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Crimean-Congo hemorrhagic fever and expansion from endemic regions

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Abstract

Crimean-Congo hemorrhagic fever (CCHF) is a virus-mediated hemorrhagic disease that occurs over a wide geographic region. In recent years, a variety of active and passive surveillance networks have improved our knowledge of areas with existing circulation of Crimean-Congo hemorrhagic fever virus (CCHFV), the etiologic agent of CCHF. These investigations aid in better defining the distribution of the virus. Expansion of a virus into new areas can occur through a variety of means, including introduction of infected humans, vectors, or animals. Here, these potential contributors to expansion of CCHFV into neighboring countries and geographically distant locations are reviewed, and the likelihood and possible implications of these events, based on known characteristics of the virus and its natural maintenance and transmission cycles are explored. Furthermore, this report discusses limitations in the currently described distribution of CCHFV, and the challenges in assessing viral circulation identified in a new region as geographic expansion of the virus.

Introduction

Crimean-Congo hemorrhagic fever (CCHF) was first identified in the Crimea region of the former Soviet Union in 1944, and in the Belgian Congo (present Democratic Republic of the Congo, DRC) in 1956 [1]. These independent reports were later linked, resulting in the current virus naming. This identification history encompassing two geographically distinct regions was an early indication of the potential for wide-spread occurrence of CCHF and the etiologic agent, Crimean-Congo hemorrhagic fever virus (CCHFV; family *Nairoviridae*). To date, CCHFV has been described in numerous countries, spanning Europe, Asia, and Africa [2]. The virus is maintained in nature in an endemic tick-vertebrate host-tick cycle; ticks serve as both the reservoir and vector of CCHFV. Despite evidence that other genera of ticks may be involved in CCHFV transmission under laboratory conditions, ticks of the genus *Hyalomma* are consistently reported in association with human disease in nature and are considered crucial in maintaining endemic foci [3].

Disease is often a mild, nonspecific febrile illness that, in a subset of cases, can progress to severe hemorrhagic disease [1]. The case fatality rates range from <5% to upwards of 30% depending on the region and size of the outbreak, with case fatality often inversely

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associated with the number of reported cases. Endemic areas with the largest annual incidence, such as Turkey and Russia, report much lower case fatality rates than other countries. Whether this reflects inherent differences in current circulating virus strains in the region or differences in approach to clinical management of cases is not known.

CCHF is a significant public health concern, with cases occurring over a wide geographic range and the potential for virus expansion into new regions. Here we will discuss what is known (and what remains unknown) about CCHFV epidemiology and ecology; (b) review approaches for epidemiologic surveillance, viral detection, and case confirmation; and (c) discuss methods and likelihood of geographic expansion of virus into both contiguous and non-contiguous regions by considering three main mechanisms of spread: the importation of infected human cases, ticks, or livestock (Table 1).

Defining endemic regions of CCHFV

Expansion, or new evidence of virus presence in a territory that does not reflect its prior persistence or circulation, cannot be discussed without consideration of what constitutes endemic regions. As described, the recognized geographic distribution of CCHFV is vast and includes areas spanning from western China across southern Asia to the Middle East, Spain, and the Balkans, and throughout most of Africa [1]. Areas outside of this known range may represent true absence of viral circulation, or simply a lack of detection. In geographically distant non-contiguous areas, an absence of epidemiologic data or cases likely reflects a true lack of virus presence. However, in countries bordering one or more regions with well-documented natural CCHFV transmission, a paucity of evidence interpreted as absence of circulating virus is less compelling. Notably, it is not uncommon for the first reports of virus or human cases in a region to coincide with the implementation of surveillance systems, suggesting that virus has been present in the area for some time [4].

Well-characterized, robust tools are available for CCHF diagnosis and surveillance [5]. CCHFV circulation is detected by a variety of means, including IgG and IgM serosurveys in humans and animals [6–10], and viral RNA detection in human, animal, or tick samples (of both questing, and, more commonly, feeding ticks). Retrospective serosurveys in humans provide information about exposure to the virus, but say nothing about active infection, or time or place of exposure. Serosurveys in wild and domestic animals have similar limitations. In addition, unless herds have been stationary, associating evidence of exposure to the region in which samples were collected is difficult. Other considerations include the potential for passive transfer of maternal antibodies in livestock [11●], and for cross-reactivity to antigenically related viruses [12●].

Viral genome detection is generally achieved through RT-PCR targeting the nucleocapsid gene [13], which shows the highest level of nucleotide conservation between strains. While RT-PCR can be a key tool for human case diagnosis and confirmation of CCHFV circulating in a region, data interpretations are limited for certain applications, in particular tick studies. Detection of viral genome by RT-PCR in questing ticks indicates that the virus is present in the area, but neither it provides proof of the transstadial or transovarial transmission capacity of the tick species, nor it shows that the ticks can transmit virus to vertebrates. RT-PCR

positivity in ticks feeding on hosts also indicates that virus is present, but does not differentiate whether the tick was infected before the blood meal or exposed to virus from the blood of the host. Furthermore, no conclusions can be drawn about the likelihood of transmission of the virus by that tick species.

Despite the aforementioned caveats in data interpretation, genome sequencing analysis can be a powerful epidemiological tool for tracking the origin and spread of virus. For example, single nucleotide variant analyses of complete genomes in outbreaks or clusters of infection could allow the identification of the human, tick or animal host at the origin of the infection. Minor changes in genomes are often sufficient to recapitulate transmission chains and migration of the virus without relying exclusively on epidemiological and classical laboratory testing [14●]. In addition, large scale evolution studies of complete CCHFV genomes from historical and circulating strains could provide information on the trajectory of the expansion [15], the identification of long distance migration [16] and documentation of genome reassortment events over time [17].

Serology and RT-PCR, alone or in combination, have been used historically to define the level of CCHFV presence in a country. In 2017, the World Health Organization updated the map summarizing the geographic distribution of CCHFV. Countries were evaluated based on increased measures of risk, from confirmed detection of *Hyalomma* ticks to virological and serological evidence of CCHFV and vector presence, and by case numbers (available at: http://www.who.int/emergencies/diseases/crimean-congo-haemorrhagic-fever/Global_CCHFRisk_2017.jpg?ua=1) [18]. This map highlights several countries with vector presence that neighbor those where CCHFV has been detected (some with human cases). Caution should be used when interpreting reports of viral detection or human cases in new areas as ‘expansion’. The differentiation between first-time presence in a region versus evidence of long-standing but previously undetected viral circulation must be considered to avoid an unnecessarily alarmist approach to reporting vital data for understanding the historical presence of CCHFV.

Expansion by human case introduction

CCHFV is transmissible person-to-person via exposure to virus-containing body fluids of a patient during the first 7–10 days of illness [1]; nosocomial case clusters are often reported [19–29]. Standard barrier nursing methods are sufficient to prevent the transmission of CCHFV in the patient care setting [30,31]. In general, outbreak clusters are limited to fewer than five cases, but may involve 30 or more [32,33]. Spread into urban communities and multiple chains of transmission are rare, but can occur [34].

Human cases may travel, either before or after development of clinical signs (reviewed in detail in Ref. [35●●]). Travel before onset of clinical disease presents challenges as the index of suspicion may be reduced, delaying diagnosis. Travel after clinical disease begins is not uncommon with CCHF. Human exposure occurs more frequently in remote regions; disease is often associated with a history of tick bites or livestock handling. The most active foci tend to be in rural areas, as both wild and domestic animals serve as hosts to the tick reservoir and develop a transient viremia to aid in viral maintenance in nature. Disease may

prompt patients to travel for diagnosis and treatment, providing a means for introduction into other, sometimes more populated areas. This can include travel over large distances, as was the case with a migrant worker who returned home to India after becoming ill in Oman [36●].

Confirmed imported cases of CCHF to non-endemic countries have been reported in France (from Senegal, 2004) [37], Germany (from Afghanistan, 2009) [38], and the United Kingdom (two cases—from Afghanistan in 2012 and from Bulgaria in 2014) [39,40]. Additional suspected or unpublished imported cases include, one in the UK (from Zimbabwe, 1997) [41] and one in Germany (from Bulgaria, 2001) [42]. Only a well-trained, astute medical professional would suspect CCHF in patients in non-endemic areas, since the initial symptoms are non-specific and difficult to differentiate from those with many other infectious causes. However, recent out-breaks such as the 2013–2016 Ebola virus disease out-break [43], have resulted in increased global awareness and index of suspicion of viral hemorrhagic diseases. As a result, border screening and handling of cases (i.e. basic barrier and patient isolation practices) have been re-examined and strengthened in many countries. These practices will help to limit the introduction and subsequent spread of diseases, including CCHF, from imported cases.

Expansion by infected tick introduction

In 2016, CCHF was first described in Spain [44], which, despite evidence of CCHFV in nature based on tick surveillance studies [45], had no previous reports of autochthonous human cases. It was suggested that these reports represent a change in the geographic distribution of the main vector [44]. In fact, data reveal that permanent populations of *Hyalomma* ticks have not changed in upwards of 50 years [46], though the presence of some species such as *Hyalomma lusitanicum* has been noted outside of their classic territories. As ticks only disperse large distances while carried by their hosts [47], these changes in tick populations are largely in association with bird migration or expansion of host populations. Geographic expansion of tick populations is concerning for two main reasons. First, infected ticks imported into non-contiguous countries may infect humans and start a wave of human-to-human transmission. Additionally, uninfected ticks may be brought into a country and establish novel populations able to sustain local maintenance upon introduction of the virus to the area.

Birds are considered an important vehicle for long-distance movement of ticks [48–50]. Interestingly, experimental infection of birds does not support efficient viral replication; viremia was not detectable in almost all avian species investigated, with the notable exception of ostriches [51●,52]. These reports are supported by extensive serosurveys that did not detect anti-CCHFV anti-bodies in a wide range of avian species [53]. Nevertheless, despite a seemingly minimal role in the CCHFV transmission cycle, birds appear key in potential vector introduction. For example, immature *Hyalomma marginatum* and *Hyalomma rufipes* ticks have been found in Germany [54], Hungary [55], and the UK [56●] upon introduction by migratory birds. However, these occurrences appear to be unusual at high latitudes, because along these migratory routes, birds stop to feed and rest in the Mediterranean basin where most, if not all, ticks detach. *H. marginatum* ticks have also been

found in southern France [57], another heavily visited region on migratory routes, but establishment of permanent populations in this region is quite uncommon because of the lack of hosts for adult ticks. In contrast, permanent populations of *H. lusitanicum*, once restricted to southwestern Spain and Portugal, are now in northeastern Spain because of overpopulations of preferred hosts, including rabbits and wild boars [45]. Additional means of tick introduction include illegal animal importation. For example, *Hyalomma aegyptium*, which parasitize tortoises, were introduced from Africa to Europe [58]. Interestingly, RT-PCR data support a role for *H. aegyptium* in CCHFV ecology [59], but the vectorial ability of these ticks has not been determined.

Considerations for the importation of CCHFV vectors should focus on *Hyalomma* spp., as little evidence supports a role for other ticks in maintaining endemic foci. For example, mass numbers of one of the most aggressive *Amblyomma* species, *Amblyomma variegatum*, were imported on livestock to the Caribbean from CCHFV-endemic Senegal [60,61], yet there is still no evidence of the virus in the Americas. If *Amblyomma* ticks were also involved in CCHFV circulation, this would most likely have been captured in the epidemiology of the virus, but CCHFV distribution still adheres to the distribution of *Hyalomma* ticks. *Rhipicephalus bursa* ticks are a notable exception that appear to circulate a specific genetic lineage of CCHF classified in the Europe 2 clade. However, strains of this clade were also detected in *Hyalomma* ticks [62]. Vector competence of *Rhipicephalus* ticks is not yet strongly supported as the role of *R. bursa* may reflect vector competence of the tick, or simply the prevalence of *R. bursa* in the region where strains in the Europe 2 clade circulate [3]. Furthermore, *R. bursa* are only found in the Mediterranean region and Iran, and there is no evidence to date of this strain in regions of Africa where many other species of *Rhipicephalus* exist.

A topic warranting more discussion is whether *Hyalomma* ticks would be likely to establish local permanent populations upon introduction. Ticks are sensitive to changes in several limiting abiotic factors, including temperature, which affects the timing and speed of development, and atmospheric water deficit, which affects mortality [63••]. Several studies have investigated dispersion rates, abiotic suitability, and the effects of a changing environment on the colonization potential of tick species outside their current range [63••, 64–66]. These complex analyses are based on a fundamental understanding of the life cycle of specific tick species and thus varies both between and within countries depending on landscape, climate, and host population dynamics. A drive to encourage these analyses in areas that do not border known populations of *Hyalomma* would greatly aid in providing insight into the likelihood for long-term consequences of vector introduction.

Expansion by movement of animals

A final factor involved in viral expansion is the movement of wild or domestic animals. Although some borders prohibit movement of infected animals due to geographical or political reasons, cross-border movement of animals (especially livestock) is a frequent practice and may lead to the spread of disease. Notably, almost all livestock and wild vertebrates are susceptible to CCHFV infection but present no clinical signs [51•], so

current health screening border control practices do little to prevent movement of infected animals.

Only a small percentage of livestock imports into the European Union originate in CCHFV endemic countries [67], reducing the potential for livestock-mediated introduction into these and other countries with similar trade practices. However, movement of livestock remains a concern, especially for local or cross-border exchange which is more frequent. The livestock trade has contributed to viral hemorrhagic fever outbreaks in the past, as in 1977, when the movement of infected sheep and camels between Sudan and Egypt was believed to be responsible for a Rift Valley fever outbreak [68]. Livestock trade is also an important contributor to the spread of CCHFV. For example, the first report of CCHF in Abbottabad, Pakistan, described significant movement of livestock towards the area, which might have included infected sheep and exposed the index case [69]. Several CCHF outbreaks have been reported in association with the time of Eid-ul-Adha, a Muslin religious festival, during which millions of livestock are imported into cities and sacrificed [70]. Furthermore, the movement of livestock and other animals (e.g. deer between hunting farms) can provide means to transport ticks. This may result in the introduction of CCHFV reservoir or vector species, as was the case with the report of adult *Hyalomma* spp. on a horse imported to England [71]; or the movement of CCHFV-infected ticks [72].

Several approaches are available that may reduce the potential for virus or ticks to be imported via animals into non-endemic regions. Acaricide treatment of exported livestock can be used to reduce tick introductions. In addition, as the viremic period in wild and domestic animals tends to be brief (7–14 days) [51•], quarantine periods would decrease the risk of transmission to humans or local tick populations. While these approaches are helpful, there are aspects of infection in animals that are not yet understood, limiting prevention strategies. For example, it is not known how long virus remains in tissues. As exposure to CCHFV by handling livestock is well documented [73–75], this and other questions regarding infection in host species still need to be addressed to better define the risk period when handling potentially infected animals.

Conclusions and future considerations

Much remains unknown about CCHFV and its epidemiologic history. Thus, defining expansion is a challenge, as endemic regions of CCHFV are not yet fully characterized. Available information and our ability to map data such as disease, serology, and viral genome detection are improving. While viral detection or case reports in new areas confirm CCHF as a re-emerging disease, classification of these occurrences as novel emergence should be made cautiously. What are considered new areas of CCHFV circulation are often recognized via human case reports, as was the case in the initial discovery of CCHFV and in recent occurrences. The human cases in Spain in 2016 are examples seen by many to represent expansion of the virus into new territories, although evidence of CCHFV had been described for some time in areas neighboring where these cases were reported.

Without question, frequency of disease reporting is increasing. Whether this represents expansion to new regions or changes to existing areas of sporadic circulation will continue

to be challenging to differentiate. This rise could be due to increased awareness, but awareness is unlikely to be the only contributor. The ability of virus to circulate in a higher frequency of tick and livestock populations is not known and should be investigated. Climate change is often stated as a driver for CCHFV expansion, but evidence suggests other anthropomorphic factors as more instrumental in CCHF emergence and outbreaks. These include agricultural abandonment promoting large populations of vertebrate hosts for *Hyalomma*; landscape fragmentation promoting a local increase in the abundance of suitable hosts for the vector; and proliferation of wildlife hosts that feed the adult ticks and thus may exacerbate CCHFV prevalence in tick vectors [76]. These and other factors also contribute to periodic or sustained increases in vector density (population versus geographic expansion) and changes in relative numbers of tick species; these changes may be linked to increased virus detection and incidence of human disease, as was reported in Turkey [77]. In addition to environmental and ecological factors, there may be differences in the virus or new emerging viral strains associated with increased virus circulation and frequency of disease. Sequencing of full CCHFV genomes could more precisely address virus evolution, genome reassortment events, expansion and migration over time.

If CCHFV did have the chance to transmit from imported cases, ticks, or livestock, what is the likelihood of maintenance in local tick-host cycles? CCHFV has been reliably demonstrated in unfed specimens of *Hyalomma anatolicum*, *H. marginatum*, *H. rufipes*, and *Hyalomma truncatum*, and in the eggs of *Dermacentor marginatus*, but this does not provide sufficient evidence regarding the ability of these ticks to maintain virus in nature [3]. Moreover, *Hyalomma* and related genera do not exist in some areas, including North America. Unfortunately, any question as to ability of local endemic tick populations to maintain or transmit CCHFV would at best be speculative. Without experimental data, there is no way to know how well local ticks, with their particular host preferences, can maintain CCHFV circulation and transmit it to subsequent generations of ticks or humans.

Expansion in the form of importation to areas far from endemic regions has other considerations, as discussed. Is importation possible? Absolutely; it has happened in the past and will happen again. Will importation result in widespread disease transmission? Likely not. However, the frequency of these events could be estimated using predictive modeling [78,79]. For example, possible CCHFV spread via infected ticks carried by migratory birds in northern latitudes in Europe may be investigated by estimating the flyways of the birds, the time ticks spend feeding, and the probability of ticks detaching in an area of Europe, together with the estimation of the climate suitability for the tick and the presence of adequate populations of large vertebrate hosts for adult ticks. The permissibility of native hosts and vectors in various countries should be examined, as no data exist at this point to aid country-specific risk assessment for many questions about the potential for establishing viral circulation in nature following an introduction. It is necessary to evaluate the vectorial abilities of non-*Hyalomma* ticks (e.g. *Amblyomma* in America) for transmitting the virus under laboratory conditions. These studies are feasible, as colonies of *Amblyomma* are common in North America and are well adapted to feed on laboratory animals.

Enhanced viral hemorrhagic fever surveillance has pronounced impact [80]. Active and passive surveillance for known tick vectors (e.g. *Hyalomma* spp., *R. bursa*) and CCHF cases

should be continued or initiated in countries neighboring those with evidence of viral presence. As human cases may be the first indication of virus introduction, clinical awareness for CCHF should remain high in endemic and non-endemic areas. The clinical presentation of CCHF is similar to other severe hemorrhagic diseases including those caused by Ebola, Marburg, and Lassa virus. An enhanced index of suspicion and diagnostic screening for CCHFV is essential for rapid and accurate identification of these and other agents. Improving international CCHFV surveillance will aid in overall global health security and ensure timely identification and containment in the event of a novel introduction or outbreak.

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Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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Table 1

Methods of CCHFV importation and expansion: selected reports of molecular, serological, or virological detection in human cases (suspected or confirmed), ticks, or animals imported from different countries or within country

Importation via	Imported from[a]	Imported to	Detection method	Year	Reference
Human	Rwanda/DRC	Uganda	NR	2018	20180804.5941288[b]
	Quetta (Pakistan)	Karachi (Pakistan)	NR	2018	20180609.5847730[b]
	Mianwali (Pakistan)	Karachi (Pakistan)	NR	2018	20180526.5820141[b]
	Khyber-Pakhtunkhwa (Pakistan)	Islamabad (Pakistan)	NR	2017	20170611.5094216[b]
	Oman	India	RT-PCR, serology (IgM)	2016	[36•]
	Afghanistan (9)	Pakistan	NR	2014–2015	[35••]
	Bulgaria	UK	RT-PCR, virus isolation	2014	[40]
	Namibia	South Africa	NR	2014	20140919.2788764[b]
	South Sudan	Uganda	RT-PCR	2013	[35••]
	Afghanistan	UK	RT-PCR	2012	[39]
	Balochistan (Pakistan)	Karachi (Pakistan)	NR	2012	20150524.3382053[b]
	Afghanistan	Pakistan	NR	2011	20110917.2833[b]
	Namibia	South Africa	NR	2010	20100810.2732[b]
	Afghanistan	Germany	RT-PCR, serology (IgM/IgG)	2009	[38,19]
	Çorum, Giresun, Gümüşhane, Kastamonu, Kýrklareli, Rize, Tokat (2), Yozgat (2)	Istanbul	RT-PCR, serology	2006	[81]
	Senegal	France	RT-PCR, serology	2004	[37,82,83]
	Bulgaria	Germany	NR	2001	[38]
	Zimbabwe	UK	Serology (IgM/IgG)	1997	[41]
	Zaïre (DRC)	South Africa	Virus isolation	1985	[84]
	Tanzania	South Africa	Serology	1986	[84]
Tick	Morocco (on migratory birds coming from central and southern Africa)	Potential for importation into Iberian Peninsula	RT-PCR	2011	[16]
	Sudan/Somalia (on Camels)	Egypt	RT-PCR	2009	[72]
	Somalia (Sheep)	Oman	Ag-ELISA	1996	[85]

Importation via	Imported from[a]	Imported to	Detection method	Year	Reference
	Somalia (Cattle)	UAE	RT-PCR, Ag-ELISA	1994–1995	[86,87]
Livestock	Sudan, Kenya	Egypt	Serology	1996–1997	[88●]
	Somalia	Oman	Serology, Ag-ELISA	1996	[85]
	Sudan	Saudi Arabia	Serology	1994–1996	[89]
	Turkey	Saudi Arabia	Serology	1994–1996	[89]
	Iran, Pakistan, Somalia, Sudan	UAE	Serology	1994–1995	[15]
	Zimbabwe	South Africa	Serology	1985	[12●]

Reports available at: https://www.promedmail.org. Ag-ELISA, antigen enzyme-linked immunosorbent assay; NR, not reported; RT-PCR, reverse transcription polymerase chain reaction.

[a]Case number in brackets where applicable.

[b]PROMED archive number.