severe progression (Figure 1). Other serious symptoms include dizziness, sore eyes, photophobia, agitation, headache, lethargy, hepatomegaly, abdominal pain, severe bleeding (Tabassum et al., 2023).

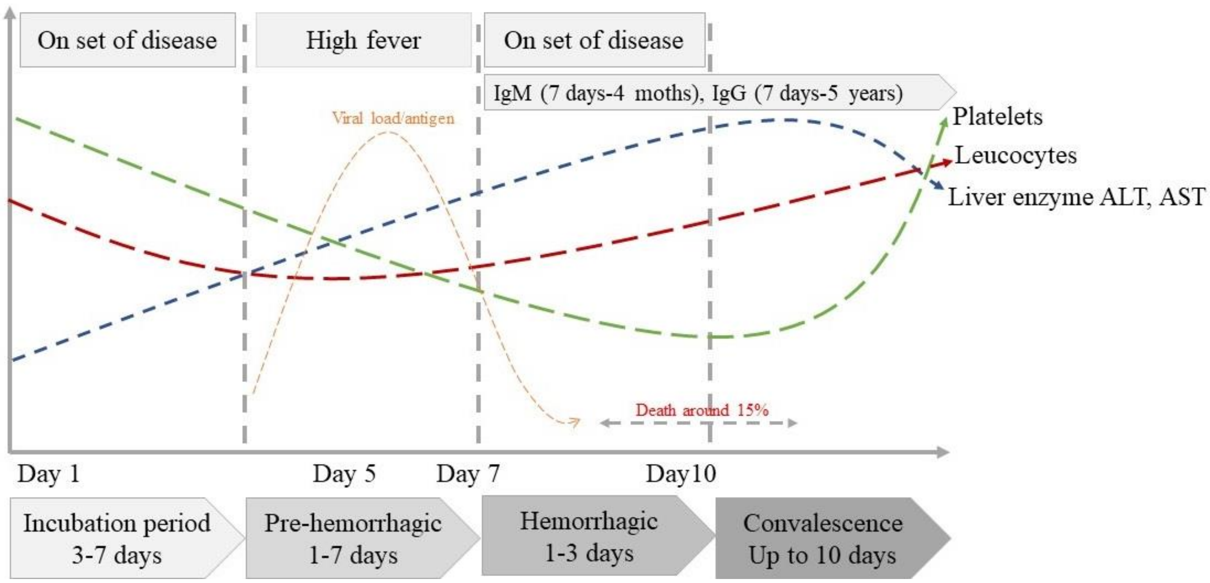

Fig. 1: Phases of Crimean-Congo hemorrhagic fever. Incubation period (lasts up to 7 days, typically symptom-free), pre-hemorrhagic fever (lasts up to 5 days with symptom onset characterized by high fever; can be detected at this stage though RT-PCR or serological tests), hemorrhagic phase (marked by hemorrhagic manifestation, including decreased platelet, leucocytes counts, elevated liver enzymes, and increase pro-inflammatory cytokines), recovery phase (Patient generally begin to feel better 10-20 days the symptoms onset). The concept of the figure is adopted from previously published works (Ergönül 2006; Fillâtre et al., 2019) and is reproduced with the kind permission of Prof. Dr. Onder Ergönül.

1.1. CCHFV Detection and Vaccine Strategies

The World Health Organization (WHO) has classified CCHF as a priority disease due to absence of an effective vaccine with the fact that treatment remains predominantly supportive particularly in emerging countries, where such measures can help to reduce potential mortality. Currently no licensed vaccines or specific antivirals exist to treat CCHF (Hawman & Feldmann 2023). Developing an effective vaccine could protect vulnerable population, including farmers who work closely with agriculture or animal husbandry and are directly exposed to tick bite. For the diagnosing CCHF, two types of laboratory procedures are used: direct and indirect tests. Direct tests include early stage diagnosis methods, such as virus isolation through cell culture, detecting the viral genome and identifying viral antigen using PCR techniques (conventional PCR, qRT-PCR and real-time quantitative reverse transcription, RT-PCR). Indirect tests involve serological techniques, including indirect immunofluorescence assays (IFAs), complement fixation assay, including direct immunofluorescence (DIF) or passive hemagglutination assay (PHA) or ELISA detection of specific antibodies including IgG (IgG-sandwich ELISA) and IgM (IgM-capture ELISA) (Muzammil et al., 2024) (Figure 2).

2. CCHF Transmission Pathways and Global Emergence

CCHF has been reported in new regions and has re-emerged in certain countries after periods of inactivity. Cases have been documented from Africa (Democratic Republic of the Congo, Uganda, and Mauritania), the Middle East (Iraq, United Arab Emirates, Saudi Arabia, and Iran), Asia (Uzbekistan, Kazakhstan, Tajikistan, Pakistan, and India), Southern and Eastern Europe (Bulgaria, Turkey, Russia (Crimea, Astrakhan, Rostov and Spain) (Logan et al., 1990; Whitehouse 2004; Aradaib et al., 2010; Patel et al., 2011; Estrada-Peña et al., 2012; Jameson et al., 2012; Messina et al., 2015; Akuffo et al., 2016; Dowall et al., 2016b; Al-Abri et al., 2017; Gargili et al., 2017; Negredo et al., 2017; Nasirian 2022; Ricco et al., 2023). Among these countries, a high rate of fatalities has been reported in Africa, Asia, and Europe (Figure 3). CCHFV introduction and exposure categorizes several countries by risk level based on animal health consequences: Austria, Belgium, Germany, Luxembourg, Netherlands, Slovenia and Switzerland fall into low risk group, while France and Italy are considered as medium-risk (Fanelli & Buonavoglia 2021) (Figure 3).

3. Risk Factors Associated with the Spread of CCHF

CCHFV has been isolated from over 30 species of ixodid ticks (Hoogstraal 1979; Leblebicioglu 2010). Various species within this genus, including *H. anatolicum, H. asiaticum, H. dromedarii, H. impeltatum, H. marginatum, H. rufipes, H. truncatum,* and *H. turanicum* are known to transmit the virus across different continent leading to significant economic losses and health challenges for both livestock and humans (de la Fuente et al., 2024). This genus favors arid vegetation types and dry climates for its proliferation. The tick transmit CCHF through multiple mechanisms: from one developmental stage to another (transovarial transmission), from one generation to the next (vertical transmission), during mating from male to female (sexual transmission) and among infected tick sharing the same non-visemic host (co-feeding host) (Gargili et al., 2017). The presence of small and large ruminants supports the ticks blood-feeding cycle (Leblebicioglu 2010). Vertebrate animals are essential to CCHFV transmission, as they (a) allow virus replication within infected vectors during blood means (b) supporting the amplification of tick population and (c) facilitate the spread of infected ticks to new regions through long-distance movements (Bernard et al., 2022).

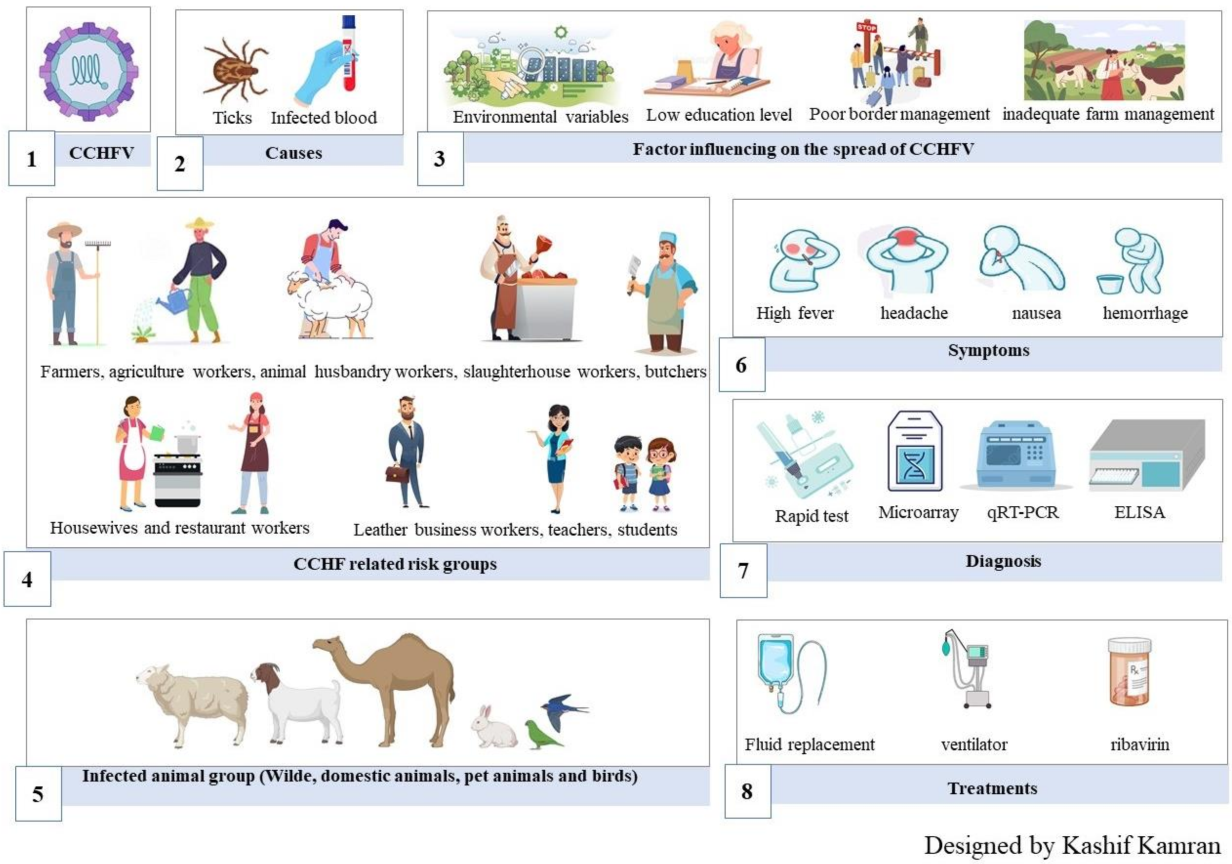

Fig. 2: Systematic overview of CCHF: 1) CCHF virus, 2) Primary causes and transmission method, 3) factor influencing on the spread of CCHFV, 4) CCHF related risk factor groups, 5) Human symptoms, 6) Common diagnostic method, 7) Diagnostic options, 8) Potential treatments.

Fig. 3: Countries with the highest fatalities due to CCHF are predominantly those engaged in active livestock trade. Illegal livestock movement across borders increases the risk of disease spread, particularly in regions where regulations are either poorly enforced or non-existent. This map is reproduced from the data given in the review of Nasirian (2020) (data elaborated with ArcGIS 10.8 and permission has been obtained from the mentioned author).

Several other factors, including the movement of infected ticks, animals, climate change and shifts in human activities promote the emergence of CCHF in region previously considered nonendemic (Figure 4). Human behaviour is considered as an important key factor contributing to the spread of CCHF particularly in non-endemic regions. Activities such as extensive use of land, recreational activities and movement and trade of infected livestock contribute significantly to the transmission of the virus. Outdoor activities, such as hiking and campaigning also contribute in the potential risks for CHF transmission. Another risk factor is the lack of specific CCHF surveillance programme in many countries of the WHO Eastern Mediterranean Regions EMR, where the disease is endemic. Global warming directly impacts on tick distribution, increasing the potential for CCHFV spread in new geographic areas (Estrada-Pena et al., 2007). Infected migratory birds, imported livestock, or both can introduce CCHFV into neighboring countries, making CCHF a silent but widespread threat (Kuehnert et al., 2021). For instance, a recent review reported over 11,000 suspected in Turkey since 2000, with 90% cases documented by the Ministry of health (Fillâtre et al., 2019).

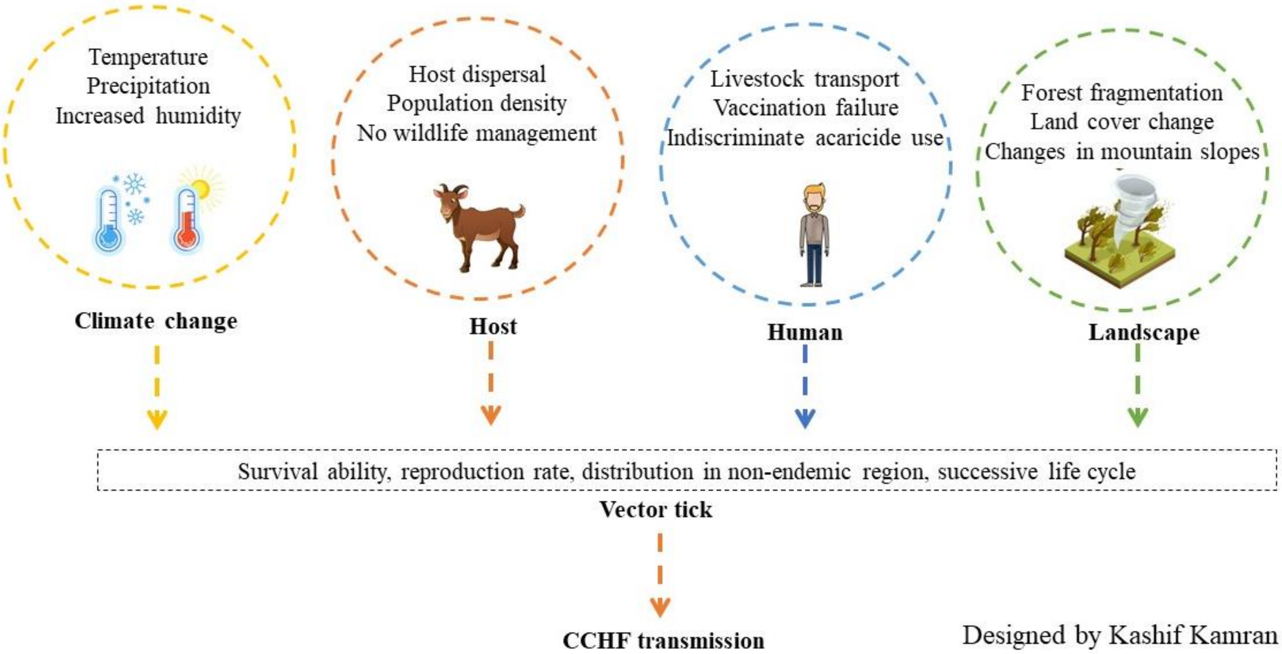

Fig. 4: The diagram highlights climate variables, host-related factors, human activities, and habitat changes as influences on tick ecology and disease transmission. The figure is created using www.biorender.com.

This disease has been considered as an emerging arboviral zoonotic diseases because of sudden climate change and increase vector bionomics (Al-Abri et al., 2017). The incidence of CCHF has recently risen in multiple countries; however, there is no accurate data on the outbreak of CCHF due to variations in surveillance systems used for CCHF. Human-to-human transmission of CCHFV has been reported in healthcare setting, often resulting in high mortality rate among health care workers. This virus is transmitted through contact with infected blood or body secretions from an infected person in hospital. The spread of this virus is more prevalent in situations where adequate personal protective measures have not been used or were unavailable during emergencies when treating patients with CCHF symptoms (Conger et al., 2015). For instance, during the pre-hemorrhagic stage, CCHFV levels in human can be extremely high (10_8-10_{10} copies/mL), putting medical professional at risk because the virus may also be present in the saliva and urine.

Healthcare workers are frequently exposed to CCHF while treating patients and numerous reports have documented fatalities among medical workers (Chinikar et al., 2013). For instance, in Balochistan province, Pakistan during 2023-2024, several healthcare workers were infected, with a number of deaths reported. CCHF outbreaks can also arise during Eid-ul Azha, a religious holiday when Muslims commonly engage in animal slaughter. During this period, people and butchers are exposed to livestock blood and tissue, which heightens the risk of transmission. No Special precaution are followed, despite government efforts to place posters and banners to convey the message to public. Furthermore, after animals are slaughtered, the remains are not properly disposed of, which contributes to the spread the CCHFV. To address this issue the role of community and local government is crucial.

4. Distribution of Claude and Genotypes of CCHF

CCHF is a trisegmented, enveloped and spherical virus with a size of approximately 90 nm. It is classified as a negative-sense RNA virus belonging to the *Orthonairovirus* genus within the *Nairoviridae* family. The tick-borne origin of CCHF was proposed after observing *Hyalomma marginatum* among volunteers and individuals with psychiatric disorders. The virus was first isolated in 1956 from a febrile teenage boy in Belgian Congo, using newborn mice, and was designated as the Congo virus strain V3011. CCHFV is classes into six clades (I to VI) and eight genotypes including Africa (I, II and III), Asia (I and II), Europe (I and II). These clades and genotypes reflect genetic diversity of CCHFV in different regions. These genetic variabilities in CCHF can affect the specificity and sensitivity of RT-PCR, as certain strains may not be detected by existing primers. Strains of CCHFV are spreading due to several reasons including unregulated wildlife trade, migratory birds, livestock import and export and extensive global human movement. In Spain, 2010 Africa 3 (genotype III) was reported in hard ticks of deer, this strain was identified in 2016 in human patient. Most probably the migratory birds from Morocco introduced this train in Spain (de Arellano et al., 2017). Further, the introduction of genotype V in Spain supports the hypothesis that this strain was introduced through the movement of livestock from Central and Eastern Europe (European Centre for Disease Prevention and Control 2024).

5. Socio-economic Impacts of CCHF

Numerous domestic animals such as small ruminants (sheep and goats), large ruminants (cattle), small mammals, rodents (rabbit) and birds (chicken) serve as reservoir of CCHFV mostly with asymptotic condition (World Health Organization 2013; Fajs et al., 2014; Bernard et al., 2022). However this virus has enzootic cycle involving ticks, these vertebrate animals and ultimately targeting the humans as dead-end hosts (Tipih & Burt 2020) (Figure 5). Several factors, including environmental variables (e.g., temperature, landscape) and socioeconomic factors (such as gender, age and occupation), can impact of the distribution and transmission of CCHF (Mertens et al., 2013). Furthermore, certain livestock-related factors, such as the grazing system and the age of farm animal can also elevate the risk of disease. For example, livestock in nomadic systems can have up to 30% probability of CCHFV infection, compared to only 4.5% in animals within stable grazing systems (Ibrahim et al., 2015). The global risk of arboviral epidemics has risen in recent years and this has driven by multiple risk factors including unplanned urbanization, progressive globalization, sudden climate change and socioeconomic inequalities in underdeveloped countries, insufficient government intervention to address these issues and low level of education (Ahmed et al., 2020; Elduma et al., 2020; Whiteman et al., 2020).

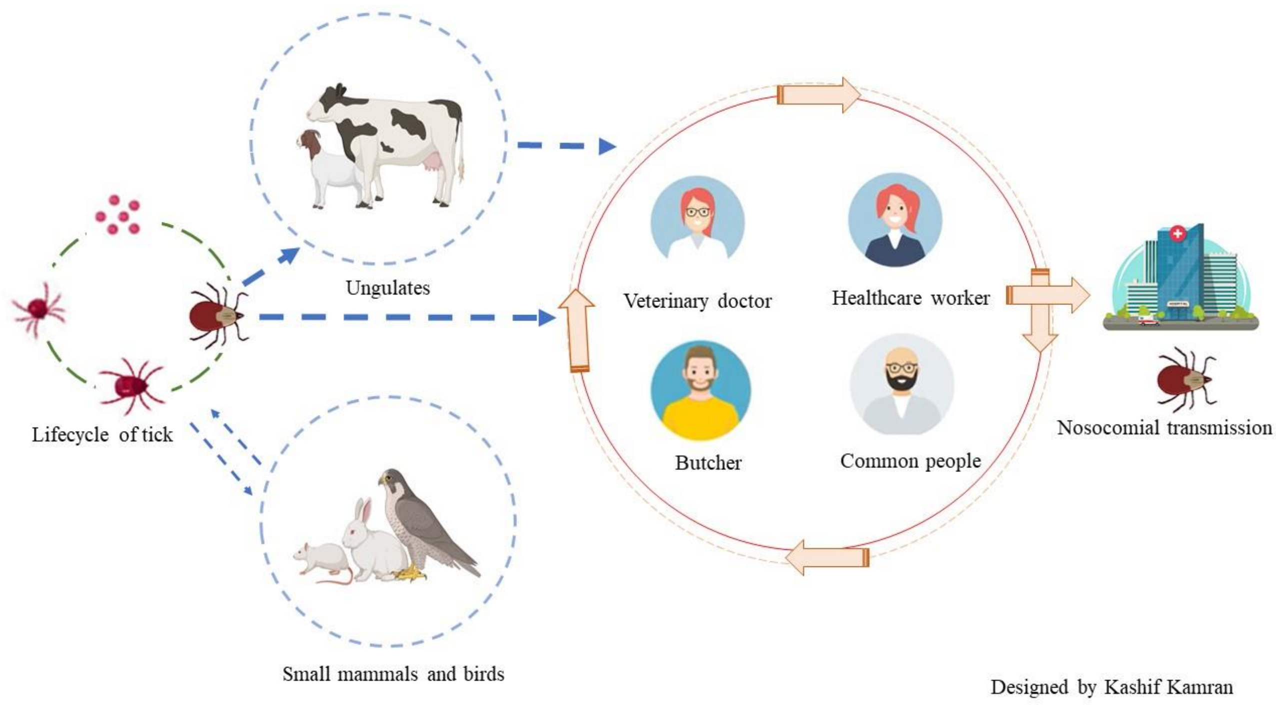

Fig. 5: This figure illustrates the interaction between human, vector (ticks) and animals in the transmission of CCHFV. Small and large animals infected by ticks are depicted within blue circle. The life cycle of ticks is represented in green, while individuals infected by hard ticks are shown in red. Arrows indicate the transmission of CCHF among different entities. Instances of nosocomial transmission, where the virus is spread in healthcare settings are depicted outside the circle. The figure is created using www.biorender.com.

In most endemic regions in Africa and Asia, livestock holders, including shepherds, farmers, ranchers, butchers, slaughter workers and abattoir workers, are at the highest risk of CCHF due to nosocomial transmission (Nabeth et al., 2004; Majeed et al., 2012). In addition, these groups are also vulnerable to contracting CCHF, including health-care workers (veterinary doctors, paramedic staff and medical professionals), agricultural and animal related workers (farmers, agricultural workers, animal husbandry workers, slaughterhouse workers, environmental agents and butchers), household and service workers (housewives and restaurant workers) and other occupations (military, leather business workers, teachers and student) (Mirembe et al., 2021).

The misperception regarding ticks and TBDs can lead to certain alarming situations where famers and healthcare workers are unable to protect themselves from tick-borne infections (TBIs) including CCHF (Ullah et al., 2024). The indiscriminate use of acaricides has also led to tick resistance including members of *Hyalomma* genus, which are major carrier of TBDs in most of the Asian countries (Kamran et al., 2021). Such acaricide resistance among ticks can pose high-risks to human health including food concerns (for example, increase in toxic residues in animal products) and certain level of food security challenges (for example, food shortage or production losses). Furthermore, agropastoral occupations, ruminant's husbandry (especially with sheep), living at an altitude ≥ 400m, slaughtering and ageing (risk markers) has been reported as risk factors (Papa et al., 2013; Sargianou et al., 2013; Papa et al., 2014; Papa et al., 2015). Individuals working in agro-pastoral or animal husbandry fields, who come into contact with fresh flesh and blood, are the highest risk of infection (Nasirian 2019). Percutaneous injuries in veterinarians are considered a risk factor for CCHFV infection (Ergönül 2006) (Figure 6). Only a few reports, such a one from Eastern Hungary near the Rumanian border, discuss how people in these areas are infected with CCHFV (Horvath 1976). Exposure to undercooked goat meat and blood, tick bite and tick crushing also transmit the CCHFV. Although, the global economic impact of CCHF has not yet been evaluated, significant direct and indirect loss associated with other TBDs has been documented in some countries. For instance, the dengue hemorrhagic fever outbreak in Brazil led to an economic loss of US$ 1,228 million in 2013 (Martelli et al., 2015). Similarly Rift Valley fever outbreak in Kenya in 2007 resulted in a loss of about US$ 32 million (Nguku et al., 2010).

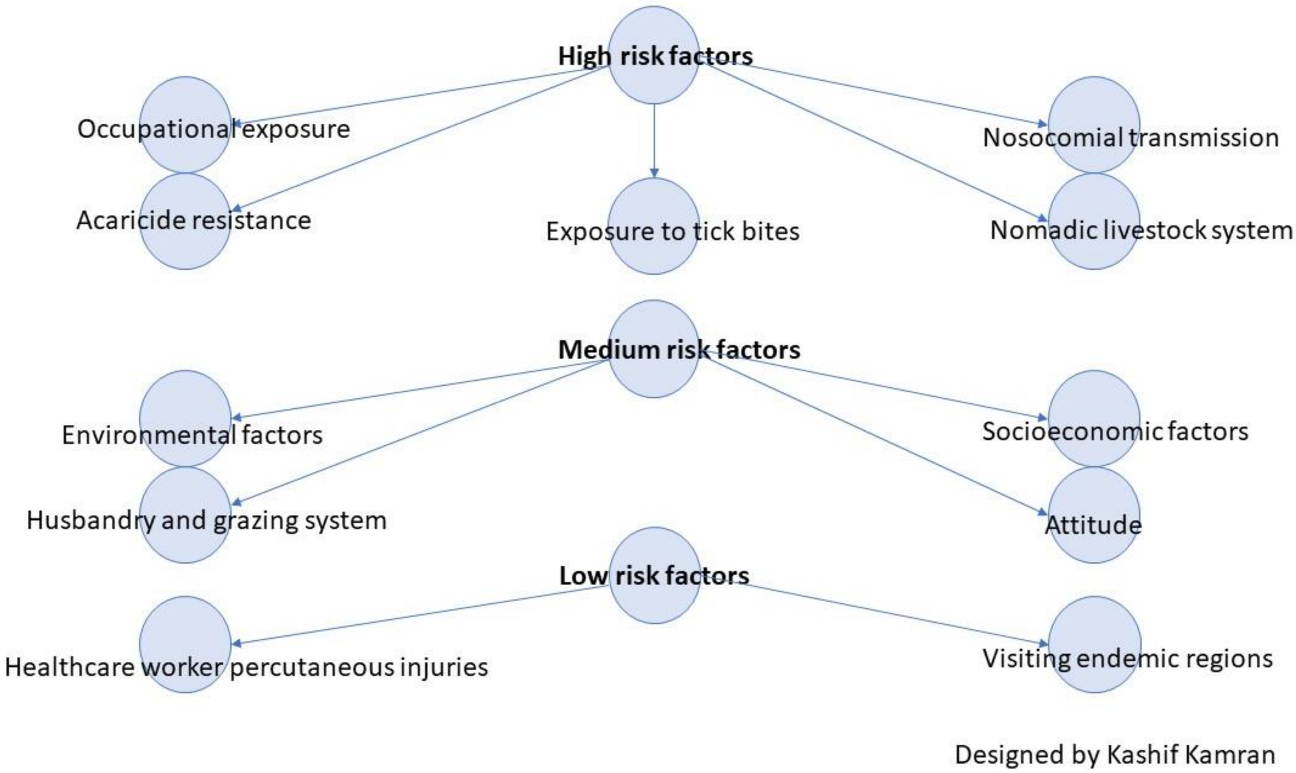

Fig. 6: Risk categorization flow chart.

7. Challenges of Cross-border Health Protection

Serological studies have been confirmed the presence of CCHF in livestock in several countries including Egypt, Somalia, and Tunisia. Afghanistan, Iran, and Pakistan (Ahmed et al., 2021; Perveen & Khan 2022). In these regions, the movement of nomadic herders with their animals is frequent and the trade of animal meat and skin is common. People who handle these animals, particularly in slaughterhouses are at significant risk of contracting CCHF, thereby posing substantial public health risks. Additionally, the migration of diverse ground feeding bird species contributes to the spread of CCHFV to vast geographic regions. These birds introduce the virus into new ecosystem along their migratory routes, further extending the potential for CCHF outbreaks. Strengthening veterinary practices could enable timely detection of CCHFV cases in animals and humans, reducing the risk of cross-border and intercontinental transmission, thereby protecting public health and ecosystems (Table 1, Figure 7).

Table 1: Major factor associated with CCHF and potential possible outcome.

Factor explanation	Current need	Source of information(s)
Species diversity of ground-feeding migratory birds associated with CCHFV	Enhanced monitoring of high-risk bird species	(Fillâtre et al., 2019)
Number of neighbouring countries that are sources of CCHFV	Improved cross-border management for early CCHFV detection	(Fanelli & Buonavoglia 2021)
Volume of live animals imported from CCHFV source countries	Decreased risk of CCHFV introduction	(Akuffo et al., 2016; Perveen & Khan 2022)
Number of CCHFV source countries that are trading partners into new continents	Reduced spread of CCHFV through trade networks	(Aslam et al., 2023)
Veterinary infrastructure in CCHFV source countries	Robust veterinary services	(Fanelli & Buonavoglia 2021; Perveen & Khan 2022)

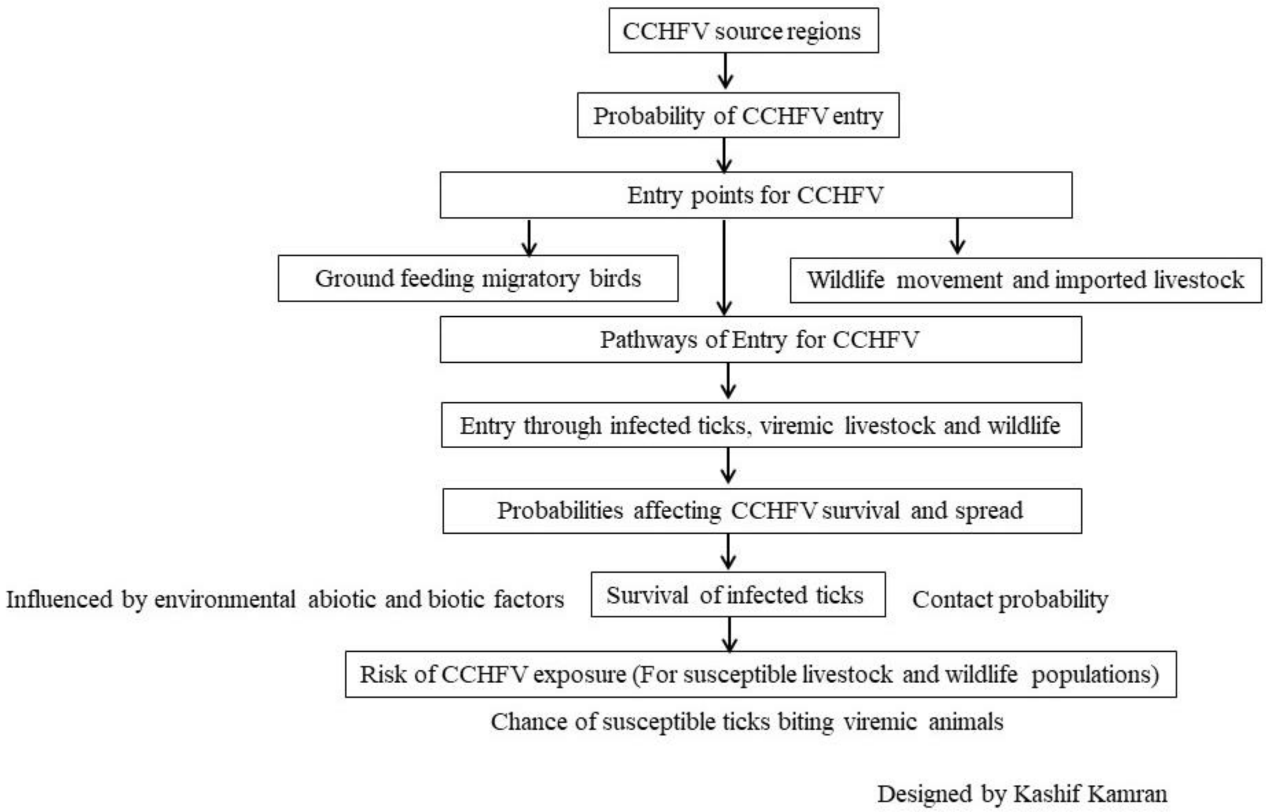

Fig. 7: A schematic flowchart illustrating the sequential steps considered in assessing the risk of CCHF spread.

In many countries, CCHFV is linked to livestock trade. However, there are cases where the virus spreads across borders between countries without official livestock trade. For instance, in neighboring countries like Pakistan and India, political factors have restricted formal livestock trade. Despite this, Pakistan have seen a progressive increase in CCHFV cases, largely due to legal and illegal movement of livestock from neighbour countries, including Iran and Afghanistan. Poor boarder management facilitates the spread of CCHFV from livestock to wild animals and local communities in Pakistan (Figure 8). India and Nepal contribute to the spread of CCHF due to the movement of sheep and cattle without proper inspection. Similarly, Turkey faces illegal cross-border livestock movement, including sheep, cattle and goat, which has led to an increase in CCHF cases due to lack of adequate veterinary checks. Neighboring countries such as Albania, Bulgaria and Kosovo also play a significant role in the spread of the disease. In Russia and Caucasus region, animals are often slaughtered or processed in formal markets without proper biosecurity measures, contributing to the CCHF outbreaks. Central Asian countries like Kazakhstan, Kyrgyzstan and Uzbekistan have seen an increase CCHF cases due to illegal ungulate trade routes that facilitate the spread of the disease. Additionally, Saudi Arabia and Yemen, both of which face sever political disputes, are experiencing frequent illegal trade of animal trade further exacerbating the situation.

8. Public Health Policies for CCHF Prevention

International collaborations with local/regional stakeholders are the key factor in controlling CCHF outbreak. In this regard, several suggestions can be adopted to control of CCHF (a) Use of personal protective equipment, it includes the use of gloves, a face shield and protective clothing or laboratory gown for individuals handling livestock, animal products or working in tick-infested areas (Fletcher et al., 2017) (b) Surveillance system, this include role of veterinary doctor to monitoring the presence of the ticks on livestock (c) Tick control strategies, this involve the use of acaricides and use of vaccine for effective control of ticks, individuals handling infested animals are required to follow these strategic approaches to control ticks (d) Public awareness campaigns: stakeholders including farmer community, veterinary doctors and government can implement educational campaigns including workshops and seminars targeting at-risk group such as the public, butchers, healthcare workers and farmers (Ahmed et al., 2021). These campaigns should focus on raising awareness about CCHF symptoms, transmission and preventive measures (Figure 9). Butchers and farmers should be given awareness session for safe handling and disposal of animal waste as well as promoting hygienic practices to minimize contact with infected blood or tissue. Ticks should not crush by bare hands because it can also infect and transmit diseases (Greiner et al., 2016; Rehman et al., 2018) (e) Enhanced surveillance programs; this includes integrating data on animal health, updates on tick population dynamics and potential zoonotic transmission pathways. A collaborative approach on cross-border surveillance with neighboring countries can also aid in monitoring and controlling tick infections animal can helping to prevent the transboundary spread of TBDs (f) Scope and limitation of surveillance system; this program should be expanded to reach rural and high-risk regions, where the access of government is often limited (g) One health approach; a multi-disciplinary approach involving the collaboration between veterinary doctors, academies, policymakers, policymakers, agriculture and animal husbandry related workers is crucial.

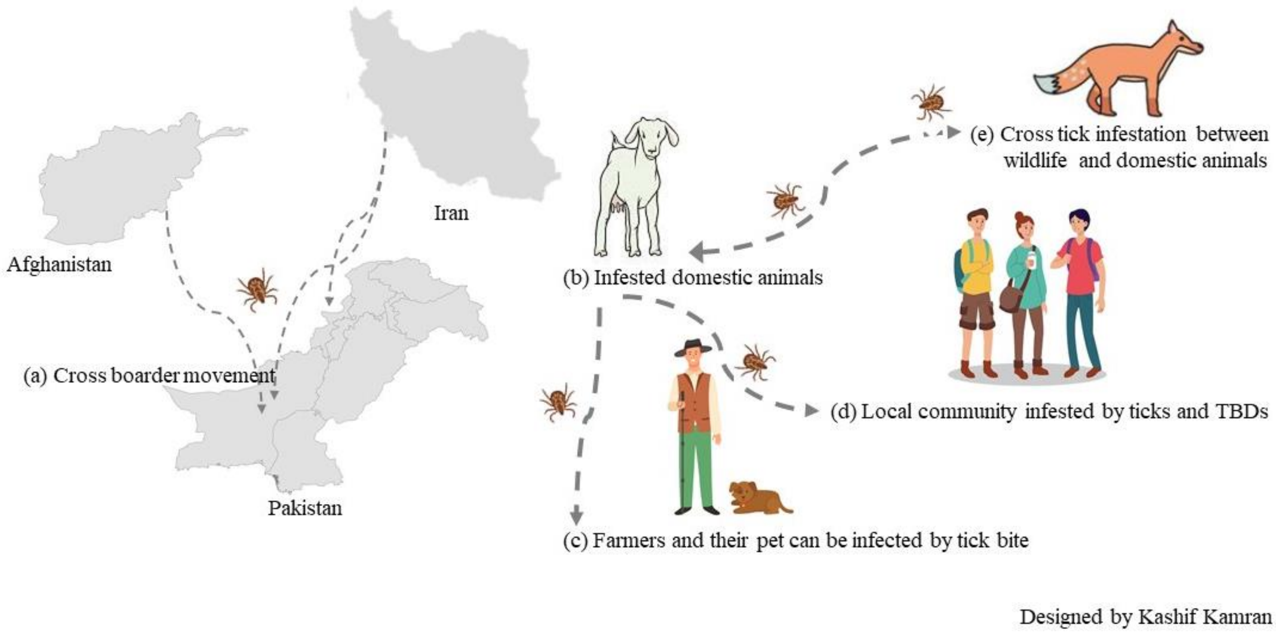

Fig. 8: Cross-broader movement illustrating Pakistan as an example. The figure on the right depicts the transmission of CCHFV from livestock to farmers, local community, and wild animals.

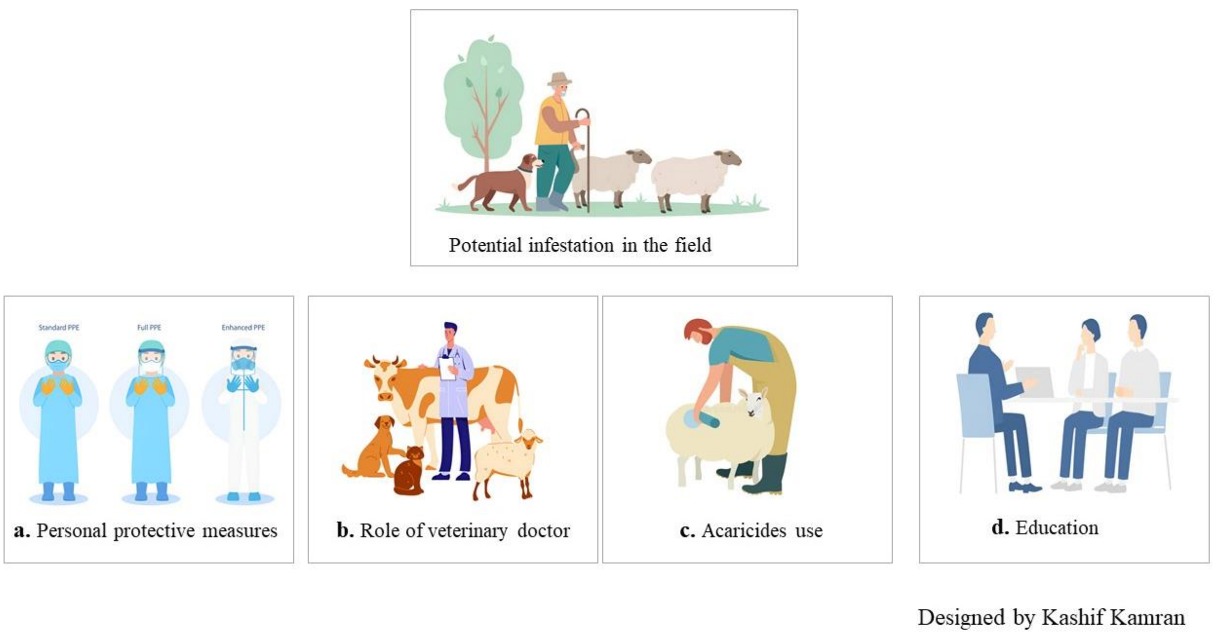

Fig. 9: Multifaceted control strategies for CCHF include the role of healthcare workers, farmers, community educators.

Conclusion

Individuals handling livestock in CCHF-endemic areas must wear personal protective equipment to minimize the exposure of virus. This includes, face shield, protective clothing, gloves and laboratory gowns. For those with high-risk exposure, administration of ribavirin, an antiviral should be considered, as it may reduce the severity of infection when given promptly. Patients diagnosed with CCHF should be admitted to high-level isolation units in hospitals to minimize the risk of accidental exposure to infected bodily fluids or contaminated materials. This approach helps prevent nosocomial (hospital-acquired) transmission, which is a significant concern in healthcare settings (de la Calle-Prieto et al., 2018). The implementation of a livestock vaccine could provide a more effective strategy to reduce viremia and consequently, the transmission of the virus to humans, ultimately preventing outbreaks. Effective boarder management is essential crucial to minimize the movement of livestock from CCHF-endemic to non-endemic countries. This can be achieved through strict monitoring and control measures including quarantine protocol for animals.

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