Crimean–Congo hemorrhagic fever: Risk for emergence of new endemic foci in Europe?

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Summary During recent years, new foci of Crimean–Congo hemorrhagic fever (CCHF) have emerged in several Balkan countries, southwest Russia, and Turkey. Starting in 2002, Turkey experiences the largest ever recorded outbreak with more than 2500 cases. Potential reasons for the emergence or re-emergence of CCHF include climate changes which may have a significant impact on the reproduction rate of the vector Hyalomma ticks, as well as anthropogenic factors (e.g. changes in agricultural and hunting activities). Given the abundance of its vector, the numerous animals that can serve as hosts, and the favorable climate and ecologic parameters in other southern Europe Mediterranean countries, CCHF is an example of a vector-borne disease which may be knocking the door in this area. There are models which show probability of CCHF extending to other countries around the Mediterranean basin suggesting that the vector, veterinarian, and human surveillance should be enhanced.

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Introduction

Crimean–Congo hemorrhagic fever (CCHF) is an acute, highly contagious viral zoonosis transmitted to humans not only by ticks, mainly of the genus Hyalomma, but also by direct contact with blood or tissues of viremic hosts. In cases of severe illness, prominent hemorrhagic manifestations occur at a late stage, with a fatality rate ranging from 5% to 50%. Because of the potential of human-to-human transmission and the onset of nosocomial outbreaks, CCHF is a disease of immediate notification to public health authorities. CCHF is also included in the list of infectious agents for potential use as a biological weapon, and also in the list of diseases for which the Revised International Health Regulations call for assessment of the CCHF event for possible notification to the World Health Organization (WHO). CCHF was first recognized as a clinical entity during an outbreak which occurred in Crimea in 1944–1945.
Subsequently it was found that the causative agent was identical to an agent isolated in 1956 from a human case in The Congo, and the name CCHF was established. At present, CCHF virus (CCHFV) is endemic in wide areas of Africa and Eurasia. During the recent years the emergence or re-emergence of CCHF was described in several Balkan countries, including Albania, Kosovo, Bulgaria, and recently in southwest Russia, Turkey, and Greece. The epidemiology and ecology of CCHF, the current situation in southeastern Europe and neighboring areas are reviewed, and the risk for CCHFV becoming endemic in other European countries is discussed.

Epidemiological and biological aspects

In nature CCHFV circulates in a tick–vertebrate–tick transmission cycle, and humans are accidental intruders of this cycle. CCHFV infection has been detected in numerous wild and domestic vertebrates. The principal animal hosts include cattle, sheep, goats, and hares. Ground-feeding birds are also a significant host of Hyalomma ticks and, at least in Africa, of CCHFV. CCHFV infection is a two-stage vector-borne disease: small herbivores are infected by the immature stages of Hyalomma ticks and serve as amplifying hosts, while adult Hyalomma ticks feed mainly on large herbivores, which have the greatest prevalence of CCHFV infection. CCHFV infection of animals is not associated with evolution to clinically overt disease, chronic infection, or death. In particular, following a tick bite, animal hosts remain viremic and thus infectious for only a few days. For this reason, the CCHFV cycle is sustained by concomitant attachment and feeding on a specific animal by more than one stage of ticks, which in turn allows for CCHFV transmission from mature to immature ticks during feeding and before dropping to the ground. This limits severely the potential for amplification; infected nymphs arising from any infected unfed larva can only infect the same host on which the larva fed. Furthermore, the infected nymphs develop after feed as adults on different types of hosts, so the cycle can only be maintained by transovarial transmission, which is essential, but apparently is of unknown limited efficiency. Infected ticks have also been detected in migratory birds and their implication in the spread of CCHFV appears likely on the basis of phylogenetic studies showing lineage links of CCHFV over long distances.

Hyalomma ticks are well-established vectors of CCHFV. The genus Hyalomma consists of 30 species of which Hyalomma marginatum marginatum is the almost exclusive CCHFV vector in Europe. H. marginatum is abundant in almost all Balkan countries, and also in Turkey, Russia, Ukraine, Italy, Spain, and Portugal. This species is also found in southern France, Cyprus, Israel, and along the northern seaside of all Mediterranean African countries. In 2006 Hyalomma ticks were detected for the first time in the Netherlands and southern Germany. Although CCHFV has been detected in other tick species (e.g. Dermacentor, Rhipicephalus, Ixodes, Boophilus), CCHFV cycle in nature is sustained almost exclusively by Hyalomma ticks. It is unknown whether these species play a significant role in CCHFV cycle, if non-biological environmental factors change.

Geographical distribution and ecological factors

In contrast to almost all other hemorrhagic fever viruses that have relatively narrow geographical ranges, CCHFV demonstrates the widest geographical distribution among all tick-borne diseases, being detected in more than 30 countries across Africa, central and southwestern Asia, Middle East, and southeastern Europe. The distribution of CCHFV coincides with the distribution of Hyalomma ticks, with a 50° north latitude limit. The numerous animal species that can serve as hosts for CCHFV indicate that non-biological factors are more likely to determine the patterns of epidemiological risk.

Temperature and humidity are major determinants for the geographical range and survival of ticks. Warmer temperatures have an impact on tick populations and their annual and seasonal patterns, mainly by shortening their inter-stadial development period which may affect their lifecycle. The key predictor variable for the presence of CCHF identified by stepwise forward selection is a minimum land surface temperature of 18.91°C, whereas a value of 18.16°C predicts CCHF absence. These temperature limits explain the consistent association of CCHF cases with warmer temperatures and the season. Compared to other ticks, Hyalomma ticks adapt better to dry climates. These characteristics are in accordance with activation of Hyalomma ticks in temperate areas in late spring and their continuous activation throughout summer to early autumn. Ixodes ricinus also shows this seasonal pattern of activity, however it is extremely sensitive to low humidity. The CCHF outbreaks which occurred in Albania and Kosovo in 2001 were preceded by mild winters. Micro-ecological factors (e.g. vegetation, microclimate) may also influence the tick–host dynamics and may provide an explanation for the heterogeneity in infection levels which may occur even within endemic regions. For example, in several Balkan countries, endemicity of CCHF occurs in well-confined areas. Hyalomma ticks are found mainly in areas of small and relatively dry vegetation that are relatively easily accessible by humans, and not in forest-type vegetation.

Humans may affect the ecology of CCHFV and thus modify the risk for transmission. Disruption of agricultural activities, changes in land use from floodplains to agricultural land, abandonment of hare hunting followed by reintroduction of livestock, and war conflicts have been associated with large CCHF outbreaks in the former Soviet Union, Bulgaria, Kosovo, and Turkey. Recreational activities may also account for the onset of CCHF cases. Animal trade may account for importation of infected Hyalomma ticks from endemic to non-endemic areas. There is a phylogenetic evidence of movement of CCHFV lineages over large distances, which may be explained by movement of CCHFV-infected or infested livestock, for example there is considerable movement of sheep and goats between Africa and Asia in the context of religious festivals. Major migratory bird fly paths may explain CCHFV lineage links between West and South Africa. Increased awareness and improvements in diagnosis of CCHF may also contribute to the apparent emergence of CCHF.
Current situation and trends

Analysis of the WHO Regional Office for Europe database reveals that CCHF emerges or reemerges in the Balkans, Turkey, and southwest Russia. In accordance with these data, 159 CCHF cases were notified from these areas to WHO during 1989–2000 compared with 3000 cases notified during 2001–2007. Turkey and Russia account for the overwhelming majority of CCHF cases after 2000 (2291 cases (76.3%) and 446 cases (14.8%), respectively). The several hundreds of cases which occurred in Russia during 2000–2006 and in Turkey during 2007 are not included in this database. In southwestern Russia, after years of paucity, CCHF re-emerged in 1999, in the areas of Stavropol, Rostov, Kalmikia, and Astrachan. During 2008, many people sought medical treatment for tick bites and the incidence in the area of Stavropol increased 1.5-fold, being the highest for the past 10 years.

Outbreaks also occurred in Albania in 2001 and 2003, in Kosovo in 2001, in Bulgaria in 2002–2003 and 2008, whereas in June 2008 the first case occurred in Northern Greece, a few kilometers away from the 2008 Bulgarian cluster. A seroepidemiological study that is in progress reveals that there are well-defined endemic foci in Northern Greece (Papa and Maltezou, under submission). CCHF is endemic in Bulgaria since the 1950s, however in 2008 a cluster of cases occurred in the southwestern part of the country which was considered a low endemic area; interestingly, cases were observed earlier (in March, 2008) than usual. Circulation of CCHFV among animals and ticks has been recorded in these countries for years. Fluctuations of annual cases may be attributed to annual weather fluctuations. Evidence of CCHF circulation can also be found in most countries in the Black Sea coastline.

Currently Turkey is experiencing the largest ever recorded CCHF outbreak since the identification of this disease in 1944. Following several decades of serological evidence of enzootic circulation of the virus, the first human cases occurred in 2002 in northeast Anatolia. Since then, more than 2500 cases have been recorded with a mean incidence rate of 3.37/100,000 habitants, although there were hyperendemic regions with incidence rates up to 190.81/100,000 habitants. Most cases came from rural areas near five cities in northeast Anatolia. The emergence of CCHF in Turkey was potentially driven by anthropogenic factors, at least in the very first events. During 1995–2000, agricultural activities and hunting were abandoned in the core CCHF endemic areas in northeast Anatolia, allowing the increased reproduction of hares. When humans returned to agricultural lands in 2001, they were exposed to a much higher population of infected ticks. In practice, emergence of CCHF in this area constituted the tip of an iceberg that was already there for decades, whereas suitable ecological and climate parameters allowed further spatial and temporal expansion of the outbreak. A spatial scan analysis model of the evolution of the CCHF outbreak during 2003–2006 revealed that higher CCHF reporting correlated significantly with zones of high climate suitability for Hyalomma ticks and fragmentation of agricultural land. Recently, 26 CCHF cases were diagnosed from May 2007 through June 2008 in western Anatolia, indicating further expansion of the outbreak in this country.

Is it possible for CCHF to become endemic in other European countries?

As for all vector-borne diseases, the establishment and maintenance of endemic CCHF within a region require environmental and climate factors and human behavior that favor an efficient contact between an abundant burden of competent vectors, hosts with relatively high prevalence of infection, and humans. Given the multiple animal species which may act as hosts for CCHF, in practice the possibility of CCHF becoming endemic within a region resolves to a question of abundance of Hyalomma ticks in a favorable environment in terms of temperature and humidity, a criterion which is already fulfilled by almost all southern European countries along the Mediterranean Sea. It should be noted, however, that in the case of CCHF the complex interaction of these parameters has been barely elucidated so far.

The second criterion is the presence of CCHFV per se, in other words, an established zoonotic CCHFV circulation. In addition to most Balkan countries with established endemic CCHF, there are a few serological data available from humans suggesting a limited presence of CCHFV in France and Portugal. To our knowledge, there are no data available from other European countries.

CCHFV could be introduced from an endemic to a non-endemic area either by infected vectors, following expansion of their geographical range, or by movement of animal hosts. Climate changes could make an environment more or less favorable for a vector. A model that studied the impact of various climate scenarios on the habitat areas of various tick species predicted that an increase in temperature and decrease in rainfall in the Mediterranean region will produce a sharp increase in the extend of suitable habitat for H. marginatum, resulting in its northward expansion, with the highest impact at the margins of the current distribution range. Since quantitative studies of interactions among non-biological factors have not been conducted so far, the impact of climate change on the risk of CCHF infection remains speculative.

In contrast to mosquitoes, ticks do not move over long distances, thus it is highly unlikely to account for CCHFV transfer far away by their own. On the other hand, infected ticks could be carried by animals or birds over long distances. Hares have large home ranges and theoretically could be implicated in CCHFV importation to a naive area as livestock through (legal or illegal) trade could do. However the emergence of a novel CCHF focus would require the importation of a significant viral load through animals infected with CCHFV-infected ticks. The short-term viremia of infected animals is an intrinsic limit, if importation of an infected animal is an isolated event. Thus, as viremia is short-term, emergence of CCHF in a novel focus as a result of tick-infested animals would also require the presence of suitable Hyalomma vectors for the ticks to establish themselves and for the virus to become endemic and not just cause an outbreak. Overall, the contribution of each parameter in the
onset and spread of an outbreak as well as the transmission rate of the disease remain largely unknown.

In a recent project on identifying climates in other parts of the world which match the climatic conditions within known endemic regions for CCHF using detailed records from 378 human CCHF cases during 1920–2006, probability of hospitable climates not only extended to Spain, Italy, and northern African countries across the Mediterranean sea, but even in large parts of North America, smaller parts of South America, and Australia.\(^{12}\) Given the presence of suitable vectors, hosts, and climate parameters in south Europe Mediterranean countries, it appears possible for CCHF to emerge in these areas within the near future. Further climatic and ecological studies are needed, in order to recognize potential foci for CCHF activity increased in southeastern Europe and Turkey during the last decade, and new foci have been determined. Vector, veterinarian, and human surveillance should be enhanced and synchronized at the national and international levels, in order to complete risk assessment for CCHF under real conditions and direct public health interventions.

**Conclusions**

CCHFV activity increased in southeastern Europe and Turkey during the last decade, and new foci have been determined. Vector, veterinarian, and human surveillance should be enhanced and synchronized at the national and international levels, in order to assess the risk for CCHF spread under real conditions.

**Conflict of interest**

No conflict of interest to declare.

**References**


