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Epidemiology, Transmission Dynamics, and Diagnostic Approaches of Crimean-Congo Hemorrhagic Fever Virus (CCHFV) in Animal Hosts: A One Health Perspective

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Abstract

Crimean–Congo hemorrhagic fever virus (CCHFV) is a highly pathogenic, tick-borne zoonotic virus with a wide geographical distribution across Africa, Asia, the Middle East, and parts of Europe. The virus is primarily transmitted by ticks of the genus Hyalomma, which act as both vectors and reservoirs, maintaining the virus through transstadial and transovarial transmission. This review provides a comprehensive overview of the epidemiology, transmission dynamics, and diagnostic approaches of CCHFV in animal hosts within a One Health framework. Vertebrate hosts, including livestock such as cattle, sheep, and goats, play a critical role in viral amplification by developing transient viremia without showing clinical symptoms, thereby facilitating virus transmission to feeding ticks. Wildlife species and migratory birds further contribute to the geographical spread and ecological maintenance of infected tick populations. The geographical distribution of CCHFV closely corresponds to the distribution of Hyalomma ticks, influenced by climatic conditions, ecological changes, and anthropogenic factors such as livestock movement and land use patterns. Diagnostic approaches, including serological assays (ELISA) and molecular techniques (RT-PCR), are essential for surveillance, although challenges persist due to short viremia and genetic diversity of the virus. Understanding the complex interactions among ticks, animal hosts, and environmental factors is crucial for predicting disease emergence and implementing effective control strategies. Integrated surveillance, improved diagnostic tools, and sustainable tick control measures are vital for reducing the risk of CCHFV transmission to humans. This review highlights the importance of a multidisciplinary One Health approach to better understand and manage this emerging zoonotic threat.

Keywords: CCHFV, Geographical Distribution, Serological Assays,Ticks, Control

Introduction

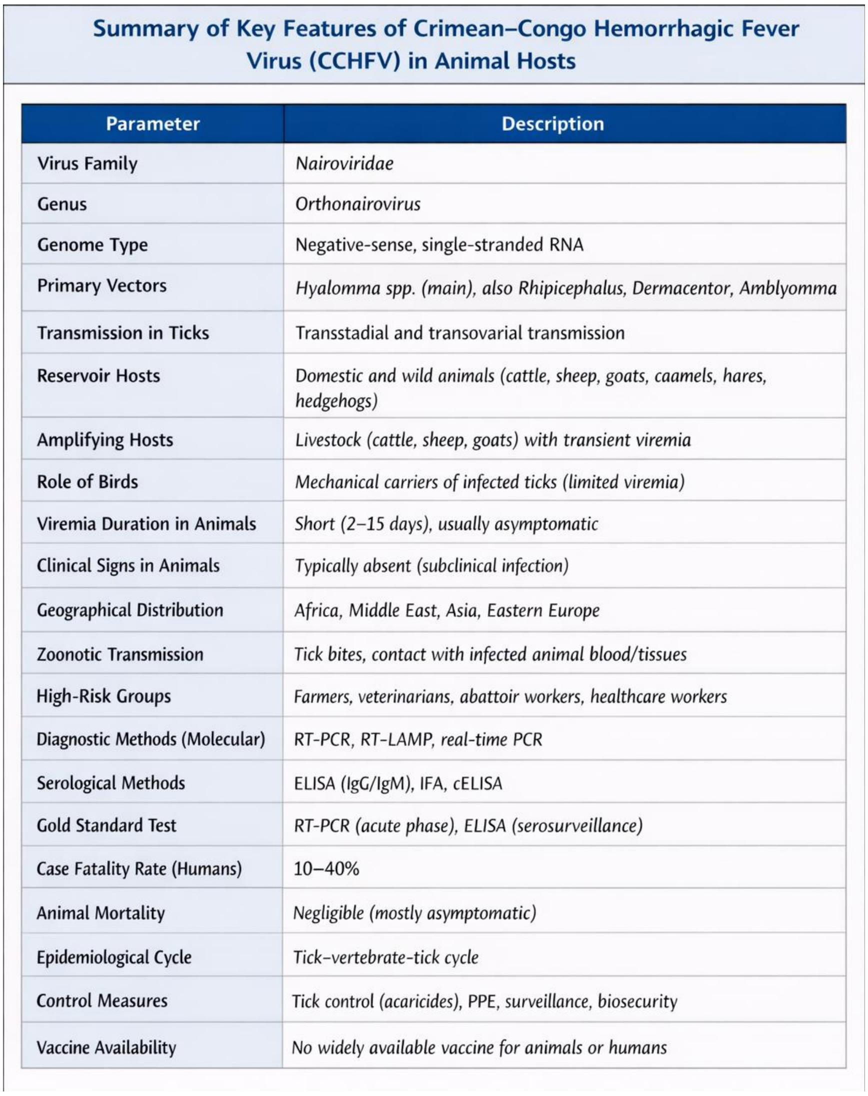
The Crimean Congo heamorrhagic virus is an arbovirus spread by arthopods belonging to the orthonairovirus genus of negative sense single stranded RNA viruses. Ticks are the main means of transmission for Nairoviridae (order Bunyavirales) [1]. There was proof of CCHFV, first found in Crimean region of former soviet union in 1944 [2]. This led to the clinical classification of CCHF as a disease during World War II. Over the following years, many more cases of infection were found in South Africa, Bulgaria, and other southern Soviet republics [3]. CCHFV was named "Crimean-Congo Hemorrhagic Fever" since the identical ailment was discovered in the Congo region in 1969 [4].

CCHFV is a global tick borne virus that spreads throughout the world and has a concerning death toll, a broad geographical distribution and allocation. Southern states have reported cases of CCHF, which were caused by CCHFV. Africa the Middle East Asia, and Eastern Europe [5]. The virus prognosis is extremely dangerous .There is a significant chance of 10-40% case fatalities [6].CCHFV spread is largely attributed to ticks belonging to the Hyalomma genus [7]. In certain regions of Middle East Central Asia and Southern Europe Hyalomma marginatum is the primary CCHFV vector [8].

Animals including cattle, goats, and sheep act as a reservoir for viral amplification, frequently exhibiting only temporary viremia [8]. Hyalomma ticks consume a range of wild herbivores, hares, hedgehogs, and some rodents in addition to domestic ruminants like cattle, sheep, and goats [9]. With the exception of humans, vertebrate animals only experience a brief viremia following infection; yet, these animals are crucial hosts for H. lusitanicum and H. marginatum ticks, and as such, they are crucial to the spread of CCHFV [10].

Adult ticks favour bigger hosts, like cattle, goats, sheep, horses, and humans, while juvenile ticks are amplified by little creatures, such as hares, hedgehogs, rodents, and terrestrial-living avians [11,12]. Numerous tick species implicated in the transmission of CCHFV can be found in ostriches that acquire measurable and persistent viremia [13]. Since they carry ticks across large geographic distances, feed on blood to sustain tick populations, and spread CCHFV to ticks and humans during viremia, vertebrates serve an essential role in the epidemiology of CCHF [13].

Effective safety measures require an understanding of the survival of virus in communities of ticks, their function as carriers, and the variables affecting dissemination of infection. Analysing CCHFV in animals, which frequently act as amplifying hosts, which sheds light on the effects of virus on veterinary well-being and possible human transmission. Furthermore, research on CCHFV in wildlife populations is crucial to comprehending its wider epidemiology.In order to provide a comprehensive resource for understanding CCHFV in animals this review collects data on vertebrate hosts and CCHFV tick vectors highlighting their roles in virus transmission (Figure 1).



Summary of Key Features of Crimean–Congo Hemorrhagic Fever Virus (CCHFV) in Animal Hosts

Parameter	Description
Virus Family	*Nairoviridae*
Genus	*Orthonairovirus*
Genome Type	Negative-sense, single-stranded RNA
Primary Vectors	*Hyalomma spp. (main), also Rhipicephalus, Dermacentor, Amblyomma*
Transmission in Ticks	Transstadial and transovarial transmission
Reservoir Hosts	*Domestic and wild animals (cattle, sheep, goats, caamels, hares, hedgehogs)*
Amplifying Hosts	*Livestock (cattle, sheep, goats) with transient viremia*
Role of Birds	*Mechanical carriers of infected ticks (limited viremia)*
Viremia Duration in Animals	*Short (2–15 days), usually asymptomatic*
Clinical Signs in Animals	*Typically absent (subclinical infection)*
Geographical Distribution	*Africa, Middle East, Asia, Eastern Europe*
Zoonotic Transmission	*Tick bites, contact with infected animal blood/tissues*
High-Risk Groups	*Farmers, veterinarians, abattoir workers, healthcare workers*
Diagnostic Methods (Molecular)	RT-PCR, RT-LAMP, *real-time* PCR
Serological Methods	ELISA (IgG/IgM), IFA, cELISA
Gold Standard Test	RT-PCR *(acute phase)*, ELISA *(serosurveillance)*
Case Fatality Rate (Humans)	10–40%
Animal Mortality	*Negligible (mostly asymptomatic)*
Epidemiological Cycle	*Tick–vertebrate-tick cycle*
Control Measures	*Tick control (acaricides), PPE, surveillance, biosecurity*
Vaccine Availability	*No widely available vaccine for animals or humans*

Figure 1: Summary of Key Features of Crimean–Congo Hemorrhagic Fever (CCHF)

Virus in Ticks

In the summer of 1944, Soviet troops reoccupying the Crimean Peninsula experienced an outbreak of a severe febrile disease marked by hemorrhage and shock, later identified as the first recorded cases of Crimean–Congo hemorrhagic fever (CCHF). Approximately 200 soldiers required hospitalization, with a case fatality rate of about 10%. An investigative response was coordinated from Moscow under the leadership of Mikhail Chumakov, who had earlier worked with Lev Zilber on elucidating the cause of tick-borne encephalitis in the Soviet Far East during the late 1930s [14].

Ticks of the genus Hyalomma, with Hyalomma marginatum as the predominant species, serve as the primary vectors of Crimean–Congo hemorrhagic fever virus (CCHFV). The capacity of adult Hyalomma ticks to transmit CCHFV was demonstrated in studies conducted during the 1960s. Subsequent isolation of the virus from field-collected eggs and unfed immature stages of H. marginatum provided definitive evidence for both transstadial transmission across developmental stages and transovarial transmission from infected females to their progeny, underscoring the role of Hyalomma ticks in the long-term maintenance of CCHFV in nature [15].

In 1956, a patient presenting with an acute febrile illness in the Belgian Congo was found to be infected with a virus antigenically indistinguishable from the Congo virus. Subsequent comparative studies revealed that viral strains isolated from Africa, Eurasia, and Asia shared a common antigenic profile with the agent responsible for Crimean hemorrhagic fever. On this basis, the virus was initially designated as the Crimean hemorrhagic fever–Congo virus and was later renamed Crimean Congo hemorrhagic fever virus (CCHFV) [15].

About 900 tick species have been recognized and categorized taxonomically worldwide. There are 223 known species of ticks in Africa alone, including 43 argasid (soft) and 180 ixodid (hard) ticks. H.marginatum is the most common and plentiful of them, and it is now known to be the main vector of the CCHFV [16].

Research indicates that Zgurskaya et al. Zeller and colleagues 1971. 1994 Lee and Kemp 1970) CCHFV infection endures throughout the ticks life cycle without known harm to the tick it can survive both vertically and transstadially in its vector species staying in the tick for the duration of life phases and passing on to the following tick generation. The percentage of infected eggs the frequency of bloodstream transmission and the number of generations the virus survives in the tick population are all unknown. Ticks allow CCHFV to overwinter because they can go for extended periods of time without feeding. Therefore even in the absence of vertebrate hosts CCFHV tick vectors function as infection reservoirs [17].

It is known that H.marginatum can spread the dangerous infectious zoonosis known as CCHF. The north could be affected. Because migratory birds that travel to temperate Europe frequently contain immature stages the establishment of permanent populations is crucial. CCHF is also found in some regions of Africa Asia the Middle East and southeast Europe is caused by H.marginatum [18]. There is currently no proof that this disease is moving farther north, although the largest known epidemic began in Turkey in 2002 and is still running strong [19].

Originating in western China and South Asia, Crimean–Congo hemorrhagic fever virus (CCHFV) has expanded its range across the Middle East, southeastern Europe, and much of Africa. A substantial part of the Mediterranean basin lies within the historical distribution of its principal vector, Hyalomma marginatum, extending across southern Europe, southern Russia, Ukraine, and the Balkan region. H.marginatum's possible geographic distribution may have grown both inside and outside of the Mediterranean basin. The current study used ecological niche modeling to reevaluate the distribution of this primary vector throughout the Old World, taking into account a number of environmental factors and occurrence records from the Global Biodiversity Information Facility [20].

An increase in H.marginatum populations is associated with anthropogenic ecological alterations, and favourable weather conditions lead to a quick increase in H. marginatum populations, which in turn causes sharp increases in CCHFV circulation. Beyond transmission by tick vectors, CCHFV may also spread through direct human contact, particularly during the acute phase of infection, as well as through exposure to the blood, tissues, or bodily fluids of infected animals. Such routes of transmission pose a significant risk to healthcare workers, livestock handlers, and individuals involved in animal slaughter or processing. Hyalomma are thought to be the main carriers of the CCHFV, which infects both people and a variety of domestic and wild animals. Furthermore, Ixodidae ticks are essential to the virus's survival in its natural enzootic cycles [21].

The survival of infected ticks and Hyalomma species that have gone at least eight hundred days without feeding highlights the crucial roles ticks play in the spread of CCHFV. Its importance from others should not be overlooked even though the genus Hyalomma species are crucial to the epidemiology of CCHF as well as primarily in charge of maintaining CCHFV in the field. CCHFV geographic dispensation is very similar to the Hyalomma species indicating that many of these species are naturally involved in CCHFV circulation. This virus has been identified and reported from species of other genera but there is currently no proof that non-Hyalomma tick species actively circulate the virus during natural transmission cycles.

The field epidemiology revealed that a few additional species belonging to the genera Amblyomma ,Dermacentor ,Haemaphysalis and Rhipicephalus harbored CCHFV [22].In Iran, a total of 26 species of argasid and ixodid ticks have been documented, including two Rhipicephalus, two Dermacentor, five Haemaphysalis, two Boophilus, one Ixodes, two Argas, and three Ornithodoros species. These ticks, which are hematophagous ectoparasites of livestock and poultry, play an important role in animal health and vector-borne disease ecology [23].

There are 61 species in nine genera that are either indigenous or established in Brazil: Argas (1 species), Antricola (3 species), Carios (10 species), Ornithodoros (3 species), Amblyomma (30 species), Dermacentor (1 species), Haemaphysalis (3 species), Ixodes (8 species), and Rhipicephalus (2 species) [24]. Furthermore 20 tick species were identified that may be linked to the spread of CCHFV by analysing 57 research that were published between 1978 and 2021 [25].

This diverse collection of tick species emphasises how many ticks may play a part in the virus's maintenance and dissemination throughout different geographic areas and host ecosystems.

A successful assay for the molecular detection of CCHFV was created using isothermal recombinase polymerase amplification (RPA). The assay demonstrated excellent target specificity and quick (less than ten minutes) detection of viral extracts and synthesized virus RNA from all seven S-segment clades of CCHFV. Using a panel of clinical samples from Tajikistan the CCHFV RPA (Recombinase polymerase amplification test) was successfully used to screen and identify CCHFV positives (26). ELISA and RT-PCR tests revealed that 3. 4% of tick pools from the Rudaki district contained CCHF viral antigen and RNA [27]. Tick samples were analyzed for CCHFV antigens using commercial antigen enzyme-linked immunosorbent assay (ELISA) test kits (VectoCrimea-CHF-antigen ELISA test kit Vector-Best Novosibirsk Russia) [28].

In addition, the prevalence of Crimean–Congo hemorrhagic fever virus (CCHFV) in ticks collected from endemic regions of central and southeastern Bulgaria was evaluated using both a conventional immunological approach,the immunofluorescence hemocyte assay (IFHA) and a modern molecular method, reverse transcription–polymerase chain reaction. RT-PCR was used in five distinct regions of Côte dIvoire to detect CCHFV using particular primers and probes [29].

An ecological niche modeling method was used to identify the primary vector of CCHFV.H. marginatum is found all over the Old World but it is concentrated in Europe and Central Europe. Hyalomma are thought to be the primary carriers of CCHFV in the wild because the virus has been found or isolated from more than 30 species [30]. Hyalomma truncatum had a greater prevalence (1.6%) of CCHFV RNA than the other species [31]. At least 33 tick species have been linked to CCHFV either as maintenance hosts or directly involved in transmission suggesting that the (Ixodidae) family is the most prevalent carrier of the virus.

H.marginatum, H.detritum, R.bursa and B.annulatus have been found to carry the virus in Turkeys CCHFV-affected zones according to tick surveys. Additionally recent research has linked Northern Anatolia to other tick species [32]. Additionally, Dermacentor species have been shown to harbour CCHFV, which may potentially spread the virus.

It has been documented that 25 tick species and subspecies serve as vectors and reservoirs for the CCHF virus. R.annulatus,R.microplus, and R. decoloratus and most likely R.geigyi are one-host ticks that infest cattle for weeks or months at a time and seem to maintain a high level of virus contact between various tick species.

H.marginatum, H.turanicum, H.rufipes, H.anatolicum, H.detritum and R.bursa are the two-host vectors that consume both adult and immature cattle. Additionally there are 13 species of 3-host ticks including two species of Dermacentor. Hyalomma (5 species). Rhipicephalus (4 spp.) Haemaphysalis punctata and Amblyomma variegatum. These species primary function is to maintain enzootic foci of CCHF virus transmission between domestic and wild mammals and ticks and they generally behave less aggressively when looking for human hosts than the hyalomma previously described [33]. Moreover none of the following species had CCHFV RNA: Rh. Sanguineus,D. reticulatus ,H. Aegyptium , H. anatolicum, (nymphs and larvae) Ha. Eranacei Ha. Inermis , Ha punctate, I Sulcata,I.Hexagonus, or I. Laguri. A Ricinus [30].

Although many tick species have been found to carry CCHFV only a few have been shown to be both vectors and reservoirs of the virus. This is primarily because most published research has been carried out in a variety of settings making final characterization impossible. While argasid ticks can go through nine nymphal stages in addition to larval and adult stages ixodid ticks only go through three active stages of development: larva nymph and adult.

Most Argasidae only nourish for 20 to 70 minutes at a time, however Ixodidae can live for days or even weeks. The circulation of numerous microorganisms is significantly impacted by these drastically divergent life cycles, as the two families' capacities to sustain active pathogen foci are obviously distinct [34].

The investigated possibility that the CCHFV could be spread by H.impeltatum explained Schulze and Schlottke. After eating mice that had contracted the CCHF virus at one day of age larval H.impeltatum. After contracting the virus,H. impeltatum used transstadial transmission to infect nymph as well as virus is spread transtadially to adults and horizontally to guinea pigs by these nymphs. The virus needs at least 13% of adult H.impeltatum to spread that bit guinea pigs after being exposed to it as larvae. The CCHF viral antigen was found in 63% of the adult ticks produced from those exposed to the virus as larvae using an enzyme linked immunosorbent assay.These tick species should be considered as a potential vector for CCHF virus [35].

Three tick species H.marginatum,H.rufipes,Amblyomma variegatum and H.truncatum that have been linked to the upkeep and spread of the CCHF virus. These species had an intracoelomic infection. The findings demonstrated that 100% of patients had H.truncatum and H.marginatum infections 15 days after injection. About 60% of A.variegatum cases occur. H.marginatum and Hyalomma truncatum both showed significant transovarial transmission (53 and 50 percent respectively). A.variegatum has a rate of about 12%. For the three species under investigation tick infections do not last past the first generation.

Although they are not permanent viral reservoirs ticks are transient carriers of the CCHF virus [36]. The requirement for a high-containment laboratory (BSL4) to handle CCHFV adds another level of complexity. Numerous prior investigations have successfully recreated CCHFV transmission from tick to tick, vertebrate to tick, and tick to vertebrate in a laboratory context [37]. The distributional map of the primary vector of CCHFV was updated in this work. H.marginatum using an ecological niche modeling method based on occurrence records from the GBIF and a number of variables throughout the Old World. Higher suitability for H. marginatum was indicated by the model.H. marginatum can be found in many parts of Asia and Africa.This model was also used to determine the environmental appropriateness of H.marginatum throughout Europe. As far north as the southern Scandinavian countries the model predicted a broad potential dispersion that would encompass the southern western central and eastern parts of Europe. Additionally the distribution included the nations of Central Europe where H.marginatum is not indigenous [18].

Vector competence refers to an arthropod's natural capacity to obtain, retain, and spread microbiological agents. A tick-borne virus can infect a competent vector by nursing on an infected host even if viremia is provisional or imperceptible [34]. Tick surveillance of CCHFV may provide valuable insights for tracking introduction or circulation, estimating human exposure risk, identifying the natural host, and predicting future CCHV outbreaks [38]. Dot ticks were employed as sentinels to detect CCHFV RNA. Combining data from feeding and questing ticks is useful for detecting viruses across large geographic regions [39]. In addition to gathering information on disease epidemiology this surveillance is critical for comprehending the function of CCHFV vectors in veterinary and public health. Figure 2 shows the geographical distribution of CCHF virus in ticks in world.

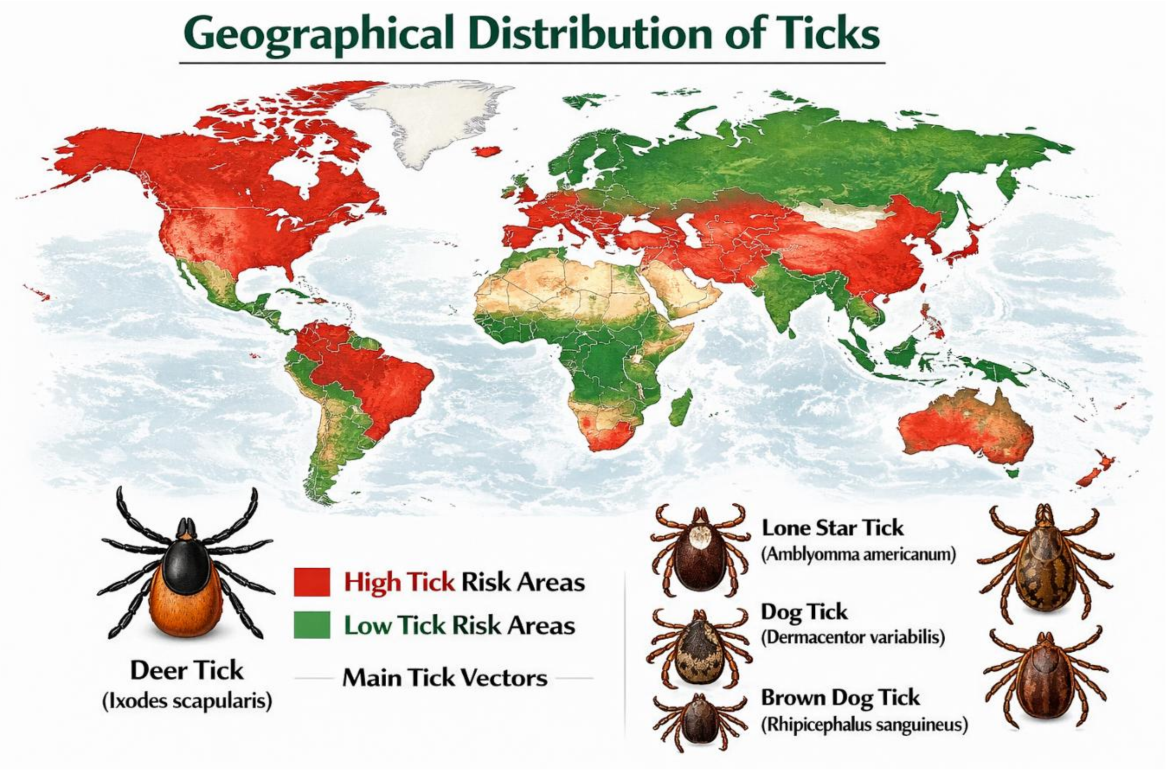


Figure 2: Geographical Distribution of CCHF Vectors Ticks with Respect to High and Low Risk Areas in World

Serological Surveillance and Diagnostic Approaches for Crimean Congo Hemorrhagic Fever Virus in Animal Hosts

Serological detection of CCHFV in animals yields critical insights into virus's ecological dynamics while preserving the same scientific meaning. Most vertebrate hosts have a brief viremia phase that lasts between two and seven days, however these hosts help the virus travel from tick to tick and amplify it [40]. Vertebrate hosts, with the exception of humans, usually do not exhibit any symptoms after contracting the CCHFV, even though they go through a brief viremic phase that lasts less than 14 days.

Keeping an eye on active CCHF infections in livestock and other sentinel animal populations is extremely difficult due to the brief infection window and lack of clinical symptoms [41].It is challenging to assess the precise involvement of CCHFV in viral replication since direct detection of the virus in field-collected samples is still limited due to the low levels of viremia in animals. As a result, the majority of field research uses serological testing, which is very useful for early detection and for shedding light on the dynamics of transmission [42].

Laboratory techniques for detecting CCHF include reverse transcription–polymerase chain reaction (RT-PCR), immunofluorescence assays (IFA), antibody detection (IgG and IgM), antigen-capture ELISA, and virus isolation.

The primary method for diagnosing people suspected of having CCHF is RT-PCR assays because they offer the highest detection sensitivity to active infection at the earliest time point. The high variability and in situ evolution of CCHFV may make lineage recognition difficult especially for RT-PCR methods that depend on a conserved genomic sequence for detection. Small genetic changes have less of an impact on serological detection.Nucleic acid amplification tests (NAAT like RT-PCR) should be used in conjunction with immunological assays for maximum detection sensitivity because CCHFV strains differ [43].

Techniques commonly employed for CCHFV serosurveillance include reverse passive hemagglutination inhibition (RPHI), immunodiffusion assays such as agar gel diffusion precipitation (AGDP), complement fixation (CF) assays, indirect immunofluorescence assays (IFA), indirect and sandwich enzyme-linked immunosorbent assays (ELISA), and competitive ELISA (cELISA).

Serological detection techniques have generally become more advanced over time. Because ELISA methods are more sensitive specific quick and repeatable than CF, IFA, RPHI or AGDP, it has been demonstrated that they can detect traces of infectious viruses or inactivated antigen and antibodies to CCHFV. ELISAs are usually considered the recommended method for serological analysis of CCHFV. However some species cannot be sufficiently screened using sandwich ELISA techniques requiring additional testing innovations such as a CELISA that was validated following a comprehensive CCHFV serological survey in South Africa. Notably species-specific validation of ELISAs has been accomplished Qing et al. assessed a technique for detecting IgG in sheep serum using recombinant nucleoproteins whereas created an ELISA with 98% diagnostic sensitivity and specificity for CCHFV IgG antibodies in bovine sera [44].

Immunological assays most commonly the ELISA using whole viral antigen are widely used for animal serosurveillance. However because of the high risk of biohazard only biosafety level 4 facilities are able to synthesize the entire viral antigen. Using the recombinant nucleoprotein (NP) of the CCHF virus as an antigen the current study creates and assesses an IgG indirect enzyme-linked immunosorbent assay (iELISA) that is safe sensitive and specific. To create clone and express the codon-optimized NP gene sequence the pET28a+ vector was utilized. Following homogeneous separation by affinity chromatography Western blotting and MALDI-TOF/MS analysis were used to characterize the recombinant NP [45].

According to WHO estimates the highly deadly new Orthonairovirus known as the CCHFV which is spread by ticks could infect up to three billion people. The closely related Hazara virus (HAZV) has not been identified as a human disease despite belonging to the same serogroup. The nucleocapsid proteins (NP) of CCHFV and HAZV have been reported to exhibit notable structural and immunological similarities across multiple species, with studies showing cross-reactive humoral responses and Western blot reactivity, suggesting that HAZV could serve as a surrogate model for CCHFV [46].

We demonstrate that the humoral immune response to HAZV and CCHFV anti-nucleocapsid protein (NP) is cross-reactive in a range of species [47]. Immunofluorescence and immunoblot tests showed a mild cross-reaction between HAZV and CCHFV in the sera of immunised animals, but not in commercial CCHFV ELISAs, which are frequently employed in field studies, likewise , a commercial species-adapted immunofluorescence assay based on cells that express the CCHFV glycoprotein has previously shown positive results for DUGV seropositive samples [48,49]. Commercial CCHFV ELISAs did not detect sera, but immunofluorescence and immunoblot experiments revealed cross-reactivities [50]. Serological differentiation in Nigerian cattle was hindered by cross-reactions between Dugbe and CCHFV antibodies [51]. The prevalence and distribution of CCHFV might be somewhat overstated in areas where DUGV is also common [51]. Thus, in regions with HAZV and DUGV, the prevalence of CCHFV may be exaggerated.

The PRNT (plaque reduction neutralisation test), mVNT (micro virus neutralisation test), and iIFA (immunolateral flow assay) have lower specificities than the ELISAs. It was intriguing to find that HAZV antibodies in PRNT also neutralized NSDV and DUGV despite the fact that cross-reactivities were mostly seen within the Nairobi sheep disease serogroup. Finally we suggest using mVNTs and ELISAs as a discriminative diagnostic method to distinguish between these antibodies. In order to detect antibodies against the human pathogen Crimean-Congo hemorrhagic fever orthonairovirus (CCHFV) NSDV antisera were also employed in serological testing. Oddly all CCHFV ELISAs—commercial and internal—achieved good diagnostic specificities despite a CCHFV iIFA showing notable cross-reactivities. Previous studies of the DUGV and HAZV antisera produced similar findings [52].

IgG ELISA, which has demonstrated exceptional sensitivity and specificity, is the most popular technique for identifying CCHFV antibodies. A neutralizing antibody is a trustworthy indicator of protective immunity against the CCHFV and the viral neutralization assay is the gold standard sero-diagnostic test for assessing the antibody response to infection and vaccination of a variety of viruses linked to human diseases. However PRNT entails working with live CCHFV under biosafety level 4 (BSL-4) containment which is only available in a few labs and IgG ELISAs usually use antigens derived from inactivated viruses that are propagated in the cells or brain tissues of nursing mice. Therefore basic serological research on the CCHFV has been severely hampered by biosafety restrictions. The creation and validation of novel serological tests was given top priority in the World Health Organizations 2019 WHO RandD Blueprint: Priority Diagnostics for CCHF paper [53]. The endemicity or non-endemicity of the region determines the level of confinement.

In the study, a recombinant glycoprotein (rGP) and a VSV-based pseudovirus expressing the CCHFV glycoprotein (rVSV/CCHFV) were employed in a BSL-2 laboratory to develop two antibody detection methods: an ELISA and a surrogate virus neutralization test (sPVNT). These approaches provide a practical, safe, and cost-effective alternative for serological detection of viral hemorrhagic fevers, enabling the assessment of serum samples and inhibitors under BSL-2 conditions. Testing a large number of serum samples assessing the antibody response to vaccination and even investigating the relationship between IgG and the neutralizing antibody can all be done with useful accessible substitutes for serological detections [53].

CCHFV in Domestic Animals

Unidentified enzootic tick-vertebrate-tick cycles are typically how CCHFV spreads in the wild. Numerous vertebrate species have been found to exhibit asymptomatic CCHFV infection which seems to be common in both domestic and wild animals. The identification of CCHFV foci increased risk of human infection and early signs of circulating virus have all benefited from the detection of CCHFV antibodies in domestic animals. International research has concentrated on a number of domestic animal species such as cattle sheep goats horses pigs dogs and chickens. Research has also been done on buffalo camels and ostriches among other domestic animals [54].

CCHFV can cause an acute potentially fatal illness in humans but it is asymptomatic in animals. The enzootic tick, non-human vertebrate, tick sylvatic cycle is how CCHFV is spread in the wild. CCHFV a zoonotic agent transmitted by ticks is maintained by an enzootic vertebrate-tick-vertebrate cycle. In non-human vertebrate hosts maintenance is mostly silent because no clinical symptoms appear [55].

Serological assays for CCHF antibodies must be made more sensitive in order to gather more precise survey data and ascertain whether CCHF virus strains differ significantly from one another. The presence of antibodies to the virus in ticks and vertebrate tissues can be detected using the fluorescent antibody technique (FAT) however the dynamics of the virus in ticks have not been studied. Research on the indirect FAT is crucial because of epidemiological surveys.

Serological assessments have demonstrated elevated antibody prevalence against CCHFV in domestic animals, including bovines, ovines, caprines, equines, camels, and others, particularly in regions where the virus is endemic.This implies that the epidemiology of CCHF is significantly influenced by these animals.

By encouraging tick reproduction and facilitating tick migration over large areas, these organisms aid in the virus's spread.Cattle and camels had the highest CCHFV seroprevalence in Mauritania, with small ruminants coming in second. The seroprevalence in cattle samples was 68.66%. camels (81%) [56]. During the 1975–1999 survey for CCHF, 32.6% of the sheep population in Kosovo and 25–80% of the sheep population in Iran's Shargi area were found to be seropositive [57].The virus enters other ticks through a bridge known as brief viremia in vertebrate tick hosts. Through co-feeding, which occurs when uninfected ticks feed near infected ticks on non-viremic hosts, CCHFV can also infect ticks [55].

Ticks can transmit CCHFV infrequently by feeding together on a parasitic host [58]. It's possible that livestock movement contributes significantly to the spread of CCHFV and infected ticks [59]. The protracted feeding period of ixodid ticks may further contribute to the spread of CCHFV-infected ticks through long-distance cattle migration [34]. The intricacy of the control measures may be explained by the poorly managed farms, the unchecked movements of domestic animals, the prevalence of wild animals, and the lack of a suitable framework to account for the ecological adaptability of some ticks [60]. The unchecked migration of domestic animals into tick-naive areas is clearly the cause of tick transmission, but it is unclear why these animals have adapted so quickly to the conditions of the local climate [60]. The CCHFV virus is endemic in various parts of Baluchistan, Pakistan, where ticks and suitable vertebrate hosts are present and maintain close contact with people. The majority of people's primary source of employment and income is livestock farming. Rangelands that are unable to support vegetation year-round make up 93% of the province's land area.In order to find food and water for themselves as well as their flocks of sheep and cattle, nomadic populations migrate intermittently to sections of Baluchistan province and surrounding regions of Afghanistan with their animals. Throughout their migratory routes, these animals may act as disease carriers or harbour ticks infected with CCHFV, making them a significant source of transmission.

There is evidence that CCHF infections typically occur in hotter regions where land farming is prevalent, which serves as a warning about the impact of ticks. Numerous cases have been documented from regions with a rise in animal husbandry, where farmers frequently interact with livestock. In endemic regions, sick livestock that noticeably show no symptoms could probably act as virus reservoirs [57]. The incidence of CCHFV antibodies in animals varies according to breed and age, indicating varying exposure and susceptibility levels. The virus was originate in roughly 15% of sheep and goats but it was much more prevalent in camels (81%) and cattle (69%).

Compared to small ruminants cattle and camels were typically two to four times older. Its interesting to note that seroprevalence and animal age were strongly correlated in all species meaning that older animals had significantly higher seroprevalence rates than younger ones. Female animals as well as adult and teenage animals had higher seropositivity than newborn animals. Older animals (OR: 3. 1 CI: 2. 4–4. 3) and juveniles (OR: 2. 0 95 percent CI: 1. 4–2. 9) had a significantly higher IgG seroprevalence than newborns [61]. Moreover, a cross-sectional seroprevalence study was conducted in southeast Bulgaria to find out more about the spread of CCHF in livestock. The study was conducted in two rural farming communities in southeast Bulgaria Topolitsa and Karageorgievo. Both villages are located in the municipality of Aytos approximately 30 kilometers from District Burgas. The prevalence of CCHF in humans is highest in this region. According to our studys findings IgG antibodies against CCHFV were present in 72% of the animals we looked at (282/392). 60% of goats 50% of donkeys 74% of sheep and 71% of cattle have CCHFV antibodies.

According to the chronological age distribution of the animals examined nearly half of them had serologic evidence of CCHF infection by the time they were one year old and more than 80% had the illness by the time they were three years old [62]. The prevalence of antibodies rose with age. The age groupings of the positive samples and the negative samples did not significantly differ, according to statistical studies. Three out of twenty-three (13%) and eight out of nineteen (42.1%) dairy cattle in Boroujen and Lordegan respectively in the Chaharmahal Bakhtiari region of central Iran had serological evidence of CCHFV infection. Six out of 29 (20.7%) dairy cattle in Sarakhs six out of 107 (5.6%) in Mashad and ten out of 52 (19.2%) in Torbat-Heydariyeh (northeast) in the cities of Razavi Khorasan province tested positive for CCHFV. The only city in Southern Khorasan (east Iran) to be tested for CCHFV antibodies was Birjand where 3.3% of 60 samples showed positive dairy animals [63]. Only three independent risk factors were statistically significant in the final models of cattle with CCHFV seropositive status. The age of the animal and the CCHFV infection rate differed noticeably. The calves began to develop CCHF after they were two years old according to data evaluating age as a risk factor.

The animals are typically allowed to graze on the field at this age where they may come into contact with an infected tick and contract CCHFV. We believe that the correlation between CCHFV infection rate and age is most likely due to older cattles frequent exposure to infected ticks in the pasture. Young calves, on the other hand, are typically housed indoors and are protected from infectious diseases, especially those spread by ticks, by their owners [64].

The frequency of CCHFV infection varied significantly depending on the animal’s breed. Due to their increased susceptibility to tick infestation and subsequent CCHFV infection, cross breeds with a high percentage of exotic blood had the highest infection rate. In contrast, native breeds were less susceptible to the disease than crossbreeds because they are more resilient to tick infestation.

Furthermore, there was a notable variation in the amount of ticks per animal and the illness infection rate. Since CCHF is known to be a zoonotic disease spread by ticks, cattle with high tick infestations are at risk of contracting CCHFV from tick bites [64]. Longitudinal studies have shown that animals with tick infestations and antibodies may be vulnerable to reinfection. In animals that contracted the virus naturally, anti-CCHFV IgM antibodies were found to last for one to two months [54].

Although only humans can contract CCHFV, livestock and wild animals have been shown to experience asymptomatic transitory viremia that can last up to 15 days [65]. Numerous vertebrate animal species have been reported to experience asymptomatic viremia that lasts seven to fifteen days and CCHFV has been isolated from small mammals and livestock [44]. When bitten by an infected tick, livestock contract the virus and have a brief, asymptomatic viraemia that lasts seven to fifteen days.Even when domestic animals get a temporary viraemia (7–15 days), they typically don’t show any symptoms [66].

Cattle, sheep, goats, camels, and buffalo were among the domestic animals from which serological evidence was frequently recorded [67]. Numerous wild species and domestic species, including horses, donkeys, sheep, goats, cattle, pigs, and dogs, have been found to have antibodies against the virus without exhibiting overt symptoms of illness [68]. The prevalence of CCHF virus (CCHFV) infection was 70. 3% (45/64) 57. 1 %(8/14) 22. 1 %(30/136) 18.2 %(2/11) 17. 2 %(5/29) and 6. 9 %(2/29) among horses cattle sheep dogs donkeys and goats in that order [69]. The primary carriers of CCHF Hyalomma and Rhipicephalus ticks are crucial to the diseases epidemiology because cattle and buffaloes serve as their definitive hosts [70]. The IDvet multispecies double-antigen IgG enzyme-linked immunosorbent test (ELISA) was used to analyze the serum of 139 cattle and 191 buffalo.

Cattle and buffalo had significantly lower seroprevalences of Crimean Congo hemorrhagic fever virus (CCHFV) (28. 1 percent and 75. 3 percent respectively p 0. 001) [71]. We determined that the prevalence of CCHFV was 75. 3 percent (95 percent CI: 68. 65-81. 32) and 28. 1 percent (95 percent CI: 20. 77-36. 30) in 191 buffalo and 139 cattle samples respectively [72]. The likelihood of tick-borne pathogen transmission is decreased since buffaloes’ larger hides naturally resist tick infestation. Additionally, their habitual practice of wallowing in dirt shields them against tick bites [70]. Even though they do not exhibit any clinical symptoms, cattle and buffaloes can contract the CCHF virus and infect humans. Cattle have a greater prevalence of CCHF (9.92%) than buffaloes (5.84%) [73]. Buffalo had a significantly higher prevalence of the Crimean Congo hemorrhagic fever virus (CCHFV) than cattle (75. 3 percent versus 28. 1 percent respectively p0. 001).

In closed wildlife-only systems buffalo had the highest seroprevalence (92. 1%) while comparable prevalences in closed-integrated and open-integrated systems were 28. 8% and 46. 1% respectively. When comparing cattle to buffalo in both closed-integrated and open-integrated systems to those that only included wildlife the regression coefficients were all negative. Cattle are a bridge species or superspreader host for CCHFV because of their ecological overlap with buffalo which raises the possibility of human transmission [72].

Serological evidence supports natural exposure to the virus even though the role of equids in CCHFV maintenance and transmission is unclear (Spengler et al. and 2016). Both horses and donkeys were used in experimental infection studies to look into the possibility of producing antibodies for possible antibody-based treatments for humans [74]. Compared to rats (6.5%, 6/93) and humans (5.9%, 29/493), livestock exhibited a significantly higher CCHFV seropositivity (11.9%, 113/951) ($p = 0.001$).

Donkeys had the greatest seropositivity rate (31.4%, 16/51), followed by goats (8.1%, 24/295), sheep (9.8%, 29/295), and cattle (14.1%, 44/310)57. It is thought that humans may contract CCHF from donkeys that are exposed to tick bites in remote areas. As a result, it has been proposed that animals like donkeys and horses are crucial to the disease's epidemiology. Furthermore, in the regions where the samples were taken, there is a considerable risk that tick species like Hyalomma marginatum, Rhipicephalus bursa, and others will move from animals to people. The likelihood that animals utilised for transportation in these regions' rural areas will come into contact with ticks indicates that these animals will be crucial to the development of CCHFV.

According to serological research, equines play a significant role in CCHFV's natural survival. However, additional research on this topic is needed in Turkey. An investigation into the incidence of CCHF in horses in Turkey's Western Mediterranean region was carried out. In the regions of Burdur and Afyonkarahisar, 86 donkeys and 11 horses of varied ages and sexes provided blood samples for this study. The blood serum of these animals which the breeders retain for a variety of reasons was tested for the presence of CCHFV-specific antibodies. The rapid and precise double-antigen ELISA test was used to identify specific antibodies. As a result the study found that 51. 54 % (50/97) of the horses were seropositive including 53. 48 % (46/86) of the donkeys and only 36. 36%(4/11) of the horses.

According to the findings equidae may be a major reservoir in the epidemiology of Crimean Congo Hemorrhagic Fever Virus-Specific Antibody Detection in Equids. percentage of sera in different livestock species that have antibodies against CCHFV. Goats (9. 8%) sheep (8. 1%) cattle (14. 2%) and donkeys (31. 4%) had the highest levels of serotonin. Compared to the other livestock species (goats sheep and cattle) donkeys had a significantly different seropositivity. But there was no discernible difference between sheep goats and cattle [58]. A separate investigation was conducted in Topolitsa and Karageorgievo, two rural farming communities in southeast Bulgaria. About 30 km from District Burgas, both villages are situated in the county seat of Aytos.The greatest human CCHF seroprevalence rates have been found in this region. Many of the people in the two communities keep a few animals.

A separate investigation was conducted in Topolitsa and Karageorgievo, two rural farming communities in southeast Bulgaria. About 30 km from District Burgas, both villages are situated in the county seat of Aytos. Goats and donkeys were kept in smaller numbers but sheep and cattle were the most frequently kept animals. The animals graze outside during the day and spend a portion of the day in a barn or enclosure. According to our studys findings IgG antibodies against CCHFV were present in 72% (282/392) of the animals we looked at. 71% of cattle 74% of sheep 50% of donkeys and 60% of goats have CCHFV antibodies [62].

Serums from 3772 wild animals and 1978 domestic dogs were analyzed using indirect immunofluorescence. Between 1964 and 1985 species gathered in Zimbabwe and South Africa were examined for the CCHF virus antibodies [57]. To ascertain how wild mammals fit into the natural ecology of the virus reversed passive hemagglutination inhibition (RPHI) was used. Giraffes (Giraffa camelopardalis 3/3 positive) rhinoceroses (Ceratotherium simium and Diceros bicornis 7/13) land mammals (Taurotragus oryx 59/127) buffalo (Syncerus caffer 56/287) kudus (Trachelaphus strepsiceros 17/78) and zebras (Equus burchelli 16/93) were among the Orders Artiodactyla and Perissodactyla). Antibodies were found in the serum of 1/74 wild carnivores 22/1305 rodents and 40/293 hares but not in 522 primates 176 insectivores or 19 hyrax. Moreover 118 out of 1978 domestic dogs had antibodies in their serum [75].

Senegal and Mauritania in West Africa have consistently reported CCHF outbreaks. Additionally the epidemiology and acquisition of the disease in humans are related to the presence and seroprevalence of the virus in animals. This studys primary goal is to present current data on the local distribution of CCHF in animals in Senegals northern region. Antibodies specific to CCHF were found in 92 (32. 5 percent confidence interval [CI]95 percent 27. 1–38. 3) of the 283 animal blood samples according to the double antigen sandwich enzyme-linked immunosorbent assay (ELISA) test. The percentage of horses cattle sheep dogs donkeys and goats that were infected with the CCHF virus (CCHFV) was 70. 3 percent (45/64) 57. 1 percent (8/14) 22. 1 percent (30/136) 18. 2 percent (2/11) 17. 2 percent (5/29) and 6. 9 percent (2/29). The antibody titers were found to be significantly influenced by age and gender (p0. 0001 and p0. 05 respectively). High levels of Hyalomma tick infection and Rhipicephalus were discovered in horses. The significant seroprevalence of CCHFV among animals in the northern region of Senegal found in this study suggests that the infection is a recurring issue there and that Senegal needs to strengthen its CCHF surveillance protocols [69].

Numerous domestic animal species such as cattle sheep goats horses pigs dogs and chickens have been the subject of international research.Because there are so few studies on companion animals, it is challenging to draw general conclusions. In South Africa and Zimbabwe, 6% (n = 1978) of dogs were found to have CCHFV antibodies(44). Although domestic animals are essential for the spread of disease, CCHFV infections can go undetected because infected animals do not exhibit clinical symptoms and their viremia is brief [76].

The least understood part of CCHFV transmission and maintenance is the role of birds. Despite thorough examination most bird species did not show serological evidence of CCHFV-specific antibodies indicating that most birds are primarily resistant to CCHFV infection. Grobov gathered young H. marginatum during the 1944 Crimean outbreak. H.marginatum ticks from both domestic and wild birds because it was thought that birds were probably the source of the infectious agent at the time. Due to their remarkably high tick infestation rates and infestation indexes (measured as [no. ticks/ no. infested animals] × [% of infected animals])birds were thought to play a significant role in virus maintenance. Eight species of ground-feeding birds collected in the Volga River delta between 1963 and 1964 had H.marginatum infection indices ranging from 3.3 to 68.9. Corvus frugilegus roosts have the highest infection index with hundreds of H.marginatum.

In places where CCHFV is common marginatum have been seen eating a single rook. By carrying feeding immatures that were transovarially infected from adult ticks birds that do not develop viremia probably contribute to the spread of infected ticks into new areas. In red-beaked hornbills (Tockus sp.) persistent anti-CCHFV antibodies were found. and shiny starlings (Lamprotornis sp. along with ostriches. Additionally reports of the production of anti-CCHFV antibodies without any obvious viremia have been made. Moreover, research has shown that the tick-borne encephalitis virus or CCHFV can spread from one co-feeding tick to another even in the absence of detectable viremia in the host even though viremia may have gone undetected because of assay sensitivity or timing problems [74].

It has been found that young *Hyalomma rufipes* ticks can be infected with CCHFV by the red-billed hornbill (Tockus erythrorhynchus) without showing signs of viremia. The blue-helmeted guineafowl (Numida meleagris) showed low-level viremia followed by a transient antibody response in another experimental infection study of primarily ground-feeding birds indicating that anti-CCHFV antibodies may be generated following infection. On Anseriformes and Galliformes species conflicting studies have also been conducted. Pathogenicity tests showed that domestic chickens with experimental infections were resistant to contracting CCHFV. However Kazakhstan reported a 0. 2 % CCHFV seroprevalence in ducks and chickens (n = 428). Shepherd et al. found no CCHFV antibodies in the serum of 460 birds from 37 different species. In terms of carrying and potentially infecting humans with CCHFV ostriches seem to be unique among bird species. In the Shepherd and others, Anti-CCHFV antibodies were detected in 22 out of 92 (23. 9%) ostriches (Struthio camelus) in the aforementioned studies.

Its interesting to note that six out of nine ostriches (66. 6%) had antibodies linked to a human case of CCHF in a laborer who fell ill after killing ostriches on a South African farm. Furthermore it was shown that 1/5 (20%) of the ostriches examined in connection with four cases of CCHF in workers from two Iranian ostrich farms tested positive for CCHFV IgG. Ostrich viremia is quite temporary based on experimental infections(44). After a 1996 outbreak of Crimean-Congo hemorrhagic fever (CCHF) among employees at a South African ostrich butcher nine vulnerable young ostriches were subcutaneously infected with the virus to investigate the type of infection they experience.

On days 1-4 after infection the ostriches experienced viraemia on day 2 one bird showed a peak intensity of 4. 0 log10 mouse intracerebral LD50/ml. Up until day five following inoculation the virus was detected in visceral organs like the kidney liver and spleen. After a day the blood no longer contained it. Reverse transcription-polymerase chain reaction was used to test muscle samples from a bird that died three days after infection for viral nucleic acid however no infectious virus was found. Ostriches at slaughterhouses were found to be less susceptible to infection when kept tick-free for 14 days prior to slaughter [77]. There have been reports of significant viremia associated with human CCHFV infection despite their uncertain role in spreading the virus to humans.

Molecular Detection Of Cchfv In Animals:(Genomic Detection Techniques For Crimean Congo Hemorrhagic Fever Virus In Animals)

There are currently no approved vaccines or targeted antivirals to treat CCHF and the Hyalomma tick vectors expanding range puts new communities at risk. Even though CCHF cases are reported annually little is known about the host and viral factors that contribute to CCHFV pathogenesis. Although CCHFV can effectively infect many animal species, only humans have a serious sickness. Subclinical infections in human populations may account for a significant percentage of clinical outcomes, although they are not well understood [78]. Although animals do not show indications when sickened, they are the main source of infection for humans. Since 2013, there have been intermittent reports of CCHF human outbreaks in Uganda in different regions of the nation. To find out how common CCHF is in livestock, we planned a national epidemiological research. In all, 3181 animals were sampled, including 1091 goats (34.3%) , 358 sheep (11.3%), and 1732 cattle (54.4%). As a result, 31.4% (999/3181) of livestock had IgG antibodies against the CCHF virus (CCHFV). 16.9% of cattle and 48.8% of sheep and goats were carriers of the virus. Seropositivity was higher in mature and adolescent animals than in newborns and it was higher in female animals (33. 5 %) than in male animals (24. 1 %).The percentages of exotics (2.8%) and crossbreeds (19.3%) were lower than those of local breeds (36.8%). Animals having a history of stillbirth or abortion had higher levels of seropositivity than animals without such a history(61).

CCHFV can cause fatal infections, mild to severe clinical signs, or no symptoms at all. equency and the potential to become an epidemic. It presents a serious public health risk that needs to be investigated right away due to the high mortality rate of human clinical infections the possibility of epidemics and the absence of efficient mitigation techniques [5]. Furthermore, Sequencing of Rhipicephalus appendiculatus ticks revealed the presence of CCHFV, but not of domestic animals [66]. There are however few reports of animal-derived CCHFV. A goat used as an arbovirus sentinel in Senegal European hares in Crimea a hedgehog in Nigeria a feverish cow in Kenya and cattle and a goat in a Nigerian butcher have all been found to have CCHFV. Over 350 bird specimens from 35 species were examined in an extensive study conducted in endemic foci in Russia (Astrakhan Oblast) and no virus was discovered in any of them. This finding is corroborated by serological data [44]. The Crimean-Congo hemorrhagic fever virus was found to be more common in livestock ticks and animal handlers at a Ghanaian abattoir indicating that both the verified disease vectors (ticks) and the abattoir workers had been exposed to the virus. Only ticks taken from cattle, one of the animals known to contribute to the multiplication of the CCHF virus, contained the CCHFV. 57 (13. 3 %) 52 (34. 9%) 4 (3. 1 %) and 1 (0. 7 %) of the 428 recently deceased animals,130 sheep ,149 cattle and 149 goats had 144 ticks from the Ambylomma Hyalomma and Boophilus genera. Five of the 97 tick pools that were tested positive for CCHFV four of these tick pools originated from cattle and one of them contained Hyalomma excavatum. Of the 188 human blood samples taken from 108 abattoir workers seven (3. 7%) showed positive results for anti-CCHF IgG and one of them also had CCHF IgM. The CCHFV seroprevalence found in this study was 5. 7% [79]. It has been demonstrated that animals with a question mark are seroconverted. However, no virus isolation has been proven as of yet [80]. These sporadic instances highlight the difficulties in identifying and isolating the virus because of the typically short viremic phase in infected animals and the absence or mildness of clinical symptoms. As a result most successful isolations come from tick or human cases where the virus is more common. The recommended detection technique in the early stages of illness and in severe cases where no antibody is produced is reverse transcription-PCR or RT-PCR. Real-time RT-PCR methods for CCHF virus identification and quantification have been reported in recent years [81]. Reverse transcription-PCR (RT-PCR) antigen-detection EIA antibody-detection EIA and virus culture can all be used to diagnose CCHF. The primary diagnostic tool in the acute stage of illness is RT-PCR which is the most sensitive method of virus detection. However all existing RT-PCRs either lack sensitivity or only concentrate on identifying local CCHFV variations due to the striking genetic variation among CCHFV strains. 63 serum samples from 31 patients with laboratory-confirmed CCHFV infection were evaluated and quantified using real-time RT-PCR the samples were taken 1–18 days after the start of symptoms. Both the novel real-time RT-PCR and the nested RT-PCR revealed that every sample was positive for CCHFV. The viral load of 21 individuals with confirmed CCHF (17 from South Africa 3 from Iran and 1 from Pakistan) was assessed and contrasted with other common diagnostic techniques in order to identify CCHFV. Once more the novel assays sensitivity was at least as good as nested PCRs [82]. Low density macroarrays high density resequencing arrays padlock probes with colorimetric readout loop-mediated isothermal amplification (LAMP) and polymerase chain reaction are test instruments for CCHFV that may identify viral nucleic acids. The gold standard for quantitative sensitive and specific CCHFV detection is still real-time reverse-transcription polymerase chain reaction (RT-PCR) however these assays have sensitivity problems because of the genetic diversity of the numerous CCHFV strains [83]. Potential methods for diagnosing CCHFV include antigen-capture enzyme-linked immunosorbent assay (ELISA) reverse transcription polymerase chain reaction (RT-PCR) and virus isolation attempts. To detect CCHFV a fast economical and effective technology—including biosensors—must be created. This articles goal is to provide an overview of the advantages and disadvantages of the assays as well as other cutting-edge detection techniques like CCHFV biosensors and contemporary laboratory tests that are currently accessible. Nested RT-PCR and real-time RT-PCR5 were used to confirm the Crimean-Congo hemorrhagic fever case. The nucleoprotein gene region in the S segment the most conserved region of the CCHFV genome is frequently the focus of RT-PCR-based methods [84]. Furthermore primer sets and probes that target the nucleoprotein gene region (S segment) were used in the construction and execution of the CCHFV-S RT-qPCR [85]. One-step reverse transcriptase PCR (RT-PCR) was performed on the extracted RNA sample using the forward primer CCHF-SF (5′TCTCAAAGAAACACGTGCCGC3′) and the reverse primer CCHF-SR (5′TCTCAAAGATATCGTTGCCGC3′). The MB rRT-PCR assay was created to quickly accurately and sensitively detect CCHF in clinical samples [86]. The quick identification of CCHFV that targets the small (S) RNA segment a reverse transcription (RT) loop-mediated isothermal amplification (RT-LAMP) test was created and contrasted with nested RT-PCR. Because it didnt require any specialized equipment and was carried out at 63 °C under isothermal conditions the RT-LAMP proved more practical and affordable than real-time PCR in developing nations like Sudan. Sensitivity testing revealed that the RT-LAMP found 10 fg of CCHFV RNA based on the turbidity reading that was visible to the unaided eye. The RT-LAMP test identified as little as 0. 1 fg of viral RNA or 50 viral particles using agarose gel electrophoresis [87]. Reverse-transcription loop-mediated isothermal amplification (RT-LAMP) could be an effective alternative for the diagnosis of the disease. Both genotypes were amplified in urine by RT-LAMP which was more sensitive than RT-qPCR. In rural or resource-poor areas where CCHF typically occurs molecular diagnostics can be readily applied as a single-tube isothermal colorimetric technique on a portable platform in real-time and without the need for costly equipment [88]. Real-time and end-point RT-PCR and serodiagnostic tests are currently used to diagnose Crimean Congo hemorrhagic fever virus (CCHFV) infections. These tests take a lot of time and are not appropriate for routine screening. We created a quick and accurate single tube reverse transcription loop-mediated isothermal amplification (RT-LAMP) test for CCHfv detection in this work.A portable heating block device can be used to perform the assay, which is a quick, isothermal, and easy molecular diagnosis. Low-resource labs can monitor CCHFV outbreaks in isolated rural areas of impacted nations using the CCHF RT-LAMP assay [89]. The results of laboratory tests of the reagent kit for the quick identification of Crimean-Congo hemorrhagic fever virus (CCHFV) RNA using loop-mediated isothermal amplification with reverse transcription (RT-LAMP) are compiled in this paper. When compared to real-time PCR laboratory tests of the RT-LAMP kit demonstrated a high analytical and diagnostic sensitivity and specificity for RNA detection of the CCHFV as well as a high analysis speed (60–70 min with sample preparation). The kit field versions approval has demonstrated that it is possible to set up the RT-LAMP reaction and identify viral RNA without the need for analytical tools [90]. To completely comprehend the involvement of different animal species in the ecology of CCHFV, intensive monitoring programs, longitudinal research, and improved molecular detection techniques are necessary. This information is crucial for reducing the risks of human transmission and stopping the spread of this dangerous zoonotic illness.

Experimental CCHFV Infections In Animals:(Preclinical Evaluation Of Cchfv In Animal Models)

Immunological reactions, infection dynamics, and susceptibility patterns have all been clarified by experimental studies on CCHFV infections in a variety of animal species.In people, CCHF can present as anything from a severe hemorrhagic fever to an asymptomatic infection. During outbreaks, the case-fatality rate (CFR) usually ranges from 5% to 30% (1), however CFRs as high as 62% have been seen. It has been demonstrated that livestock and wild animals have asymptomatic transient viremia (lasting fewer than 15 days), despite the fact that the CCHF virus (CCHFV) only infects humans [91]. There is a human viremic phase, although it is not well understood. The viremic phase can last anywhere between two and fifteen days in both domestic and wild animals that show no symptoms. It's unknown, but CCHFV can live in the environment for a brief period of time, particularly in organic materials.Blood stored at 4°C (39°F) had infectious virus for as long as 10 days, and sometimes longer.(CRIMEAN-CONGO HEMORRHAGIC FEVER VIRUS). Although CCHFV can effectively infect many animal species, only humans have a serious sickness. Subclinical infections in human populations may account for a significant percentage of clinical outcomes, although they are not well understood [78].

Spanish reports have identified Hyalomma lusitanicum ticks as CCHFV vectors and reservoirs, and they have proposed a relationship between animal abundance and the local circulation and maintenance of the virus.Since mammals bitten by ticks have a sustained immunological response and remain viremic for 2–10 days, serologic surveys are a useful tool for tracking the dynamics of CCHFV. In the same population seroprevalence rose sharply from 0 (0/86 rabbits) in 2021 to 5. 77 % (95% CI 1. 98–15. 64 % ,3/52 rabbits) in 2022 before falling to undetectable levels in 2023 (0/78 rabbits). Based on rabbit density data obtained using capture-recapture techniques in the same population (peak densities of 3. 0-3. 8 rabbits/hectare in 2021–2023) we estimated that the captured rabbits would comprise 40% to 75% of the total population annually.(Crimean-Congo Hemorrhagic Fever Virus Circulation in Wild European Rabbits, Portugal, 2018–2023). The earliest report on the Crimean epidemic stated that the European hare (Lepus europaeus) played a significant role in the spread of CCHFV during the first CCHF outbreak in the Crimea the population of L. Europaeus seemed to take off. A number of CCHF outbreaks such as the first one in Crimea and others in the former Soviet Union Bulgaria Kosovo and Turkey were marked by an increase in the number of hares (and the tick population that accompanied them) and an overabundance of vegetation caused by the cessation of cultivation [13]. The Crimean-Congo hemorrhagic fever (CCHF) virus infected 11 species of small African wild mammals lab rabbits guinea pigs and Syrian hamsters. Scrub hares (Lepus saxatilis) Cape ground squirrels (Xerus inauris) red veld rats (Aethomys chrysophilus) white-tailed rats (Mystromys albicaudatus) bushveld gerbils (Tatera leucogaster) striped mice (Rhabdomys pumilio) and guinea pigs were all found to have low-titered viremia followed by the development of antibodies. The maximum viremic titer of four scrub hares was 10^(1. 7-4. 2) mouse fatal doses/ml. Infected laboratory rabbits had viremia in 1 out of every 17 cases. Only two species of multimammate mice (Mastomys natalensis and M. coucha) Syrian hamsters Namaqua gerbils (Desmodillus auricularis) and South African hedgehogs (Atelerix frontalis) exhibited an antibody response. The results of the study indicate that while some infected scrub hares have CCHF viremia to a level demonstrated in the Soviet Union to be sufficient for infecting and feeding immature ixodid ticks South African hedgehogs and wild rodents are unlikely to be significant maintenance hosts for the virus in southern Africa [92]. Shepherd et al. (1989) found that strain SPU 4/81 infected African hedgehogs (Atelerix frontalis) SC.Although viremia was not found, RPHI identified anti-CCHFV antibodies beginning at 8 dpi and peaking at 256 dpi [74].

Cattle sheep goats water buffalo hares (including the European hare Lepus europaeus) African hedgehogs (Erinaceus albiventris) and multimammate mice (Mastomys spp.) are among the domestic and wild animals from which CCHFV has been isolated. I). Donkeys horses camels water buffalo dogs Pallas cats (Felis manul) red foxes (Vulpes vulpes) wild dogs (Lycaon pictus) genets (Genetta genetta) and a number of African ungulates (e. g. A g. hedgehogs (Erinaceus europaeus,Hemiechinus auritus) rhinoceroses (Diceros bicornis,Ceratotherium simum) giraffes (Giraffa Camelopardalis,African buffalo Syncerus caffer) rodents and bats have also been discovered to have been exposed. However,this virus may not affect certain mammals. One group for example isolated CCHFV from the blood of long-eared hedgehogs (Hemiechinus auritus) that were experimentally infected but not from European hedgehogs (Erinaceus europaeus). (Crimean-Congo Hemorrhagic Fever Congo Fever, Central Asian Hemorrhagic Fever, Uzbekistan hemorrhagic fever Hungribta (blood taking), Khunymuny (nose bleeding), Karakhalak (black death). The different results amongst hedgehog species suggest that even within closely related species, there may be differences in CCHFV susceptibility and infection dynamics.

Additionally, Zgurskaya et al. showed that hares produced antibodies following CCHFV infection and that viremia occurs (7–15 days) [67]. Although the highest virus titers (1. 6 × 10^4 LD50/mL) were reported between 2 and 5 dpi93 viremia was found between 1 and 7 dpi. Two long-eared hedgehogs (H) and all seven European hedgehogs (Erinaceus europaeus) [44]. Inoculated SC with strain Sudarkina (auritus) did not exhibit any symptoms [93]. Although H. Auritus showed viremia between 2 and 6 dpi with a peak at 4-6 dpi E. *europaeus* showed no signs of viremia [13]. Scrub hares (Lepus saxatilis) Cape ground squirrels (Xerus inauris) red veld rats (Aethomys chrysophilus) white-tailed rats (Mystromys albicaudatus) bushveld gerbils (Tatera leucogaster) striped mice (Rhabdomys pumilio) and guinea pigs were found to exhibit low-titered viremia followed by the development of antibodies. Only two species of multimammate mice (Mastomys natalensis and M. coucha) Namaqua gerbils (Desmodillus auricularis) South African hedgehogs (Atelerix frontalis) and Syrian hamsters showed antibody responses [92]. The varied responses of small mammals demonstrate the intricacy of CCHFV interactions and emphasize the need for species-specific understanding in ecological dynamics. For a more comprehensive list we advise reviewing the comprehensive experimental infection data of various small mammals infected with CCHFV which are thoroughly discussed in these works. The length of viremia antibody response absence or presence of clinical illness and the role of vertebrate species as hosts in CCHFV maintenance and transmission have all been evaluated through experimental infection studies conducted in a variety of domestic and wild animals. The information gathered from these studies can be used to pinpoint knowledge gaps guide future investigations evaluate the risk of direct human contact with potentially infected animal tissues and bodily fluids and concentrate One Health countermeasures to lessen endemic viral transmission (e. g. The g. by administering a targeted acaricide). Numerous domestic species are exposed to CCHFV according to seroepidemiological studies but experimental infection studies have been far less extensive and have primarily focused on viremia assessment. Despite their small numbers a variety of livestock species including ruminants (cattle sheep) and equids (horses donkeys) have been subjected to experimental infections [74]. Sheep also showed evidence of maternal transmission of anti-CCHFV antibodies [74]. Fever acute viremia and associated viral shedding and indicators of possible liver and kidney dysfunction such as an early decline in neutrophil recruitment are the main clinical manifestations of the infection when no obvious symptoms are present [94]. We use CCHFV Kosovo Hoti a highly pathogenic clinical isolate that has been used more and more in recent studies to challenge domestic sheep. The infection causes a high fever acute viremia concurrent viral shedding and indications of possible liver and kidney impairment even in the absence of obvious clinical symptoms. The subclinical infection in sheep and the fatal infection in humans are distinguished by different host reactions. Although neutrophil infiltration and elevated IL-8 are characteristics of lethal CCHFV infections reported in immunocompromised mice and humans these include an early decline in neutrophil recruitment and its chemoattractant IL-8 in the bloodstream of infected sheep [94]. Zarubinsky et al. used the Sudarkina strain to experimentally infect calves. from 1976. Two 2-month-old calves received both SC and ID inoculation while two 6-month-old calves received either IM or SC vaccination. None of the animals showed clinical symptoms and the six-month-old calves did not have viremia. However at 3 and 7 days postpartum CCHFV was found in the blood of one of the 2-month-old calves indicating that humans could contract the virus by contact with the blood of infected animals. Anti-CCHFV antibodies were detected in the 6-month-old calves samples by agar-gel diffusion precipitation (AGDP) analysis 5–20 days post-infection (dpi) the SC-infected and IM-infected calves showed these antibodies at 13 and 17 days post-infection (dpi) respectively only the IM-infected animal showed CF antibodies (17 dpi). One calf had antibody titers of 1:10 on days 9 14 and 20 after infection rising to 1:80 at 35 dpi. The SC/ID-injected 2-month-old calves were also tested for antibodies using the indirect hemagglutination inhibition test 5e35 dpi [13].Calves Horses, guinea pigs, hamsters, and rabbits are examples of experimentally infected animals that do not exhibit clinical symptoms of the disease but instead generate large levels of neutralising antibodies and little to no viremia. In contrast to the majority of hemorrhagic fever viruses, CCHFV has not been shown to infect regularly utilised nonhuman primate species. Immunocompetent adult mice do not exhibit any symptoms of illness and are not prone to contracting CCHFV. On the other hand, there have been reports of high viral titers in the liver and blood of a baby mouse infection model. The virus could not be isolated from the spleen which contains a significant number of mononuclear phagocytes despite indications of systemic viral dissemination and macrophage infection in these animals which is consistent with the paradigm of viral hemorrhagic fever(95). Due to its extreme virulence which necessitates work under biosafety level 4 (BSL-4) containment the fact that it primarily occurs in areas lacking modern medical infrastructure and the absence of an appropriate animal model to study the disease the pathophysiology of CCHF is poorly understood. The majority of current knowledge is inferred from what is known about other viral hemorrhagic fevers and comes from human case reports and a few in vitro tests. Since the virus was first discovered in 1956 many domestic and lab animals have been studied as possible animal models [95].

Until recently the only animal models of CCHF were the suckling mouse-passaged IbAr 10200 or the intraperitoneal or intracranial infection of newborn mice or rats with Hodzha CCHFV strains. Despite some intriguing results from their use newborn mice are highly susceptible to a variety of diseases and their value as disease models is debatable [96]. Only newborn mice and rats were susceptible to CCHFV aside from humans. Newborn rodents are the first animal models used in CCHF research because intracranial or intraperitoneal inoculation causes illness symptoms and mortality in both human and newborn mice and rats [97]. Both intraperitoneal and intracellular infection can occur in newborn mice and rats, and both can cause a uniformly lethal condition with neurological symptoms that are rare in human instances. Paralysis weight loss viremia and increased viral organ titers are all present in newborn mice the average time to fatal illness is eight days following infection. Although they do not show symptoms adult mice rats hamsters guinea pigs rabbits ostriches cattle sheep goats donkeys horses and NHPs can contract CCHFV [98]. According to our research, mice lacking the STAT-1 signalling protein were extremely prone to infection and died within three to five days.This suggests unchecked viral growth when STAT1 signalling is not present [95]. In interferon α/β receptor knockout (IFNAR−/−) mice the deadly Crimean-Congo hemorrhagic fever virus induces coagulopathy proinflammatory responses and elevated viral loads [99]. Current mice models of CCHFV infection differ in their ability to mimic human-like illness symptoms despite the fact that they consistently die when challenged by the virus. In order to increase the number of animal models of CCHFV pathogenesis that may be utilized for treatment development we created a signal transducer and activator of transcription 2 (STAT2) knockout hamster model in this work. These hamsters displayed symptoms of a deadly systemic disease when they were infected. Human disease symptoms including petechial rash blood clotting issues and anomalies in blood cell count and biochemistry were observed. We also demonstrated the utility of this model for assessing anti-CCHFV treatments. In addition to offering a way to evaluate possible medication and vaccine candidates the STAT2 knock-out hamster model of CCHFV infection may offer some additional understanding of clinical illness and viral pathogenesis [100]. All animals inoculated intravenously or by a combination of intravenous and subcutaneous routes suffered from severe disease when cynomolgus macaques were infected with CCHFV strain Hoti, a human clinical isolate. By the seventh day after infection, four out of eight animals in each of these groups were put down because they met the humane end-point requirements. Like severe human disease, severe disease was linked to coagulation problems, high viral loads, inflammatory cytokines, and liver damage [101]. Four macaques were exposed intravenously to CCHFV Afghanistan, while eleven cynomolgus monkeys were exposed intravenously to CCHFV Hoti. Even while all 15 macaques experienced temporary viremia and clinical pathology alterations such leukopenia and thrombocytopenia, none of them experienced serious illness by the study's endpoint [102].

Prevention And Control Of Cchfv In Animals

For the benefit of both human and animal health it is crucial to stop and manage the spread of CCHFV in animals since the virus poses a serious risk to human health. These measures areintended to reduce the risk of human viral transmission and stop CCHFV from spreading to non-endemic areas. As alternatives to acaricides a number of strategies are being used such as maintaining naturally tick-resistant hosts using pheromone-impregnated decoys to attract and kill ticks biological control with natural enemies monitoring resistance strategically applying effective acaricides and developing natural anti-tick formulations and vaccines. An integrated approach considerably decreased the need for acaricides while controlling tick infestations as demonstrated by the combination of acaricide treatment with vaccine-controlled field experiments. These studies show that vaccinating ticks has additional benefits in terms of cost-effectiveness safety and stopping the spread of drug-resistant ticks [103].

As a result the following actions can be taken to control ticks sustainably and lessen the need for acaricides:
- Consistent resistance monitoring by molecular, biochemical, and bioassay testing.
- Using resistance data to create tick prevention plans specific to a region.
- Applying recognised biological formulations.
- Using biological control to manage outbreaks of ticks.
- Raising local poultry, birds, and animals, as well as being an avid tick-stage feeder.
- Preventing wild animals from invading pasture areas.

However, in the majority of nations, Infection and Treatment Method (ITM) deployment and monitoring are challenging tasks. To increase the degree of acceptability of the technology at the farmer level ITM must be gradually adopted at the policy regional and sectoral levels [103]. Moreover, There is Gavac™ and the Bm86 immunomodulator vaccine are availavle but currently no vaccination to prevent specifically Hyalomma ticks, and reliance on acaricides is growing [103]. Figure 3 graphically shows the prevention and control measures.

Figure 3: Control Measures for Prevention and Control of CCHF

Systems for surveillance are essential for the early identification and handling of animal CCHFV outbreaks. To find possible reservoirs and comprehend disease dynamics animal populations in endemic areas should be routinely examined for the presence of CCHFV antibodies or virus RNA. Early detection allows for timely efforts to stop the spread. In general treating cattle lowers the tick population among these animals which lessens the risk of tick bites for animal care personnel. Biosecurity is crucial for managing preventing and controlling animal diseases as well as safeguarding human health worldwide [104]. By adhering to conventional infection control protocols, veterinarians and abattoir workers can lower risk while handling potentially infectious blood or ticks.

Simple tick bite prevention strategies, such wearing appropriate clothing (long sleeves, pants, etc.), using chemicals (repellent, etc.), and visually inspecting skin and clothing, will lower the likelihood of transmission [105]. Put on protective apparel, such as long sleeves and long trousers. Apply authorised repellents and acaricides on skin and clothing. When handling animals or their tissues, especially during butchering or slaughter, put on gloves and other protective gears.

The main ways to prevent CCHF in animals are to avoid tick bites, wear personal protective equipment, and use acaricides in cattle production areas [16,106]. When killing or dressing animals or coming into contact with their meat products, wearing protective gear including goggles, protective gloves, masks, boots, and work clothes can help stop the disease from spreading to people through their skin or tissue [107]. In order to lower the risk of vertebrate amplification of the virus which lowers occupational risks for animal processing workers it is essential to prevent naive animals from traveling to endemic areas. Educating the general public veterinarians and livestock owners about CCHFV transmission animal symptoms and preventive measures is essential. Promoting suitable biosecurity measures emphasizing the importance of early reporting of suspected cases and expanding awareness of the diseases effects are all crucial components of effective disease management initiatives.

Conclusion

The extremely dangerous Crimean Congo hemorrhagic fever virus (CCHFV) is spread by Hyalomma ticks primarily Hyalomma marginatum which serve as both a vector and a reservoir.It gives rise to a pervasive health threat due to its potential to cause grievous haemorrhagic fever in humans as well as in animals. Many tick species like Amblyomma, Rhipecephalus,and Dermacenter are auxiliary to CCHFV but pivotal one is still Hyalomma.Its voluminous dispensation over Asia, Africa and Europe emphasizes how crucial it is to comprehend, and its behaviour in tick vectors and animal hosts. As it spreads silently through the tick-vertebrate-tick cycle in the wild CCHFV vitiates a range of domestic animals without causing any symptoms. Serological studies have shown that camels cattle buffalo and donkeys have higher antibody prevalence suggesting that they are important contributors to CCHFV pestilence. Poor agricultural management tick infestation and livestock transportation are the main causes of CCHFV prevalence in both humans and animals. We need to improve these parameters to prevent the spread ofCCHFV. The preliminary epidemiological methodology for evaluating CCHFV was ELISA, but improved recombinant-antigen assays emerged as a result of its fleeting findings. Reliability is nevertheless hampered by cross reactivity with kindred viruses, underscoring the need for more specialised instruments. RT-PCR is still the most popular method for molecular detection, although RT-LAMP is becoming a quick and inexpensive substitute. For the purpose of reducing the risk of human infection and elucidating the role of animals in CCHFV ecology, further advancements in diagnostic and surveillance techniques are essential.Managing CCHFV in animals efficiently serves as vital for minimising transmission to humans and guaranteeing public health. Comprehensive approaches including targeted vaccination, biological control, and low acaricide use are necessary for sustainable tick management. Rapid identification and containment are made practicable by increased biosecurity, surveillance, and farmer awareness. Infection risks can be further reduced by teaching livestock workers safe handling techniques and preventative measures.

RT-PCR is the gold standard for molecular detection of CCHFV because of its greater sensitivity and specificity. In an environment with limited resources new methods like RT-LAMP offer faster more economical and field-adaptable solutions. Due to asymptomatic and momentary viremia, virus isolation from animals is still uncommon despite extensive animal exposure. Sustained progress in molecular surveillance and diagnostics is essential to reducing human transmission risks and better understanding the roles of animals in CCHFV ecology. According to experimental research, CCHFV only causes drastic illness in humans animals simply get asymptomatic infections. whereas most Propagation dynamics are governed by the diversified viremia levels, immunological responses, and roles in virus maintenance disposed by different species. In order to comprehend the pathophysiology of CCHFV and create vaccinations or treatments, animal models particularly knockout mice and hamsters are essential. CCHFV in animals must be successfully controlled to halt human transmission and safeguarding public health. Biological control, vaccination, and limited acaricide uses are examples of integrated solutions for sustainable tick management that lessen reliance on chemicals. Early discovery and containment depend on increased biosecurity, surveillance, and farmer awareness. To further reduce the risk of infection, livestock workers should be educated, handle animals safely, and protect themselves.

Declaration of Generative AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work the authors occassionally used ChatGPT 3.5 in order to improve readability and language. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Conflicts of Interest

There is no conflict of interest between authors.

Credit Authorship Contribution Statement

Kanza Fatima Writing – original draft, Visualization, Formal analysis. Asmat Nawaz: Writing – review & editing,Supervision. Khadija Tariq: Review and Visualization.

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