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Review Article

An Emerging Biothreat: Crimean-Congo Hemorrhagic Fever Virus in Southern and Western Asia

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Abstract. Tick-borne Crimean-Congo hemorrhagic fever virus (CCHFV) is endemic in numerous countries, but the epidemiology and epizoology of Crimean-Congo hemorrhagic fever (CCHF) remain to be defined for most regions of the world. Using a broad database search approach, we reviewed the literature on CCHF and CCHFV in Southern and Western Asia to better define the disease burden in these areas. We used a One Health approach, moving beyond a focus solely on human disease burden to more comprehensively define this burden by reviewing CCHF case reports, human and animal CCHFV seroprevalence studies, and human and animal CCHFV isolations. In addition, we used published literature to estimate the distribution of *Hyalomma* ticks and infection of these ticks by CCHFV. Using these data, we propose a new classification scheme for organizing the evaluated countries into five categories by level of evidence for CCHF endemicity. Twelve countries have reported CCHF cases, five from Southern Asia and seven from Western Asia. These were assigned to level 1 or 2. Eleven countries that have evidence of vector circulation but did not report confirmed CCHF cases were assigned to level 3 or 4. This classification scheme was developed to inform policy toward strengthening CCHF disease surveillance in the Southern and Western Asia regions. In particular, the goal of this review was to inform international organizations, local governments, and health-care professionals about current shortcomings in CCHFV surveillance in these two high-prevalence regions.

INTRODUCTION

Crimean-Congo hemorrhagic fever (CCHF) was originally described in Crimea in 1944–1945 after a disease outbreak was noted by Soviet military personnel.[2] Since that time, CCHF is now recognized as the only "viral hemorrhagic fever" that is broadly endemic in both Africa and Eurasia, with more than 30 countries reporting cases.[3] During the past two decades, 11 countries have reported their first confirmed CCHF cases (Table 1). Crimean-Congo hemorrhagic fever is caused by Crimean-Congo hemorrhagic fever virus (CCHFV; order *Bunyavirales:* family *Nairoviridae*).[4,5] Depending on the available health-care system infrastructure, the case fatality rate of CCHF can range from 5% up to 80% during limited outbreaks.[6,7] Most cases of CCHF are reported from the Western and Southern Asia, with incidences increasing during the past two decades.[8]

Crimean-Congo hemorrhagic fever virus is a vector-borne virus that is primarily transmitted via *Hyalomma* tick bites.[9] The strength of evidence supporting the role of various *Hyalomma* ticks as CCHFV vectors varies.[10,11] Thus, only ticks with the highest level of evidence, *Hyalomma rufipes* and *Hyalomma marginatum*, were included in our search. Various ungulates serve as mammalian CCHF reservoirs.[12] Therefore, agrarian countries are more vulnerable to CCHFV endemicity. Indeed, livestock and ticks are the primary source of sustained environmental CCHFV circulation. Humans are infected most frequently by tick bites and primarily serve as dead end hosts.[12] The frequency of transmission from animals to humans via direct contact is not well-defined. Studies indicate high CCHFV seroprevalence in abattoir workers.[13,14] These data indicate that CCHFV transmission occurs via direct contact with animals or animal products, although tick exposure cannot be ruled out. Furthermore, human-to-human infections have been well-described but are less likely to occur than infection via tick bites. Thus, although several mechanisms are postulated for transmission occur, *Hyalomma* ticks are required for sustained CCHFV circulation in a given region. Therefore, the future incidence of CCHF is multifactorial and is dependent on changes in human, animal, and tick populations.

Most reports on first autochthonous CCHF cases in individual countries were preceded by epidemiologic surveys that provided evidence of local CCHFV circulation. For example, serologic evidence of CCHFV in animals and humans in Iran was described in 1975 and evidence of CCHFV antigen was found in ticks in 1978.[15,16] Yet, it was not until 1999 that the first human case was described.[17] In addition, serologic evidence of CCHFV in Turkey existed already in 1975,[18] but the first confirmed CCHF case in Turkey was not reported until 2002. This country has since reported the highest number of CCHF cases in the world, totaling more than 10,000 cases.[7] Yet, published epidemiologic data are especially sparse for most countries in Southern and Western Asia and have not been updated in great detail since 1979.[19] This absence of updated human data is largely because only few countries in these regions have established active surveillance systems.[20]

This article focuses on Southern and Western Asia to describe regions that are highly affected by CCHFV with an emphasis on countries that may not have been considered CCHFV hotspots in the past. These regions were selected for

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TABLE 1
For the past 20 years, since 1998, 11 countries reported their first autochthonous Crimean-Congo hemorrhagic fever cases

Year	Country	References
2016	Spain	41
2012	Egypt	44
2011	India	43
2009	Georgia	42
2008	Sudan	47
2008	Greece	48
2003	Senegal	49
2002	Turkey	50
2000	Kenya	51
1999	Iran	52
1998	Afghanistan	53

multiple reasons. First, CCHF case numbers have increased in Afghanistan and Pakistan during the past few years.[21,22] To look into entire regions, we therefore turned to the United Nations Geoscheme to determine the official region that Afghanistan and Pakistan belong to ("Southern Asia") and which countries of that region should also be considered to achieve consistency of our analysis (Bangladesh, Bhutan, India, Iran, Maldives, Nepal, and Sri Lanka).[23] Second, the arguably largest expansion of CCHF cases in recent years occurred in Turkey (United Nations Geoscheme: "Western Asia"). Hence, we added the countries of Western Asia to our analysis. Both regions are well-defined areas for political action. Because the vast majority of CCHFV literature is not indexed in open-access medical databases, such as PubMed, and because significant proportions of the CCHFV literature are written in languages other than English (in particular Persian and Russian) in journals that are not easily accessible, this concise review was limited to these two UN Geoscheme regions. Prior reviews on these regions have not fully incorporated governmental human CCHF case detection available through internet search engines or through electronic communication.[8,20]

To accurately use the epidemiologic results available, we incorporated a One Health approach to our strategy in describing CCHF endemicity. The One Health concept promotes the integration of interdisciplinary ecologic data to guide predictions of pathogen emergence.[24] Data on human cases are only one factor in understanding the burden of disease and potential for emergence. We reviewed human, animal, virus, and tick data to assess CCHFV endemicity or potential for emergence to provide more accurate epidemiologic information. Because of the unpredictable effects of environmental changes, we used country-level vector data rather than a strict latitude cut-off that had been used previously.[8,25] Our objective was to integrate ecologic research to define the current status of CCHFV circulation. Therefore, we sought to perform a comprehensive search strategy to provide the most up-to-date and accurate overview of CCHF in two regions with the aim of highlighting urgent surveillance needs to inform global health security policy.

METHODS

We searched PubMed, Google Scholar, Scopus, GenBank, GIDEON, ProMED, and Web of Science records indexed from the original description of CCHF in 1945[2] until December 31, 2017, to identify and review the scientific literature on reported CCHF cases from each country of Southern and Western Asia as defined by the UN Geoscheme (Southern Asia: Afghanistan, Bangladesh, Bhutan, India, Iran, Maldives, Nepal, Pakistan, and Sri Lanka; Western Asia: Armenia, Azerbaijan, Bahrain, Cyprus, Georgia, Iraq, Israel, Jordan, Kuwait, Lebanon, Oman, Palestine, Qatar, Saudi Arabia, Syria, Turkey, United Arab Emirates, and Yemen).[23] We also reviewed conference proceedings and relevant articles that were cited. Our review included English, French, Georgian, Persian, and Russian language articles. We used Internet search engines for government reports and e-mailed government officials for unpublished data. In addition, we reviewed published human and animal serology data suggestive of CCHFV exposure or infection, data on CCHFV detection or isolation from ticks or vertebrates, and data indicative of the existence of CCHFV surveillance systems. We also reviewed the U.S. National Tick Collection database for data on the presence of CCHFV vectors. Our search was limited to the hard (ixodid) ticks *H. marginatum* and *H. rufipes* based on their capacity to transmit CCHFV transstadially, transovarially, and to animals.[9,26] For database queries, we used a combination of search terms, including "Crimean," "Crimean-Congo," "Congo-Crimean," "CCHF," "CCHFV," "*Hyalomma*," and the name of each country of interest.

One health country-level classification scheme. Based on the results of our search, we developed a classification scheme that integrated vector, animal, and human data to define CCHFV circulation. A similar classification scheme with integration of virus circulation data had been developed by the World Health Organization (WHO) for Zika virus.[27] We placed countries in categories defined as follows: level 1: CCHF cases reported annually through established surveillance; level 2: CCHF cases reported intermittently in absence of robust surveillance; level 3: no CCHF cases reported; no robust surveillance established, but available data point toward the possibility of undetected/unreported CCHF cases (animal/human serology, CCHFV detected in *Hyalomma* ticks); level 4: no CCHF cases reported; no robust surveillance or epidemiologic/epizoologic studies, but *Hyalomma* ticks are present; and level 5: no available data.

RESULTS

During the past few decades, cases have been reported annually from certain CCHFV-endemic countries (i.e., Georgia, Iran, and Turkey). For example, during the past 10 years, Iran reported 65 confirmed cases each year on average (range 44–150 per year).[28–30] Cases have been decreasing in Turkey during the past 3 years, but the incidence of CCHF remains the highest worldwide with 371 confirmed cases reported in 2016.[31] Turkey has reported more than 10,000 cases since 2002 (Table 2).[7,31] Although cases have been declining in Turkey, Afghanistan and Pakistan have reported increasing numbers of cases during the past few years. In Pakistan, 55 and 103 cases were confirmed in 2016 and 2017, respectively.[22,32] In Afghanistan, 242 suspected and 57 confirmed CCHF cases occurred in 2017, a steady increase from 42 suspected and six confirmed cases in 2014.[21,33]

We categorized countries from Southern and Western Asia into five levels that reflect our current CCHFV endemicity assessment (Tables 3 and 4, Figure 1). We assigned 12 countries, five from Southern Asia and seven from

TABLE 2

Total confirmed cases in Southern and Western Asia by country from 1974 to 2017 based on peer-reviewed literature or reports from government organizations

Country	Total confirmed cases	Total deaths	Cases per year (range)	Years cases reported	References
Turkey	10,333	469	150–1,318	2002–2017	7,31
Iran	1,256	177	18–150	1999–2017	28–30
Pakistan	429	94	3–83	1976–2017	32,38,39,54–61
Iraq	377	39	0–55	1979–1980, 1990–2010, 2013, 2015	62,63
Afghanistan	334	88	1–237	1998–2017	21,33,64–67
Georgia	56	7	0–25	2009, 2012–2017	42,68,69
India	47	19	6–18	2011–2015	43,70–75
Oman	34	14	0–33	1995–2014	76–79
United Arab Emirates	24	14	0–11	1979, 1994–1995, 2010	6,80–82
Saudi Arabia	8	0	0–7	1989–1990	83
Kuwait	2	0	0–2	1980, 1982	46
Armenia	1	0	0–1	1974	45

Total deaths are those among confirmed cases only. Therefore, the case fatality rates were not calculated, as cases were more frequently reported confirmed or suspected than deaths. A conservative approach was used by limiting data to peer-reviewed literature, but this approach likely underestimates the true burden of Crimean-Congo hemorrhagic fever (CCHF). For instance, Pakistan reported 1,339 suspected CCHF cases from 2011 to March 2017, but only 429 cases were confirmed.

Western Asia, to level 1 or 2 because these countries have reported confirmed CCHF cases. Eleven countries, one from Southern Asia and 10 from Western Asia, were assigned to level 3 or 4 because these countries have not reported confirmed CCHF cases, but CCHFV vectors have been found in these areas. Four countries from Southern Asia were assigned to level 5 because no evidence was found for CCHFV endemicity within those countries (Table 3, Figure 1).

DISCUSSION

Crimean-Congo hemorrhagic fever virus presents a significant threat to human health within these high-prevalence regions and throughout the world. The WHO included CCHF in its blueprint of priority diseases, which lists emerging diseases that are understudied.[34] We assessed the burden of CCHF in Western and Southern Asia because these regions report the most cases of CCHF worldwide. However, there is significant variability in surveillance activities and capabilities between countries.

The increasing incidence of CCHF cases in Afghanistan is unlikely to have been noticed if it were not for a Disease Early Warning System (DEWS) established in 2006.[21,35] This system was developed with the technical assistance of WHO and financial assistance from the United States Agency for International Development. Given the recent increasing incidence of CCHF in Pakistan and Afghanistan, strengthening of human surveillance systems in this region is critically important. Only with intergovernmental collaborations and support similar to the development of the Afghanistan DEWS can we strive toward global health preparedness in level 2–5 countries, where the true burden of CCHFV remains largely unknown.

Certain general trends in the epidemiology of CCHF cases have been observed. First, CCHF cases occur most frequently during the summer months because tick populations are lower during the colder winter months.[36] CCHF cases may increase during more temperate winters.[36] It is therefore speculated that climate change has contributed to the increasing incidence of CCHF cases worldwide.[37] With milder winters projected, CCHF emergence may continue to be observed. Further research should evaluate historical climate change data with trends in CCHF incidence. Second, it has been speculated that increasing trends in CCHF could be related to livestock migration and sacrifice for the Eid al-Adha festival in Pakistan.[38] However, this migration has occurred in late summer during the past few years and would be difficult to differentiate from the effects of temporal variation.[39] Yet, given livestock and population migration, increased surveillance and infection precautions are warranted.[36] By contrast, Saudi Arabia, a country with intermittent CCHF cases, has developed surveillance systems for Eid al-Adha and has not encountered increased cases.[40] Third, CCHF cases have been increasingly recognized in areas that were not historically reporting cases. Although outside the scope of this review, Egypt, Georgia, India, and Spain have reported their first autochthonous cases within the past

TABLE 3

Current evidence for CCHFV circulation in Southern Asia

Country	CCHF cases reported	Human serology	Animal serology	*Hyalomma* ticks	Virus detected in *Hyalomma* ticks
Afghanistan	1998–2017[21,53]	1998[84]	1974[53,64,84]	Yes*	NA[19,38,64]
Bangladesh	No	NA	NA	NA	NA
Bhutan	No	NA	NA	NA	NA
India	2011–2017[43,70]	1973[85]	1973, 2010–2011[72,85]	NA	1973, 2010–2011[72,85]
Iran	1999–2017[28,52]	1975†, 2004–2005, 2017[13,15,86]	1975†, 2004–2005, 2010–2011[15,86–89]	Yes[10]	2004–2016†‡[10,89–91]
Maldives	No	NA	NA	NA	NA
Nepal	No	NA	NA	NA	NA
Pakistan	1976–2017[60,92]	2007–2013[56]	2016[38,93]	Yes*	1970†[94]
Sri Lanka	No	NA	NA	NA	NA

CCHF = Crimean-Congo hemorrhagic fever; CCHFV = Crimean-Congo hemorrhagic fever virus; NA = no information available. Years are listed if there is peer-reviewed evidence of anti-CCHFV antibodies in humans or animals, CCHFV vector endemicity, or CCHFV antigen or genome detection.

* Information from the United States National Tick Collection.

† Year represents time of publication rather than time of sample collection.

‡ CCHFV antigen was isolated from an *Ornithodoros* (*Alveonasus*) *lahorensis* soft tick in Iran in 1978.

TABLE 4
Current evidence for CCHFV circulation in Western Asia

Country	CCHF cases reported	Human serology	Animal serology	*Hyalomma* ticks	Virus detected in *Hyalomma* ticks
Armenia	1974[45,95]	1972[96]	1972[96]	Yes[97]	1972–1974[97,98]
Azerbaijan	No	2007[99]	1967–1970[100]	Yes[97]	1972–1974[97,101]
Bahrain	No	NA	NA	NA	NA
Cyprus	No	NA	NA	Yes*	NA
Georgia	2009–2017[42,68,102]	2014[68,102–105]	NA	Yes[19]	NA
Iraq	1979–1980, 1990–2010, 2013, 2015[62,63,106]	1979–1980[63]	1980[107]	Yes*	NA
Israel	No	NA	NA	Yes*	NA
Jordan	No	NA	NA	Yes*	NA
Kuwait	1980, 1982[46]	1979–1982[108]	NA	Yes*	NA
Lebanon	No	NA	NA	Yes*	NA
Oman	1995–2017[79,109,110]	2000†[14]	2000†[14]	Yes*	2000†[14]
Palestine	No	NA	NA	Yes*	NA
Qatar	No	NA	NA	NA	NA
Saudi Arabia	1990, 2009[83]	2009[83,111,112]	1995[111]	Yes*	1995[113]
Syria	No	NA	1996[14]	Yes[114]	2014†[11]
Turkey	2002–2017[7,31]	1974, 2012, 2016†[115–117]	2011[118]	Yes*	2013–2015[119]
United Arab Emirates	1979, 1980, 1994–1995, 2010[6,80,82]	1997†[81]	1997†[81]	Yes*	1997†[81]
Yemen	No	NA	NA	Yes[120]	NA

CCHF = Crimean-Congo hemorrhagic fever; CCHFV = Crimean-Congo hemorrhagic fever virus; NA = no information available. Years are listed if there is peer-reviewed evidence of anti-CCHFV antibodies in humans or animals, CCHFV vector endemicity, or CCHFV antigen or genome detection.
* United States National Tick Collection.
† Year represents time of publication rather than time of sample collection.Years are listed if there is peer-reviewed evidence of anti-CCHFV antibodies in humans or animals, CCHFV vector endemicity, or CCHFV antigen or genome detection.

decade.[41–44] This review was limited to UN Geoscheme regions with the highest CCHF endemicity, but because of international travel, increasing human population density, and climate change, CCHF is silently expanding its boundaries.

The WHO map for demonstrating CCHF endemicity[25] is limited to numbers of reports of human disease, positive human serology, and presence or absence of ticks. Our country classification more comprehensively integrated other factors

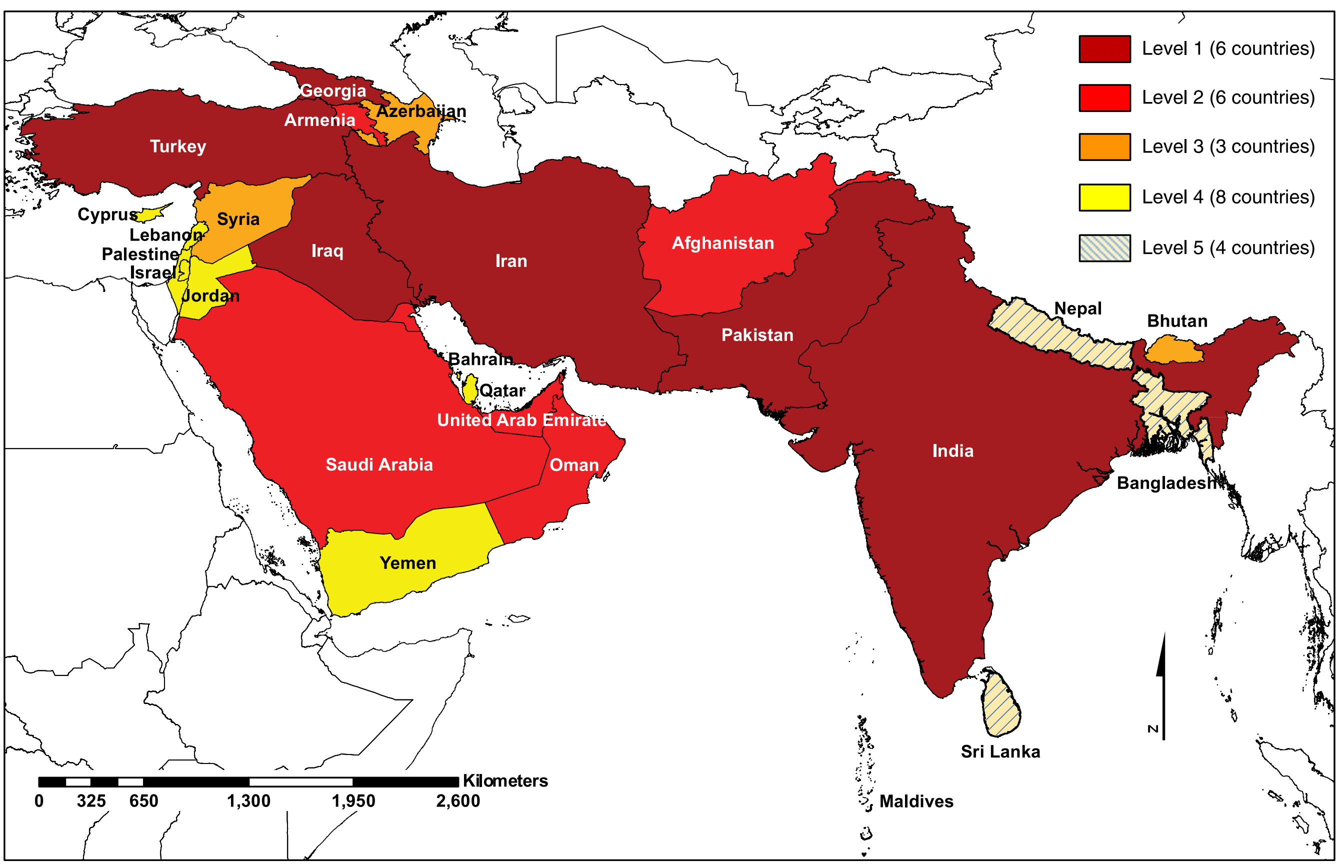

FIGURE 1. Burden of CCHF in Southern and Western Asia using a One Health approach. Data support CCHFV circulation in lower Level (1 and 2) countries, whereas further study and surveillance of CCHFV circulation is recommended in countries of higher Levels (3, 4, and 5). Classification at the country level was performed for policy implications. Country boundaries do not necessarily reflect the geographic area at risk. Map was created using ArcGIS Release 10.61. Source: Database of Global Administrative Areas (GADM). This figure appears in color at www.ajtmh.org.[1]

as part of a One Health approach, including animal serology and inclusion of more granular data on CCHFV vector presence. Our broad search strategy updated and uniquely integrated epidemiologic information to make the following recommendations:

1. Countries of Southern and Western Asia in general would benefit from intergovernmental support and multi-institutional collaborations to develop or to strengthen human and ecologic CCHF surveillance networks.
2. *Hyalomma* ticks are present in countries clustered by the Eastern Mediterranean basin, including Cyprus, Israel, Jordan, Lebanon, and Syria. However, information about CCHFV circulation is limited. These countries may benefit from testing of *Hyalomma* ticks for CCHFV and from performing seroprevalence studies in humans and animals.
3. Countries with civil strife, particularly Syria and Yemen, have weakened health-care infrastructures and the presence of the *Hyalomma* tick vector. These countries may be at high risk for propagated CCHF outbreaks and would benefit from mobile diagnostic support and personal protective equipment (PPE).
4. Armenia, Azerbaijan, and Kuwait are associated with strong evidence of CCHFV circulation in the past, but no data have been published over the past three decades. Reported CCHF cases in Armenia (in 1974) and Kuwait (in 1980 and 1982) have been largely ignored.[45,46] Cases may be occurring undetected and, therefore, these countries may benefit from active surveillance for CCHF cases.
5. Multi-institutional collaborations should focus on establishing improved health-care infrastructures to prevent community and nosocomial CCHFV transmission from index cases with provision of resources for PPE.
6. Regional reference laboratories should be established or strengthened to provide rapid diagnostic support during CCHF outbreaks.

There are limitations with our approach. Our data are only as good as the surveillance systems in the countries for assessing endemicity. In addition, in countries with widely varying topography and risk for disease spread, it would be more accurate to categorize the risk by regions within a country rather than a country as a whole. In addition, borders are artificially created and have little to no effect on the transmission of disease by arthropods. We maintained the unit of country political borders to emphasize the need for policy to improve regional and country-level surveillance strengthening. Future research should integrate human, animal, and vector data to define or predict hot spots for precise geographic estimates on CCHFV distribution.

In summary, we call on public health organizations, including WHO or the World Organization for Animal Health, to consider creating or expanding partnerships with local governments to provide support for human, tick, and animal CCHFV surveillance in high priority areas in Southern and Western Asia.

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