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Crimean–Congo Hemorrhagic Fever in Spain — New Arrival or Silent Resident?

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Crimean–Congo hemorrhagic fever (CCHF) is a tickborne viral zoonosis. The causative agent, CCHF virus (CCHFV), is a negative-strand RNA virus in the family Nairoviridae. The virus circulates in nature in a vertebrate host–tick cycle, in which the vertebrate hosts are transiently infected and show no overt signs of disease. Ticks are both the vector and the reservoir for CCHFV. Although virus has been detected in a wide range of ticks, not all of these species can transmit or maintain it in nature. Viral epidemiology and experimental studies indicate that ticks of the genus *Hyalomma* are the main CCHFV vectors and reservoirs. They maintain virus by transmission from one life stage or generation to the next and infect vertebrate hosts, which amplify the virus and infect additional tick populations.¹

The report of autochthonous CCHF in Spain by Negrodo et al. in this issue of the *Journal* (see pages 154–61) highlights fundamental characteristics of the epidemiology of this disease.² CCHFV, like other tickborne pathogens, circulates silently. Outbreaks occur when a range of factors related to tick, vertebrate host, and human behavior align, increasing the level of viral circulation, the interactions between humans and sources of infection, or both. Changes in ecologic balance caused by anthropogenic factors, such as land fragmentation, are common contributors to CCHF outbreaks; indeed, the first recognized outbreak of CCHF occurred in the summer of 1944 in the Crimean peninsula, when Soviet troops reoccupied abandoned agricultural areas, resulting in about 200 cases in agricultural workers and soldiers.

CCHFV infection in humans is incidental; exposure occurs through a tick bite, contact with infected blood or tissues, or the crushing of engorged infected ticks. There is a broad spectrum of CCHF disease, from mild flu-like illness to bona fide hemorrhagic fever with such hallmark signs as bleeding from puncture sites and orifices, petechial hemorrhage, and diffuse ecchymosis. A brief incubation period of 2 to 7 days is followed by a prehemorrhagic period characterized by fever and a variety of nonspecific signs. In severe cases, patients have elevated levels of liver enzymes and proinflammatory cytokines, prolonged elevation of bleeding markers, and thrombocytopenia, all of which may culminate in either convalescence or death on day 5 to 14 because of shock and multiorgan failure.³

Cases are typically sporadic, occur in remote or agricultural regions, and are seasonal in association with the life cycle and activity levels of local tick populations. Clusters of disease spread by human-to-human transmission most often occur in nosocomial settings when an infectious cause is not suspected early enough to permit employment of proper barrier precautions.

So why has CCHFV hit Spain now? The virus is widely distributed, having been found from western China, across southern Asia to the Middle East and southeastern Europe, and throughout most of Africa. Although the cases in Spain were unprecedented, they were not unimaginable: evidence of CCHFV circulation was reported more than 6 years ago only 300 km from where exposure of the index case occurred, and Negrodo et al. phylogenetically link the virus detected in these recent cases to the virus in the previous report.

The virus has most likely been in Spain for a while, supported by sufficient populations of two competent tick vectors, *Hyalomma marginatum* and *H. lusitanicum*.¹ The two species generally do not coexist: *H. marginatum* prefers open habitats at low elevation, whereas *H. lusitanicum* is found at higher elevations and in colder areas. The lack of clinical recognition of CCHF in this region predominantly reflects the overall infrequency of human infection; a lack of reported cases in humans in recognized areas of viral presence (infected ticks or serologically positive vertebrate hosts) is not unusual. Either humans are not exposed to hyalomma ticks often enough or the percentage of infected hyalomma ticks is small — or both. Contributors to spillover from enzootic cycles have been identified in previous outbreaks and usually include increases in the population density of vertebrate hosts and ticks to above the maintenance level. At this time, however, the specific ecologic contributors to the recent cases in Spain remain unclear.

Without active surveillance and local access to diagnostic assays (viral RNA detection and serologic tests), the virus could be circulating unnoticed. The absence of reported cases may also reflect lack of recognition of the disease, whether severe or mild. Severe hemorrhagic disease is the most well described clinical presentation of CCHF, but the full spectrum of disease is not known. We are learning that mild or sub-clinical infections occur more frequently than previously thought. A case in point is Turkey: after CCHF was first recognized there in 2002, Turkey became the first endemic region with consistently high disease incidence, with nearly 10,000 cases reported to date, along with hundreds in neighboring Iran. These cases have had a lower fatality rate — less than 5%, as compared with up to 70% observed in several previous outbreaks.

We do not know when CCHFV was originally introduced into Spain. The viral sequences found there are most closely related to CCHFV strains in northwestern Africa — a finding that supports the theory that the virus was spread northward by migrating birds, rather than entering from the east. General mechanisms of the expansion of CCHFV include transport of ticks by migrating birds and transport of ticks or virus through livestock trade. Another factor influencing gradual changes in tick distribution is climate change, which has contributed to the northward expansion of *H. marginatum* populations; however, such gradual expansion would not result in the sudden emergence of CCHF in new or distant regions.

The occurrence of CCHF cases outside the historical range of virus circulation highlights the need for enhanced public awareness and education of clinicians both in areas where cases have been reported and where they have yet to occur. Reduced exposure to tick bites and prompt tick removal can help prevent or greatly reduce disease occurrence. In addition, safe practices in other high-risk activities, such as slaughtering of potentially infected livestock, can aid in disease mitigation. Clinicians must recognize that CCHF presents with nonspecific signs that are also seen with several other agents, both hemorrhagic and nonhemorrhagic. A detailed patient history, including occupation, travel, and leisure activities, is important for prioritizing CCHF in the differential diagnosis. Tick bites can go unnoticed, so the lack of reported tick exposure should not cause clinicians to rule out CCHF.

CCHF cases will inevitably occur again in other areas where there is unrecognized viral circulation. As in Spain, these cases will serve as reminders of the largely inconspicuous cycle of CCHFV maintenance in nature. Whereas the natural reservoirs of some other causes of hemorrhagic fever, such as Ebola, have not yet been definitively confirmed, we know how CCHFV is maintained and how virus spillover occurs. When CCHF cases do occur, the transmission potential can be reduced by timely identification of the disease and implementation of barrier-protection and patient-isolation practices. Supportive care remains the mainstay of treatment, and therapeutic intervention requires timely case identification. Although the efficacy of current antiviral options remains debatable, data on ribavirin use promote early administration as more likely to improve patient outcomes. Additional management options, supported by clinical efficacy data, are needed. It is promising that researchers are actively engaged in advanced high-throughput screening of therapeutics and in development of vaccine candidates to aid in these efforts.

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References

1. 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; 144:93–119. [PubMed: 28579441]
2. 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.* 2013; 100:159–89. [PubMed: 23906741]
3. Ergönül O. Crimean-Congo haemorrhagic fever. *Lancet Infect Dis.* 2006; 6:203–14. [PubMed: 16554245]