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PERSPECTIVE

Crimean-Congo hemorrhagic fever in southeastern Europe

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Summary Crimean-Congo hemorrhagic fever (CCHF) is an acute, tick-borne viral disease, affecting only humans and newborn mice, with hemorrhagic manifestations and considerable mortality in humans. CCHF virus circulates in nature in an enzootic tick–vertebrate–tick cycle; migrating birds and livestock transferred from endemic to non-endemic areas may carry large numbers of infected ticks thus spreading the CCHF virus into novel areas. From 2000 through 2008, the infection emerged or re-emerged in Bulgaria, Albania, Kosovo, and Turkey. It has also recently emerged in Greece, where the first human case has been recognized. This has been attributed to mild winters and to the disruption of agricultural activities, both accounting for an increased tick population, as well as to the migration or transportation of tick-infested birds or animals. CCHF cases occurring as an expected event in endemic areas should be notified to clinicians in the international neighborhood. They should be aware of the probability of importation of CCHF cases from endemic areas, of human-to-human transmission, particularly in the nosocomial setting, and of the potential transmission of the virus via tick-infested and infected imported livestock. This novel European CCHF geographic distribution is a challenge for the scientific community of medical microbiologists, epidemiologists, medical entomologists, and veterinarians that could be followed by acceleration of a European Standardized Response at the national, regional, and international level.

Introduction and epidemiology

Crimean-Congo hemorrhagic fever (CCHF) is an acute, tick-borne viral disease, affecting only humans and newborn mice,[1] with hemorrhagic manifestations and considerable mortality in humans.

CCHF virus circulates in nature in an enzootic tick–vertebrate–tick cycle, the ticks of the genus *Hyalomma* serving as vectors and reservoirs of the virus[1–4] and defining the worldwide distribution of the CCHF virus.[1,2,5,6] Viremia or antibody production has been demonstrated in numerous domestic and wild vertebrates that suffer an asymptomatic infection,[1,5,7,8] while reptiles and birds appear to be refractory to infection with the exception of ostriches.[1] Small herbivores are infested by the nymphal stages of ticks, which transmit the virus transstadially.[2] Migrating birds may carry large numbers of infected ticks, thus spreading

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the CCHF virus into novel areas.[1] Livestock transferred from endemic to non-endemic areas may be infested with infected ticks.[8–12]

Close contact with viremic animals is the second most frequent route of transmission after tick bite.[1,2] Healthcare worker contact with a patient, nosocomial contact of a secondary patient with the index patient,[13] family contact, and breastfeeding have been reported as modes of transmission.[14]

CCHF virus is endemic in parts of Eurasia and Africa, and demonstrates the widest distribution, in an ever-extending range of geographic areas, among all the tick-borne viruses.[1–5,7,9,15–17]

Southeastern Europe depicts a rapidly changing epidemiology of CCHF

From 2000 through 2008 a considerable number of outbreaks in the community and the nosocomial setting were reported[18] in southeastern Europe; in Bulgaria in 2002, 2003,[17] and 2008,[19] and in Albania and Kosovo in 2001, with as yet undefined reservoirs.[17,20,21] Social disruption, conflict, and war have been the major factors identified.[17,20–22]

Similarly to Kenya, Senegal, and South Africa, the 2002 outbreak in Northeastern Anatolia, Turkey, an eastern Black Sea extended geographic region,[14] followed several decades of serologic evidence of a zoonotic focus,[1,3,5,16,23] not preceded by any human case in the country.[14] In 2007 and 2008 a considerable number of CCHF confirmed cases occurred in southeastern and western areas of Turkey, which in 2008 contributed 9% of cases.[24] The infection has spread to previously non-endemic areas of Turkey, near the Aegean coast of the country and in a rural area of Ankara.[13]

There is serologic evidence, but not clinical evidence as yet, in France, Portugal, and Hungary.[1–3]

In northern Greece the appearance of a fatal human case in June 2008, the first ever reported in Greece, followed serological evidence attributed to the non-pathogenic AP92.[25] It is not feasible to speculate whether this was associated with the cases in Bulgaria in March 2008, as retrospective surveys jointly coordinated by public health and veterinary public health sectors are pending.

Climate change and/or socioeconomic factors increase the incidence

In temperate areas, the pattern of seasonality of CCHF cases reflects the period of year with high tick activity—between spring and early autumn.[17,20,21] Climate and environmental changes may trigger community outbreaks.[3,7] Mild winters were followed by CCHF outbreaks in Kosovo in 2001 and in Turkey in 2004.[3,20] Disruption of agricultural activities and expansion of the hare population infested with infected ticks, followed by the reintroduction of cattle and sheep, have been associated with the CCHF outbreaks in the former Soviet Union, Bulgaria, Kosovo, and in the Middle Anatolia Turkish areas.[3] Illegal animal transportation accounts for the expansion of the disease.[22]

International dissemination of reports of cases within endemic areas increases awareness among neighbor countries

Legal and potentially illegal animal transportation among neighboring countries

Animal transportation imposes a risk of international spread from endemic well-prepared countries to non-endemic unprepared ones.[22] Consequently, even if the CCHF cases occur as a usual or expected event in endemic areas, notification of CCHF cases as a public health emergency of international concern is deemed imperative. Both the International Health Regulations and the Early Warning and Response System are competent tools for the dissemination of this information.

National centers for disease control and prevention should increase physician awareness

Physicians should be aware of the probability of importation of CCHF cases from endemic areas, of human-to-human transmission, particularly in the nosocomial setting, and of the potential transmission of the virus via tick-infested and infected imported animals. Prompt suspicion and diagnosis trigger the timely implementation of infection control measures in the community and the hospital.

At this point, the role of the national centers for disease control and prevention is crucial, as they may generate and disseminate warnings and the relevant diagnostic and therapeutic approach to clinicians soon after the emergence or re-emergence of CCHF in the international neighborhood of each distinct country.

Therapeutic consensus

The administration of ribavirin, oral or intravenous, is recommended by the World Health Organization[26] and it has been associated with higher survival rates, shorter recovery time, and earlier return to normal levels of laboratory parameters.[27] Replacement therapy with blood products, according to the results of the complete blood count, is indispensable in the management of severe CCHF cases.

Treatment with ribavirin in suspected cases[28] and post-exposure prophylaxis for healthcare workers potentially exposed to CCHF virus[29] should be considered.

Coordinated actions of the public health sector with the veterinarian authorities ensure preparedness and response

Experts from all relevant disciplines, experienced medical microbiologists, epidemiologists, medical entomologists, and veterinarians, should reach a consensus regarding yearly monitoring before the active period from March through October.

Empowerment of the veterinary sector

Farmers and animal husbandry workers, who might handle animals imported from the endemic areas of neighboring

countries, are potentially high-risk groups even if they reside in a non-endemic country. They should be made aware of the need to consult with the local veterinary authorities, and if indicated the need to conduct serologic examinations on the imported animals, especially those with an evident tick infestation.

Veterinary inspections and the accompanying strict recommendations could also prevent any illegal animal transportation among countries so as to reduce the probability of cross-border spread of infected ticks and subsequent expansion of CCHF. The empowerment of the veterinary sector throughout southeastern Europe and the enhancement of their cooperation and rapid information sharing with the human public health sector at the local, national, regional, and international level are highly recommended.

In endemic areas, professional groups in contact with animals should be educated to take precautions against contact with ticks and blood or other tissues: the wearing of gloves, use of long trousers and long sleeves if possible, the application of repellents on exposed skin, and the thorough inspection of skin and clothes for ticks.

Veterinarians should be trained to convey their knowledge of CCHF epidemiology, mode of transmission, and particularly precautions to farmers of backyard cattle or other animals. They should conduct consultation meetings and guide rural populations on how to minimize the likelihood of acquiring any zoonoses including CCHF, in close collaboration with the public health sector.

Environmental interventions

Free-range areas should be clearly oriented and accurately differentiated from residential and tourist areas.

Regular agricultural activities to keep farms neat and tick control measures protect domestic animals from ticks and tick-borne diseases.[19]

Animal serologic surveys and medical entomologists are capable of detecting virus circulation early

Serology of imported animals is an important subsidiary to consistent strict measures against illegal animal cross-border trafficking.

Medical entomology has a vital role in the characterization of tick species according to international taxonomy, and medical microbiology in the examination of pooled samples of ticks for the CCHF virus RNA.

Conclusions

Monitoring of the virus circulation in probable zoonotic foci is of paramount importance in the temperate countries of southern Europe, where there are densely populated coastal areas, many of which are also major tourist destinations. Early virus detection in ticks, large herbivores, and small mammals, particularly when they originate from endemic areas of the same or a neighboring country, is the cornerstone of prevention of human cases. Periodic education of high risk groups by those in the veterinary and public health sectors and regular updating of clinicians also play an important role in the early diagnosis of cases and in the prevention of establishment of the virus in novel areas and the subsequent outbreaks. This will also contribute to the containment and elimination of the disease in already endemic areas.

Under intense media and public interest or even in the panic that CCHF emergence generates, there may be unreasonable allocation of resources and an increased economic burden for tourism and the farming industry of a country. The cross-border transmission of CCHF virus via legal or illegal animal movement should be prevented via strict veterinary monitoring.

The novel European CCHF geographic distribution is a challenge for the scientific community that could be followed by acceleration of a European Standardized Response at the national, regional, and international level.

Conflict of interest: No conflict of interest to declare.

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