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Crimean-Congo haemorrhagic fever virus in Kazakhstan (1948-2013)

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ABSTRACT

Crimean-Congo haemorrhagic fever (CCHF) is a pathogenic and often fatal arboviral disease with a distribution spanning large areas of Africa, Europe and Asia. The causative agent is a negative-sense single-stranded RNA virus classified within the *Nairovirus* genus of the *Bunyaviridae* family.

Cases of CCHF have been officially recorded in Kazakhstan since the disease was first officially reported in modern medicine. Serological surveillance of human and animal populations provide evidence that the virus was perpetually circulating in a local enzoonotic cycle involving mammals, ticks and humans in the southern regions of the country. Most cases of human disease were associated with agricultural professions such as farming, shepherding and fruit-picking; the typical route of infection was via tick-bite although several cases of contact transmission associated with caring for sick patients have been documented.

In total, 704 confirmed human cases of CCHF have been registered in Kazakhstan from 1948-2013 with an overall case fatality rate of 14.8% for cases with a documented outcome.

The southern regions of Kazakhstan should be considered endemic for CCHF with cases reported from these territories on an annual basis. Modern diagnostic technologies allow for rapid clinical diagnosis and for surveillance studies to monitor for potential expansion in known risk areas.

1. Introduction

Crimean-Congo haemorrhagic fever (CCHF) is a virulent haemorrhagic human disease caused by single-stranded, negative sense RNA virus classified within the *Nairovirus* genus of the family *Bunyaviridae*. The virus is maintained in nature in an enzoonotic cycle involving tick-mediated transmission between several species of vertebrate. Both vertebrate hosts and tick vectors act as reservoirs of viral infection with transmission to humans occurring through bite from an infected tick, or through contact with infected tissue including blood. The CCHF virus (CCHFV) genome is comprised of single-stranded negative-sense RNA divided into 3 distinct segments designated small (S), medium (M) and large (L). The L segment encodes the RNA-dependent RNA polymerase, the M segment encodes the precursor of the two envelope glycoproteins Gn and Gc, and the S segment encodes the nucleocapsid protein.

Human cases of CCHF have been reported from more than 30 countries across Africa, Europe with a distribution that correlates with the predominant tick vector *Hyalomma marginatum marginatum*. Case-fatality rates range from 10-50% for

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infection via tick-bite, but rates can be higher in cases of nosocomial transmission.[1,2]

The modern medical description of CCHF was first reported during an expedition in 1944 to the Crimean peninsula to investigate an epidemic affecting Soviet troops assisting in the recently war-ravaged region.[3,4] It would be a further 23 years before collaborative work elucidated that the 'Crimean haemorrhagic fever' virus responsible for this outbreak was identical to the 'Congo haemorrhagic fever' virus identified in Africa; these investigations eventually led to the designation 'Crimean-Congo haemorrhagic fever virus' (CCHFV).[1]

This discovery also prompted questions into the nosology of several haemorrhagic fevers similar to CCHF known by different colloquial terms within the former Soviet Union. Historical reports from Central Asia describe a human disease with haemorrhagic manifestations, resulting from a tick-bite, dating back as far as the 12th century known locally as "*khungribta*" (blood taking), "*khunymuny*" (nose bleeding), or "*karak halak*" (black death); in the 20th century these diseases were typically termed either 'Uzbek haemorrhagic fever' (UHF) or 'Central Asian haemorrhagic fever' (CAHF).[1] Characterisation studies performed in the late 1960s confirmed that the causative agents of UHF and CAHF were identical to CCHFV by serological analysis.[3,5] The similarity between CCHFV and the pathogens causing CAHF/UHF may seem self-evident; however, historical reports imply a more clinically severe form of disease in Central Asian regions in comparison to the Crimea leading to speculation as to whether these were distinct aetiological agents.[6,7] Modern day molecular techniques have shown that CCHFV forms 7 distinct clades with strong geographical associations when comparing full S segment sequences;[8] it is possible that genetic differences between strains may result in different severities of clinical disease.

Treatment of human cases involves several distinct priorities. Suspected cases of CCHF require hospitalisation in a specialist infectious disease unit in order to prevent contact-transmission. Intensive care utilising barrier nursing techniques is implemented for patients suffering overt clinical symptoms, while ribavirin and/or intravenous immunoglobulin from convalescent sera may be prescribed if the disease is considered in the early phase. All confirmed cases of CCHF are contact-traced to identify the potential for transmission events, and the route of exposure is investigated to assess whether further exposure can be prevented.

This report summarises the history of CCHF in Kazakhstan by reviewing key historical texts documenting the expanse of known foci in the country and provides data on incidence of disease in Kazakhstan.

2. Materials and methods

Until the virus was successfully isolated in the Soviet Union for the first time in 1968, all cases of CCHF in Kazakhstan were diagnosed clinically. Subsequently laboratory diagnosis of CCHF was developed using purified virus antigen.[9] Assays based on complement fixation (CF) and, more recently, using ELISA-based detection have been the primarily diagnostic tools for several decades. In recent years, molecular based techniques including both conventional RT-PCR and real-time RT-PCR[10] have been used to augment detection capabilities for confirming human cases of disease.

CCHF has been a reportable disease in Kazakhstan since 1965 with central records documenting instances of human cases from this date up to the present day. Upon implementation of central records in 1965, an analysis was undertake to retrospectively ascribe probable cases of CCHF preceding this date based on reports meeting the initial case definition. Official reports were collated and cross-referenced against descriptions of human disease published in Russian/English literature to assure accuracy; all human cases reported in published literature were accounted for in the central records.

All confirmed cases included the administrative region (oblast) reporting the cases and the majority (82%) listed the eventual outcome of disease. This information was tabulated to provide annual incidence of disease for each year up to the end of 2013 (Supplementary data); these data were further collated to provide summaries by decade (Table 1). Case fatality rates were calculated using only data with a documented outcome.

Epidemiological data were obtained from historical publications investigating risk areas for CCHF in combination with recent local studies to provide an assessment of endemicity.

3. Results

3.1. History of endemicity

In Kazakhstan, the first official medical reports attributable to CCHF date from 1948 and were originally listed as CAHF; while these were the first centrally recorded cases, locals had known of this disease for many decades and referred to it as "*Coc-ala*": Kazakh for "mottled" on account of the characteristic haemorrhagic manifestations on the skin of patients. The first official cases resulted from an 'outbreak' of haemorrhagic disease in the Mahtaaral and Keles areas of the South Kazakhstan oblast in the summer of 1948. In total, 6 farmers were identified with overt

Table 1
Confirmed human cases of CCHF reported in Kazakhstan from 1948-2013.

		1948-1969[1]	1970-1979	1980-1989	1990-1999	2000-2009	2010-2013	Total
Zhambyl	Cases (CFR)	0	0	95	103	68	4	270
Oblast		(NA)	(NA)	(21.1%)	(6.8%)	(2.9%)	(0%)	(10.7%)
Kyzylorda	Cases	8	13	32	55	32	15	155
Oblast	(CFR)	(25.0%)	(30.8%)	(18.8%)	(14.5%)	(15.6%)	(6.7%)	(16.8%)
South Kazakhstan	Cases	81	20	21	64	62	31	279
Oblast	(CFR)	NA[2]	NA[2]	NA[2]	(14.5%)[3]	(25.8%)	(19.4%)	(19.7%)[3]
Combined	Cases	89	33	148	222	162	50	704
Data	(CFR)	(25%)[4]	(30.8%)[4]	(20.5%)[4]	(10.9%)	(14.2%)	(14.0%)	(14.8%)[4]
	Cases/yr	4.0	3.3	14.8	22.2	16.2	12.5	10.7

[1]Cases registered from1948-1964 were reported cumulatively for the first report on CCHF within Kazakhstan; these data cannot be further subdivided into decades.
[2]Mortality data for cases in South Kazakhstan Oblast are not available for cases before 1991.
[3]Mortality data are absent for the 2 confirmed cases reported in South Kazakhstan Oblast in 1990; these cases are recorded in the cumulative cases section, but were not including when calculating CFR.
[4]CFRs calculated from cases with mortality data and excludes specific cases from South Kazakhstan where outcome is not recorded.
CFR = cases fatality rate (calculated from cases where the outcome is officially documented).
Cases/yr = average cases per year within data set.
NA = not applicable.

haemorrhagic manifestations with a fatal outcome recorded in half of these cases. This original report did not prove to be an isolated occurrence – similar instances of human disease with severe haemorrhagic symptoms were identified in subsequent years in several locations across the South Kazakhstan oblast with a total of 67 cases registered between 1948-1963 of which 38 (57%) proved fatal.[11]

In 1964, CCHF contracted outside of the South Kazakhstan oblast was identified clinically for the first time with a fatal case in the Kyzylorda oblast. The index case was a shepherd near Sheili suspected to have contracted the disease via tick-bite; a family member and two hospital workers contracted CCHF via contact transmission. All three contacts survived including a nurse who developed severe haemorrhagic manifestations.[12]

A serosurveillance programme using the CF test in 1973-74 investigated potential exposure to CCHFV in humans and animal species including cattle, sheep, goats and horses across endemic areas (South Kazakhstan and Kyzylorda oblasts) and surrounding non-endemic areas (Zhambyl and Almaty oblasts). This report provided the first evidence of CCHFV circulation in the Zhambyl oblast with antibodies to CCHFV detected in 1.9% of animal sera, and the first evidence of CCHFV in the Almaty oblast with the detection of complement-fixing antibodies in healthy human sera.[13] Although reports from the Almaty oblast remain rare, the Zhambyl oblast is now considered endemic for CCHFV with the first human cases diagnosed eight years after this study. A similar investigation in the 1980s found serological evidence of CCHFV exposure in human and animal sera in several western regions of the country (Atyrau, Mangystau, Aktobe and West Kazakhstan oblasts) although, to date, only a solitary report of human disease has been recorded from these regions.[14]

Despite serological evidence of virus circulating in additional regions of the country, only the South Kazakhstan, Kyzylorda and Zhambyl oblasts are considered endemic risk areas for CCHFV and for transmission of the virus resulting in human disease.

3.2. Incidence and epidemiology

There is a pronounced seasonality to CCHF in Kazakhstan with cases occurring predominantly between April and June (97.8% ± 1.0%) with the highest incidence occurring in May (50.2% ± 3.3%). Cases are reported outside of this timeframe on rare occasions with one notable case occurring as late as November in 2002.

The clinical presentation of disease in Kazakhstan has been documented;[11,12,15] as with other Central Asian countries such as Tajikistan, both 'moderate' and 'severe' haemorrhagic forms are common in cases presenting with overt symptoms of disease.[9] Over half of patients with clinical symptoms will suffer from the moderate form of disease characterised by fever, headache and haemorrhagic manifestations such as scleral injection, epistaxis and a petechial rash; these cases have a favourable outcome typically resulting in complete recovery after a prolonged convalescent period. A severe form of disease is also prevalent; such cases have a similar prodrome but progress to more numerous/significant haemorrhagic symptoms including those associated with intestinal, urinal and respiratory tracts. Cases with more complex manifestations commonly result in a fatal outcome.

Human infection in Kazakhstan is typically mediated by the bite from an infected tick; therefore cases of CCHF are associated with rural agricultural occupations such as farming, shepherding and fruit picking. The first case of CCHF in Kazakhstan to fall outside of this category was the infection of a worker in a 'meat combine' who skinned animal carcasses in a factory setting;[15] however, this occupation has the potential to expose workers to both ticks and infectious tissues so is not atypical in a global context of CCHF infections. There have also been several cases of CCHF mediated by contact transmission associated with the care of infected individuals including an 'outbreak' in 1957 involving three separate transmission events both in the home and hospital settings resulting in 10 cases and 7 fatalities.[11] Contact transmission to family members through care of sick patients at home was reported routinely in historic reports in Kazakhstan but is no longer common – this is presumably due to the reduction in communes and the improvement in medical and transport infrastructure.

The endemic oblasts of Kazakhstan share a continental climate characterised by hot dry summers and cold winters with little precipitation. Different landscapes provide a wide number of inhabiting tick species including *Hyalomma asiaticum, H. anatolicum, H. scupense, H. marginatum, H. punctata, H. sulcata, Dermacentor daghestanicus, D. marginatus. D. niveus* and *Boophilus calcaratus.* Tick densities in CCHF endemic regions of Kazakhstan can be extreme; over 1,500 adult ticks or 2-3,000 nymphs can be collected from a single farm animal (with the majority known vector species for CCHFV). Local studies associate more than 10 ticks parasitising one animal with the potential for the CCHFV enzootic lifecycle maintenance while more than 100 ticks parasitising a single animal causally linked with potential for CCHF disease occurrence in humans (unpublished data).

Analysis of records for CCHF in Kazakhstan (Table 1) show that cases have been registered in every year since 1965 with an average of less than 11 cases per year. 704 cases have been officially registered in this period with a CFR of 14.8% based on cases with a documented outcome. Epidemic years with 20 or more cases have been recorded on 9 occasions; the majority of cases in these years originated in the Zhambyl oblast.

3.3. CCHF in South Kazakhstan oblast

The South Kazakhstan oblast was the first to report incidence of CCHF with 6 cases in 1948. Sporadic isolated cases were reported in most subsequent years with occasional 'outbreaks' with several cases linked to a single origin; these occurrences were typically the result of contact transmission associated with the care of sick patients. The occurrence of tick-bites in this region is high: 3,495 people sought medical attention after receiving tick bites in 2011; 108 were hospitalised for observation, 47 developed a low-grade fever, 27 developed a severe febrile illness with a final diagnosis of CCHF made in 6 cases. The predominant tick vector for CCHFV transmission to humans in this oblast is *H. anatolicum*; this is the predominant CCHF vector for most Central Asian regions.[16] Other notable tick species capable of CCHFV transmission in this region include *H. asiaticum, H. punctata, H. sulcata, H. scupense* and *H. martginatum*.

Central records for this region (Table 1) document 279 human cases of CCHF from 1948-2013. Since 1991, the first year with mortality data for patients from this region, 155 cases of CCHF have been recorded in South Kazakhstan of which 31 resulted in a fatal outcome (19.7% cases fatality rate - CFR). Annual data (supplementary data) for this region show that human tick bite cases have been reported every year since 1989 with the exception of 2003 implying maintenance of CCHFV in competent tick vectors within the region. The number of cases recorded rarely reaches double figures although a notable increase was evident in 2009 and 2010; investigations into this anomaly identified distinct peaks in tick-bite activity that mirrored the increase in registered cases of CCHF in these regions implying a causal relationship between tick activity and human CCHF disease.[17] Routine tick reduction strategies in this region were cancelled due to a lack of funding 4 years before the first epidemic year.

3.4. CCHF in Kyzylorda oblast

Since the first report of human disease in the Kyzylorda oblast in 1964, a total of 155 human cases of CCHF have been recorded with 26 fatalities giving an overall CFR of 16.8% (Table 1). The majority of cases were reported from the Shieli region; this territory is located approximately 30 miles from the main focus of human cases in the South Kazakhstan oblast suggesting a single risk area that happens to span two administrative districts (data not shown).

As with the South Kazakhstan oblast, cases of CCHF in the Kyzylorda oblast have been recorded in most years since initial identification but with low incidence; the highest numbers of cases in a single year for this region was 10 cases in 1993.

In comparison to the South Kazakhstan oblast however, the predominant tick vector in the Kyzylorda oblast seems to be *H. asiaticum* or *H. scupense*[18] with virtually no evidence of *H. anatolicum* in the region. A tick surveillance study of the region conducted in 2012 identified 24,878 ticks with *H. scupense* (26.8%) and *H. asiaticum* (11.7%) the only species present known to act as competent vectors for human transmission of CCHFV (unpublished data). 57% of ticks collected were *Dermacentor niveus*; this species is likely to play a role in the enzootic lifecycle of CCHFV although the true importance of this species as vector for human transmission is not well established.

3.5. CCHF in Zhambyl oblast

While evidence of CCHFV circulation in the Zhambyl oblast was detected through animal serosurveillance studies in 1974,[13] the first confirmed human cases were not reported for a further 8 years. As summarised in Table 1, 270 confirmed cases of CCHF have been reported from this region since the first identification in 1982 with 29 fatalities (10.7% CFR). Cases are restricted to two districts; 73% in the Sarysu district and 27% registered within the Moyinkum district. Unlike the two other endemic regions in Kazakhstan, the Zhambyl oblast has a markedly variable number of cases including several epidemic years with more than 20 cases reported (1989, 1995, 1999, 2000, and 2001) but is also notable for periods of low/no incidence; just 7 cases have been registered in the last 10 years with a complete absence of disease recorded between 2007-2010 (supplementary data).

As with other endemic regions, tick-bite is the predominant route of exposure although a significant number of cases were attributed to 'crushing of ticks' during sheep shearing (31% - data not shown). Only three cases of contact transmission have been reported from this region to date.

The predominant tick vector in this region is thought to be *H. asiaticum* and *H. scupense* although significant numbers of *Dermacentor* species are present. The ratio of *Hyalomma* ticks to *Dermacentor* ticks varies markedly across the region ranging from 2:1 in the CCHF endemic areas to 1:95 in the non-endemic regions.

4. Discussion

Official reports of CCHF in Kazakhstan date back to the inception of this disease in modern day medicine; however, local reports suggest that human cases in the region predate this identification. At present, three oblasts within Kazakhstan are considered to be endemic for CCHF: South Kazakhstan, Kyzylorda and Zhambyl with isolated instances of virus/disease detection in other regions across the south of the country. The endemic oblasts form the northern limit of the Central Asian desert zone and share a similar terrain, flora and fauna with other CCHF-endemic neighbouring countries such as Uzbekistan. To the north lies the Kazakh steppe; while it is likely that the necessary ecological conditions for CCHFV transmission exist in this steppe region, it is possible that reduced density of vertebrate hosts could impact upon the enzootic transmission cycle and/or the scarcity of humans in this large expanse would prohibit evidence of disease. The distribution of competent vector/reservoir species also remains unclear in the steppe region and to date there are no reports of established colonies for tick vectors associated with CCHFV transmission in Kazakhstan. This boundary also marks the known northern limit for the global distribution of CCHFV with reports frequently citing parallels bisecting the Kazakh steppe.[19,20]

Human exposure to CCHFV in Kazakhstan appears to be predominantly via tick-bite, although a significant number of cases have resulted from treatment of the disease either in the home or hospital settings. The incidence of exposure through patient care has been estimated at approximately 8% of cases in Kazakhstan.[15,21] While contact transmission may be relatively rare, such instances often lead to multiple instances of secondary infection and such cases serve as a reminder of the importance of appropriate barrier nursing techniques in controlling the spread of infection. It is interesting to note that the region with the lowest CFR (10.7% in Zhambyl compared to 16.8% in Kyzylorda and 19.7% in South Kazakhstan) has only 3 cases of CCHF associated with contact transmission implying that the greatest burden of disease with CCHF in Kazakhstan occurs as a result of contact transmission. Both Kyzylorda and South Kazakhstan oblasts had several 'outbreaks' of disease associated with contact transmission, especially in the formative years of CCHF as a medical disease, which resulted in high mortality rates.

Genetic analysis of CCHFV strains circulating in Kazakhstan is uncommon, although international collaborations to transfer this capability are ongoing. Assessment of strains submitted to GenBank indicate that CCHFV from this region clusters within the Asia 2 clade.

Knowledge surrounding CCHF is increasing in Kazakhstan with hospitals now following algorithms for the management of human cases of CCHF. The requirement for barrier nursing techniques when dealing with suspected cases of CCHF is common-practice, and substantial efforts are made to reduce the abundance of ticks in localities associated with confirmed cases. It is interesting to note that two epidemic years were recorded in the South Kazakhstan oblast after cessation of local tick reduction schemes due to funding cuts. The importance of preventing tick bites for at-risk professions, especially sheep-shearers, is promoted in endemic regions, as is the necessity for the general public to seek medical assistance to remove ticks as soon as they are noticed; evidence of this is seen with statistics showing 1,135 sought such medical advice in 2012 in Kyzylorda following a tick bite compared to just 188 in 2007.

Despite these advances, improvements are required in particular with regards to the speed of diagnosis. CCHF is often not considered until severe overt haemorrhagic manifestations are observed by which time medical personnel may have been exposed to CCHFV. In addition, the administration of ribavirin and/or convalescent immunoglobulin will likely be too late to have effect at this late stage although to date neither has been shown conclusively to be effective treatments for CCHF.[22,23] It is hoped that real-time RT-PCR technologies can be adopted in infectious disease hospitals across the endemic southern oblasts; this capability will allow rapid diagnostic detection for of cases within hours of admission and reduce the potential for nosocomial spread.

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Figure 1. Administrative oblasts in Kazakhstan. CCHF is considered endemic in the Kyzylorda, South Kazakhstan and Zhambyl oblasts; evidence for virus circulation and/or human exposure has been documented in the West Kazakhstan, Atyrau, Mangystau, Aktobe and Almaty oblasts but to date only a solitary human case of CCHF has been reported from any of these regions.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ijid.2015.07.007.

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