REDVET - Revista electrónica de Veterinaria - ISSN 1695-7504
Vol 23, No. 3 (2022)
http://www.veterinaria.org
Article Received: 25 March 2022; Revised: 15 April 2022; Accepted: 17 May 2022; Publication: 02 July 2022

Ticks: Major Vectors to Blame for the Spread of Crimean Congo Hemorrhagic Fever

Nawras Kadhum Mahdee [1], Salah Mahdi Karim [2] and Alfatlawi MAA [3]

1,2 Department of internal and preventive Medicine, College of Veterinary medicine, University of Al-Qadisiyah University, Al-Qadisiyah province, Iraq.
3 Department of Microbiology, College of Veterinary medicine, University of Al-Qadisiyah University, Al-Qadisiyah province, Iraq.
Email: [1] nawras.alnakeeb@qu.edu.iq , [2] Salah.karim@qu.edu.iq , [3] monyerr.abd@qu.edu.iq
Corresponding author: Alfatlawi MAA, monyerr.abd@qu.edu.iq

Abstract
The present review was performed to identify the importance of ticks in the transmission of the Crimean Congo Hemorrhagic Fever (CCHF) to new regions with no previous records of the CCHF virus (CCHFV) presence. One of the critical methods for such transmission is the movement of migrating birds that carry the infected ticks. Tick immune system and salivary glands can be the most important barriers for the entry of the virus, which when is overcome, the viral replication can occur in many sites of the tick body, especially the reproductive system. The current review shares important information regarding the critical situation of the escalating transmission of the CCHF, especially of ticks and ticks via migrating birds, which may introduce the disease to new virus-free regions.

Keywords: Crimean Congo Hemorrhagic Fever, *Hyalomma*, ticks.

Introduction

CCHF is the planet 's highest common tick-borne viral illness in different continents, such as Asia, some regions in Europe, and Africa, and the following largest widespread hemorrhagic fever after dengue among tick-borne diseases (1). There is a wide range in the severity of the infection's clinical manifestations, ranging from asymptomatic to severe and even deadly instances (2). According to certain research, asymptomatic illnesses may account for up to 90% of cases in high-risk locations. It is possible to contract CCHF from infected animals when blood and body fluid based contact occurred from slaughtered animals, abortion, etc., or form tick bites. Nosocomial infections are often documented in the hygienic setting, particularly those associated to aerosol formation (3–5).

It appears that exposure to infected bodily fluids does not raise the risk of CCHF as much as contact to other hemorrhagic viruses like Ebola in the healthcare settings. Nosocomial dissemination may occur when the illness is not suspected or the appropriate preventative procedures are not followed. Pregnancy-related nosocomial dissemination of CCHF is prevalent (6). CCHF distribution may also be acquired via the bloodstream and by sexual contact (7,8). Accidental occurrences of virus contamination in the laboratory have also been reported. CCHF virus (CCHFV) is an enveloped virus with segmented negative-sense based

REDVET - Revista electrónica de Veterinaria - ISSN 1695-7504
Vol 23, No. 3 (2022)
http://www.veterinaria.org
Article Received: 25 March 2022; Revised: 15 April 2022; Accepted: 17 May 2022; Publication: 02 July 2022

single-stranded (ss) RNA *Arbovirus*. Based on the most current categorization of viral genomic and metagenomic comparative research breakthroughs, CCHFV falls in the genus; *Orthonairovirus* (family: *Nairoviridae*, order: *Bunyavirales*) under the domain *Riboviria*. Three nuclear segments contains S; small, M; medium, and L; large, which code for the nucleoprotein (NP), glycoprotein precursor (GPC), that results in the structural glycoproteins (GN and GC) and RNA-dependent RNA polymerase, respectively (9–14).

CCHFV has greater varieties in the genetic materials than viruses transmitted by tick vectors, which indicates a large geographic distribution of the pathogenic agent. In the past several years, new viral categories have emerged as more comprehensive genomic sequences of CCHFV have been accessible (12). Formerly divided by geographic region into six major groups, the most recent genomic investigation of the S-RNA segment's whole sequence and its geographic origins have led to up to nine genetically distinct groups being postulated for CCHFV. The illness solely impacts human beings, while CCHFV exists in the wild animal-cattle-bird-tick cycle. There are three ways in which hard ticks spread the virus among other ticks in the natural world: transovarial, transstadial, and venereal (15).

Epidemiology and migrating-bird based transportation of ticks

Viruses have been found in at least 32 hard and Three soft species members, but only *Hyalomma* ticks were declared as vectors, and the highest successful carrier appears to be *Hyalomma marginatum* (broadly prevalent in the Mediterranean region). As it turns out, the areas where *Hyalomma* ticks are most common and where CCHF patients are most prevalent correlate. For the CCHFV, *Rhipicephalus bursa* appears to also be an important factor. According to *Dermacentor marginatus*, CCHFV has been found in its eggs; however, no investigations have been done to determine whether *D. marginatus* can transmit or maintain the virus. In certain tick species, CCHFV infection is more or less common (16).

The rate of CCHF occurrence has increased in recent years. In addition, the fatality rate of CCHF is very varied across outbreaks and in various geographic regions. Because mild or nonspecific infections may go unrecognized, epidemiological statistics may reduce the total prevalence of CCHF (17,18).

Variables such as host biology, tick circulation, and environmental variables all have a role in the virus's transmission. Particularly by changing critical routes of tick-life cycle and influencing the existence and spread of the vectors and vertebrate hosts, such as interacting with bird migration, climatic variations may impact CCHF occurrence (19,20). A rise in the number of CCHF cases has been seen over the last decade, and this has been accompanied by an unprecedented synchronization among nations with comparable geographies and environments. European health authorities have thus called for new research to be carried out in countries where the virus is now assumed to be absent in order to identify and restrict probable CCHFV importation pathways. The juvenile stage of *Hyalomma marginatum*'s life cycle is triggered by the increase in temperature that occurs in the spring, and it lasts until the end of the summer. *Hyalomma* spp. are better able to survive in drier environments than many

REDVET - Revista electrónica de Veterinaria - ISSN 1695-7504
Vol 23, No. 3 (2022)
http://www.veterinaria.org
Article Received: 25 March 2022; Revised: 15 April 2022; Accepted: 17 May 2022; Publication: 02 July 2022

other tick species; yet, winter and cold temperatures restrict the growth of tick populations. CCHF's incidence follows a seasonal pattern, like that of other tick-borne infections. CCHFV-bringing ticks may spread to new locations because to alterations in animal allocation and natural biogeographical shifts (20–22).

A study of productive hotspots on the Crimean regions found that the viral agent is able to thrive in vertebrate hosts, including birds, ungulates, hedgehogs, and species of birds. Immature *Hyalomma* ticks, especially those that feed on rodents and rabbits, are the most effective hosts for CCHFV survival and dissemination in nature, according to a set of system studies performed by Spengler and Estrada-Pea on 133 tick species (23). CCHF seroprevalence in people and animals was evaluated and determined by Nasirian et al. (18,23,24) in 2019 using a meta-analysis technique. Immature ticks have probability to be transported by the movement of migrating birds and transmit the disease along their paths. It was proven in 2018 that migratory birds from endemic regions are possible vectors for CCHFV establishment in Central Italy (25). Many areas have a high prevalence of CCHFV infection, such as Middle East, Africa, some regions in Western and South CentraIncidents of the CCHF was revealed in Nigeria, Congo, Senegal, Tanzania, Iraq, Iran, Oman, the United Arab Emirates, Saudi Arabia, Bulgaria, Russia, Albania, Greece, Turkey, and Spain (26).

Turkey revealed the greatest prevalence of CCHF patients (480 cases in the first six months of 2020) with a vectors identified as extensively widespread in Europe (27,28). August, 2016, two instances were documented in Spain: the first sufferer, male (62 years old), was presumably attacked by a vector insect while on some trips and died following in a hospital. The other person was a hospital worker that was in a close contact with first case. There was no prior trip record abroad of Spain previous to the beginning of the illness for any of the above mentioned individuals. The tick vectors were found as related to *H. lusitanicum* species, in the West of Spain, near to the borders of Portugal. It is obvious that these cases from Spain would have been expected with sufficient investigations that dealt with the wild animals, where a significant CCHFV burden was discovered. Furthermore, in the beginning of August 2018, the local officials in the Northwest of Spain, announced another deadly incidence of CCHF, verified by PCR (29–31).

Also, it is noted that nosocomial infection may happen in regions with no endemic characteristics, if appropriate prophylaxis and controls are not performed. In the United Kingdom, two instances were recorded in 2012 and 2014, and verified as incidents that came from abroad (Afghanistan and Bulgaria). Earlier in 2004 and 2001, imported infections were documented in France (Senegal) and in Germany (Afghanistan and Bulgaria), respectively. Some other new imported incidence was observed in Greece in 2018: A Greek worker that traveled to Bulgaria and came back to Greece with high temperature and a hemorrhagic condition, who recalled that a tick was removed from his abdomen (32–34).

Whereas the migratory of birds spanning extremely wide ranges permitting the transmission of the viral agent, Europe nations are in a condition of awareness for the risk of CCHFV

REDVET - Revista electrónica de Veterinaria - ISSN 1695-7504
Vol 23, No. 3 (2022)
http://www.veterinaria.org
Article Received: 25 March 2022; Revised: 15 April 2022; Accepted: 17 May 2022; Publication: 02 July 2022

importation of the virus-carrying ticks. The Mediterranean lines are at danger, because to the continual temperature variations that might render the spot favorable for the infected immature ticks (nymphs) of the species *Hyalomma* delivered by the long-distance-moving birds to grow into mature ticks. To the alternative side, mature affected tick vectors might be transmitted to Italy by animals; in reality, by meat products, which are brought from the East of Europe to the regions of Italy (26). According to De Liberato and colleagues, the newest strategy to determine if the virus is present in some countries, such as Italy, was built on tick collection of birds coming from endemic regions as well as the surveillance of populations of animals that may be infected with the virus, such as sheep (35). It is especially important to observe the passage of migrating birds in the seaside districts of Latium and Tuscany due of the existence of the carrier vectors. In reality, earlier was noticed that ticks and nymphs of *H. marginatum* and *H. rufipes* were recognized among 41 migrating birds by the wildlife investigations done in Italy (36).

Tick-borne transmission of CCHFV

CCHFV, among the major significant viruses transmitted by ticks, may be transferred to humans by many pathways, including tick biting or destroying of blood-distended infected tick vectors, or the exposure to the bodily fluids and infected or contaminated tissues of viremic humans and animals, across cutaneous or mucosal means (37,38).

Medical researchers are particularly interested in ticks because of their role as vectors in the transmission of several illnesses. The Argasidae (or "soft ticks") and the Ixodidae (or "hard ticks"), the latter of which is implicated in CCHFV dissemination, have over 900 species for both. When an Ixodid nymph or adult tick feeds on blood for both adult transformation and reproductive performance, two hosts must be used to fulfill a cycle; of note. For the long persistence of CCHFV, ticks play a key function as both vectors and reservoirs. Since ticks feed on contaminated blood supplies from vertebrates, they act as a viral booster and storage, even if they only cause a brief spike in viral levels. Larva-to-nymph-to-adult transmission is demonstrated for some species that belong to the genera; *Hyalomma, Rhipicephalus*, and *Dermacentor*, while the transovarial direction, is indicated by the virus existence in unfed insects), and the horizontal transfer of the CCHFV was proven to occur during feeding on infected blood (18,20,21,39).

Aside from insect sexual distribution, CCHFV can be transmitted when infected and non-infected ticks both feed on a single nonviremic human or animal; however, the particular processes of CCHFV persistence remain mostly unknown. Due to the obvious high viral survivability in unfed ticks and the eagerness with which *Hyalomma* ticks search out human hosts, research has shown that these ticks are critical to human CCHFV infections. *H. marginatum, H. rufipes, H. anatolicum, H. truncatum, H. dromedarii, R. appendiculatus, R. evertsi, and R. decoloratus* were all shown to have the virus (26).

It is well accepted that CCHFV spreads by direct contact with contaminated bodily fluids throughout the first 7–10 days of sickness in poor nations. Personal protection is regarded to

REDVET - Revista electrónica de Veterinaria - ISSN 1695-7504
Vol 23, No. 3 (2022)
http://www.veterinaria.org
Article Received: 25 March 2022; Revised: 15 April 2022; Accepted: 17 May 2022; Publication: 02 July 2022

be the most effective method of preventing the transmission of CCHFV nosocomial infection. It is also necessary to examine CCHF as a work-related illness among farmworkers, gardeners, slaughterhouse workers, veterinarians, and healthcare professionals in order to strengthen management measures. Evidence shows that CCHF, like other arboviruses, may be a sexually transmitted illness. As far as feasible maternal of transmission, whether intrauterine or postnatal, has been recorded. While airborne transmission of the CCHFV virus has been postulated to be a concern, particularly during aerosol-generating in clinical processes, more research into the epidemiology of this is needed (40,41).

The life of CCHFV within the vector tick

Transovarial, transstadial, and venereal transmission are effective methods of CCHFV infection. Ticks, especially those in the *Hyalomma* genus, are regarded the main carriers of CCHFV, whereas other tick vector species may sustain the CCHFV-enzootic centers and flow between the life cycle members, such as ticks and domestic and wild animals. The barriers from the tick midgut and salivary glands must be bypassed in order for viral transmission to occur. The capacity of transmitted infectious agents to avoid the tick's innate immune response affects the vector tick's performance (42).

Tick-pathogen interactions are not well understood at the molecular aspect. There is a good chance that CCHFV envelope glycoproteins will initially engage with the ticks' epithelial cells. A class II viral fusion protein was found to be presented by the glycoprotein Gc in the case of CCHFV. Because of their innate immune system and lack of adaptive immunity, ticks are no different from other invertebrates in that they are dependent on the hemolymphatic release of humoral substances and phagocytosis in order to fight disease. Ticks inherent antiviral protective system, in which RNA interference (RNAi), was studied on the *Hazara nairovirus*, which is used as a replacement CCHFV model for RNAi research. Simultaneous administration of ribavirin and a small interfering RNA (siRNA) targeting the *Hazara nairovirus* N protein mRNA suppressed viral multiplication (43,44).

The tick's midgut is where CCHFV first multiplies and then spreads to the bloodstream, where it attacks a variety of organs, with the greatest virus titers seen in tissues that are actively reproducing (such as the salivary glands and genital tissues). The minimal virus titer required for ticks to get infected differs across different kinds of ticks. It is only blood feeding that has a positive correlation with virus titer after intracoelomic CCHFV injection, and neither the tick's gender nor its feeding condition (unfed or engorged) affects it. It's possible that CCHFV replication is boosted by tick adherence and sucking blood from a vulnerable host, which may decrease the stress on the tick while it's searching for its next host, but improve its ability to transmit the virus once it's found one (45).

Following a single transstadial transmission, CCHFV mutations in ticks were exhibited to be more numerous than in the host organisms, indicating that ticks have a higher level of viral intra-host variety from tick vectors than vertebrates. This was confirmed by a sequencing analysis and a CCHFV distribution scenario (46). Endosymbionts and multiple

REDVET - Revista electrónica de Veterinaria - ISSN 1695-7504
Vol 23, No. 3 (2022)
http://www.veterinaria.org
Article Received: 25 March 2022; Revised: 15 April 2022; Accepted: 17 May 2022; Publication: 02 July 2022

infections may be presented at the identical moment as CCHFV in a tick. Tick fitness, pathogen infection, and transmission are all affected by the tick microbiome, according to metagenomic research. *Hyalomma* spp. ticks have been shown to contain endosymbionts that resemble those of *Francisella* (47). Ticks' physiological and immunological responses may be affected by new pathogens or endosymbionts, although no research has looked at this. The tick's lifespan, activity, and gene expression may be affected by viral infections. Pathogen-tick interactions may be better understood with the help of next-generation sequencing of tick microbiome (48).

Conclusion

The current review shares important information regarding the critical situation of the escalating transmission of the CCHF, especially of ticks and ticks via migrating birds, which may introduce the disease to new virus-free regions.

References

1. Bente DA, Forrester NL, Watts DM, McAuley AJ, Whitehouse CA, Bray M. Crimean-Congo hemorrhagic fever: history, epidemiology, pathogenesis, clinical syndrome and genetic diversity. Antiviral Res [Internet]. 2013 [cited 2022 May 21];100(1):159–89. Available from: https://pubmed.ncbi.nlm.nih.gov/23906741/
2. Bodur H, Akinci E, Ascioglu S, Öngürü P, Uyar Y. Subclinical Infections with Crimean-Congo Hemorrhagic Fever Virus, Turkey. Emerg Infect Dis [Internet]. 2012 Apr [cited 2022 May 21];18(4):640–2. Available from: /pmc/articles/PMC3309668/
3. Tsergouli K, Karampatakis T, Haidich AB, Metallidis S, Papa A. Nosocomial infections caused by Crimean-Congo haemorrhagic fever virus. J Hosp Infect [Internet]. 2020 May 1 [cited 2022 May 21];105(1):43–52. Available from: https://pubmed.ncbi.nlm.nih.gov/31821852/
4. Sidira P, Maltezou HC, Haidich AB, Papa A. Seroepidemiological study of Crimean-Congo haemorrhagic fever in Greece, 2009-2010. Clin Microbiol Infect [Internet]. 2012 [cited 2022 May 21];18(2):E16–9. Available from: https://pubmed.ncbi.nlm.nih.gov/22192082/
5. Pshenichnaya NY, Nenadskaya SA. Probable Crimean-Congo hemorrhagic fever virus transmission occurred after aerosol-generating medical procedures in Russia: nosocomial cluster. Int J Infect Dis [Internet]. 2015 Apr 1 [cited 2022 May 21];33(4):120–2. Available from: https://pubmed.ncbi.nlm.nih.gov/25576827/
6. Ergonul O, Celikbas A, Yildirim U, Zenciroglu A, Erdogan D, Ziraman I, et al. Pregnancy and Crimean-Congo haemorrhagic fever. Clin Microbiol Infect [Internet]. 2010 [cited 2022 May 21];16(6):647–50. Available from: https://pubmed.ncbi.nlm.nih.gov/19778302/
7. Ergonul O, Battal I. Potential sexual transmission of Crimean-Congo hemorrhagic fever infection. Jpn J Infect Dis [Internet]. 2014 [cited 2022 May 21];67(2):137–8. Available from: https://pubmed.ncbi.nlm.nih.gov/24647261/
8. Pshenichnaya NY, Sydenko IS, Klinovaya EP, Romanova EB, Zhuravlev AS. Possible sexual transmission of Crimean-Congo hemorrhagic fever. Int J Infect Dis [Internet]. 2016 Apr 1 [cited 2022 May 21];45(4):109–11. Available from: https://pubmed.ncbi.nlm.nih.gov/26972040/
9. Leblebicioglu H, Sunbul M, Guner R, Bodur H, Bulut C, Duygu F, et al. Healthcare-associated

Crimean-Congo haemorrhagic fever in Turkey, 2002–2014: a multicentre retrospective cross-sectional study. Clin Microbiol Infect [Internet]. 2016 Apr 1 [cited 2022 May 21];22(4):387.e1-387.e4. Available from: /pmc/articles/PMC5023843/

10. Pshenichnaya NY, Leblebicioglu H, Bozkurt I, Sannikova IV, Abuova GN, Zhuravlev AS, et al. Crimean-Congo hemorrhagic fever in pregnancy: A systematic review and case series from Russia, Kazakhstan and Turkey. Int J Infect Dis [Internet]. 2017 May 1 [cited 2022 May 21];58:58–64. Available from: /pmc/articles/PMC5421160/
11. Ahmeti S, Berisha L, Halili B, Ahmeti F, von Possel R, Thomé-Bolduan C, et al. Crimean-Congo Hemorrhagic Fever, Kosovo, 2013–2016. Emerg Infect Dis [Internet]. 2019 Feb 1 [cited 2022 May 21];25(2):321–4. Available from: /pmc/articles/PMC6346452/
12. Kuhn JH, Adkins S, Alioto D, Alkhovsky S V., Amarasinghe GK, Anthony SJ, et al. 2020 TAXONOMIC UPDATE FOR PHYLUM Negarnaviricota (Riboviria: Orthornavirae), INCLUDING THE LARGE ORDERS Bunyavirales AND Mononegavirales. Arch Virol [Internet]. 2020 Dec 1 [cited 2022 May 21];165(12):3023–72. Available from: /pmc/articles/PMC7606449/
13. Garrison AR, Alkhovsky S V., Avšič-Županc T, Bente DA, Bergeron É, Burt F, et al. ICTV Virus Taxonomy Profile: Nairoviridae. J Gen Virol [Internet]. 2020 [cited 2022 May 21];101(8):798–9. Available from: /pmc/articles/PMC7641396/
14. Mild M, Simon M, Albert J, Mirazimi A. Towards an understanding of the migration of Crimean-Congo hemorrhagic fever virus. J Gen Virol [Internet]. 2010 [cited 2022 May 21];91(Pt 1):199–207. Available from: https://pubmed.ncbi.nlm.nih.gov/19812264/
15. Portillo A, Palomar AM, Santibáñez P, Oteo JA. Epidemiological Aspects of Crimean-Congo Hemorrhagic Fever in Western Europe: What about the Future? Microorganisms [Internet]. 2021 Mar 1 [cited 2022 May 21];9(3):1–19. Available from: /pmc/articles/PMC8003855/
16. Gargili A, Estrada-Peña A, Spengler JR, Lukashev A, Nuttall PA, Bente DA. The role of ticks in the maintenance and transmission of Crimean-Congo hemorrhagic fever virus: A review of published field and laboratory studies. Antiviral Res [Internet]. 2017 Aug 1 [cited 2022 May 21];144(6):93–119. Available from: /pmc/articles/PMC6047067/
17. Spengler JR, Bente DA, Bray M, Burt F, Hewson R, Korukluoglu G, et al. Second International Conference on Crimean-Congo Hemorrhagic Fever. Antiviral Res. 2018 Feb 1;150(1):137–47.
18. Spengler JR, Bergeron É, Spiropoulou CF. Crimean-Congo hemorrhagic fever and expansion from endemic regions. Curr Opin Virol. 2019 Feb 1;34(1):70–8.
19. Maltezou HC, Andonova L, Andraghetti R, Bouloy M, Ergonul O, Jongejan F, et al. Crimean-congo hemorrhagic fever in Europe: Current situation calls for preparedness. Eurosurveillance [Internet]. 2010 Mar 11 [cited 2022 May 23];15(10):48–51. Available from: https://www.eurosurveillance.org/content/10.2807/ese.15.10.19504-en
20. Gargili A, Estrada-Peña A, Spengler JR, Lukashev A, Nuttall PA, Bente DA. The role of ticks in the maintenance and transmission of Crimean-Congo hemorrhagic fever virus: A review of published field and laboratory studies. Antiviral Res. 2017 Aug 1;144(6):93–119.
21. Spengler JR, Estrada-Peña A, Garrison AR, Schmaljohn C, Spiropoulou CF, Bergeron É, et al. A chronological review of experimental infection studies of the role of wild animals and livestock in the maintenance and transmission of Crimean-Congo hemorrhagic fever virus. Antiviral Res. 2016 Nov 1;135(10):31–47.
22. Gale P, Stephenson B, Brouwer A, Martinez M, de la Torre A, Bosch J, et al. Impact of climate

change on risk of incursion of Crimean-Congo haemorrhagic fever virus in livestock in Europe through migratory birds. J Appl Microbiol [Internet]. 2012 Feb 1 [cited 2022 May 23];112(2):246–57. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/j.1365-2672.2011.05203.x

23. Spengler JR, Estrada-Peña A. Host preferences support the prominent role of Hyalomma ticks in the ecology of Crimean-Congo hemorrhagic fever. PLoS Negl Trop Dis [Internet]. 2018 Feb 8 [cited 2022 May 23];12(2):e0006248–52. Available from: https://journals.plos.org/plosntds/article?id=10.1371/journal.pntd.0006248
24. Nasirian H. Crimean-Congo hemorrhagic fever (CCHF) seroprevalence: A systematic review and meta-analysis. Acta Trop. 2019 Aug 1;196(5):102–20.
25. De Liberato C, Frontoso R, Magliano A, Montemaggiori A, Autorino GL, Sala M, et al. Monitoring for the possible introduction of Crimean-Congo haemorrhagic fever virus in Italy based on tick sampling on migratory birds and serological survey of sheep flocks. Prev Vet Med. 2018 Jan 1;149(11):47–52.
26. Serretiello E, Astorri R, Chianese A, Stelitano D, Zannella C, Folliero V, et al. The emerging tick-borne Crimean-Congo haemorrhagic fever virus: A narrative review. Travel Med Infect Dis. 2020 Sep 1;37(9):101871–84.
27. Negredo A, de la Calle-Prieto F, Palencia-Herrejón E, Mora-Rillo M, Astray-Mochales J, Sánchez-Seco MP, et al. Autochthonous Crimean–Congo Hemorrhagic Fever in Spain. N Engl J Med [Internet]. 2017 Jul 13 [cited 2022 May 23];377(2):154–61. Available from: https://www.nejm.org/doi/full/10.1056/NEJMoa1615162
28. Kizito S, Okello PE, Kwesiga B, Nyakarahuka L, Balinandi S, Mulei S, et al. Notes from the Field: Crimean-Congo Hemorrhagic Fever Outbreak — Central Uganda, August–September 2017. Morb Mortal Wkly Rep [Internet]. 2018 Jun 6 [cited 2022 May 23];67(22):646–7. Available from: /pmc/articles/PMC5991810/
29. Estrada-Peña A, Palomar AM, Santibáñez P, Sánchez N, Habela MA, Portillo A, et al. Crimean-Congo Hemorrhagic Fever Virus in Ticks, Southwestern Europe, 2010. Emerg Infect Dis [Internet]. 2012 Jan [cited 2022 May 23];18(1):179–80. Available from: /pmc/articles/PMC3310114/
30. Estrada-Peña A, Jameson L, Medlock J, Vatansever Z, Tishkova F. Unraveling the Ecological Complexities of Tick-Associated Crimean-Congo Hemorrhagic Fever Virus Transmission: A Gap Analysis for the Western Palearctic. https://home.liebertpub.com/vbz [Internet]. 2012 Sep 10 [cited 2022 May 23];12(9):743–52. Available from: https://www.liebertpub.com/doi/abs/10.1089/vbz.2011.0767
31. Papa A, Pappa S, Panayotova E, Papadopoulou E, Christova I. Molecular epidemiology of Crimean–Congo hemorrhagic fever in Bulgaria—An update. J Med Virol [Internet]. 2016 May 1 [cited 2022 May 23];88(5):769–73. Available from: https://onlinelibrary.wiley.com/doi/full/10.1002/jmv.24400
32. Papa A, Markatou F, Maltezou HC, Papadopoulou E, Terzi E, Ventouri S, et al. Crimean-congo haemorrhagic fever in a greek worker returning from Bulgaria, June 2018. Eurosurveillance [Internet]. 2018 Aug 30 [cited 2022 May 23];23(35):1800432–6. Available from: https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2018.23.35.1800432
33. Papa A, Mirazimi A, Köksal I, Estrada-Pena A, Feldmann H. Recent advances in research on Crimean-Congo hemorrhagic fever. J Clin Virol. 2015 Mar 1;64(10):137–43.
34. Papa A, Dalla V, Papadimitriou E, Kartalis GN, Antoniadis A. Emergence of Crimean–Congo

haemorrhagic fever in Greece. Clin Microbiol Infect. 2010 Jul 1;16(7):843–7.

35. Bartolini B, Gruber CEM, Koopmans M, Avšič T, Bino S, Christova I, et al. Laboratory management of Crimean-Congo haemorrhagic fever virus infections: Perspectives from two European networks. Eurosurveillance [Internet]. 2019 Jan 31 [cited 2022 May 23];24(5):1800093–5. Available from: https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2019.24.5.1800093
36. Schuster I, Mertens M, Mrenoshki S, Staubach C, Mertens C, Brüning F, et al. Sheep and goats as indicator animals for the circulation of CCHFV in the environment. Exp Appl Acarol [Internet]. 2016 Mar 1 [cited 2022 May 23];68(3):337–46. Available from: https://link.springer.com/article/10.1007/s10493-015-9996-y
37. Yadav PD, Patil DY, Shete AM, Kokate P, Goyal P, Jadhav S, et al. Nosocomial infection of CCHF among health care workers in Rajasthan, India. BMC Infect Dis [Internet]. 2016 Nov 3 [cited 2022 May 23];16(1):1–6. Available from: https://bmcinfectdis.biomedcentral.com/articles/10.1186/s12879-016-1971-7
38. Leblebicioglu H, Ozaras R, Sunbul M. Crimean-Congo hemorrhagic fever: A neglected infectious disease with potential nosocomial infection threat. Am J Infect Control [Internet]. 2017 Jul 1 [cited 2022 May 23];45(7):815–6. Available from: http://www.ajicjournal.org/article/S0196655316307581/fulltext
39. Wilson ML, Gonzalez JP, Cornet JP, Camicas JL. Transmission of crimean-congo haemorrhagic fever virus from experimentally infected sheep to hyalomma truncatum ticks. Res Virol. 1991 Jan 1;142(5):395–404.
40. Ryu BH, Kim JY, Kim T, Kim MC, Kim MJ, Chong YP, et al. Extensive severe fever with thrombocytopenia syndrome virus contamination in surrounding environment in patient rooms. Clin Microbiol Infect. 2018 Aug 1;24(8):911.e1-911.e4.
41. Pshenichnaya NY, Leblebicioglu H, Bozkurt I, Sannikova IV, Abuova GN, Zhuravlev AS, et al. Crimean-Congo hemorrhagic fever in pregnancy: A systematic review and case series from Russia, Kazakhstan and Turkey. Int J Infect Dis. 2017 May 1;58(3):58–64.
42. Hajdušek O, Šíma R, Ayllón N, Jalovecká M, Perner J, de la Fuente J, et al. Interaction of the tick immune system with transmitted pathogens. Front Cell Infect Microbiol [Internet]. 2013 [cited 2022 May 23];3(7):26–40. Available from: /pmc/articles/PMC3712896/
43. Papa A, Tsergouli K, Tsioka K, Mirazimi A. Crimean-Congo Hemorrhagic Fever: Tick-Host-Virus Interactions. Front Cell Infect Microbiol [Internet]. 2017 May 26 [cited 2022 May 23];7(5):213–9. Available from: /pmc/articles/PMC5445422/
44. Flusin O, Vigne S, Peyrefitte CN, Bouloy M, Crance JM, Iseni F. Inhibition of Hazara nairovirus replication by small interfering RNAs and their combination with ribavirin. Virol J [Internet]. 2011 [cited 2022 May 23];8(5):249–59. Available from: /pmc/articles/PMC3120786/
45. Turell MJ. Role of Ticks in the Transmission of Crimean-Congo Hemorrhagic Fever Virus. In: Crimean-Congo Hemorrhagic Fever: A Global Perspective [Internet]. Springer, Dordrecht; 2007 [cited 2022 May 23]. p. 143–54. Available from: https://link.springer.com/chapter/10.1007/978-1-4020-6106-6_12
46. Xia H, Beck AS, Gargili A, Forrester N, Barrett ADT, Bente DA. Transstadial Transmission and Long-term Association of Crimean-Congo Hemorrhagic Fever Virus in Ticks Shapes Genome Plasticity. Sci Rep [Internet]. 2016 Oct 24 [cited 2022 May 23];6(10):35819–30. Available from: /pmc/articles/PMC5075774/

47. Szigeti A, Kreizinger Z, Hornok S, Abichu G, Gyuranecz M. Detection of Francisella-like endosymbiont in Hyalomma rufipes from Ethiopia. Ticks Tick Borne Dis [Internet]. 2014 Oct 1 [cited 2022 May 23];5(6):818–20. Available from: https://pubmed.ncbi.nlm.nih.gov/25108781/
48. Papa A, Tsioka K, Kontana A, Papadopoulos C, Giadinis N. Bacterial pathogens and endosymbionts in ticks. Ticks Tick Borne Dis [Internet]. 2017 Jan 1 [cited 2022 May 23];8(1):31–5. Available from: https://pubmed.ncbi.nlm.nih.gov/27686386/