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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.