



# Alkhurma haemorrhagic fever—a viral haemorrhagic disease unique to the Arabian Peninsula

Ziad A. Memish<sup>a,\*</sup>, Remi N. Charrel<sup>b</sup>, Ali M. Zaki<sup>c</sup>, Shamsudeen F. Fagbo<sup>a</sup>

<sup>a</sup> Preventive Medicine Directorate, Saudi Ministry of Health, Riyadh 11176, Saudi Arabia

<sup>b</sup> Unité des Virus Emergents (UMR190), School of Medicine, Aix-Marseille Université – IRD, Marseille, France

<sup>c</sup> Microbiology Laboratory, Doctor Soliman Fakeeh Hospital, Jeddah, Saudi Arabia

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## ABSTRACT

The emergence and re-emergence of human and animal pathogens on a global scale continues unabated. One such pathogen is the arbovirus that causes Alkhurma haemorrhagic fever, which emerged in the Kingdom of Saudi Arabia in the mid 1990s. It has since re-emerged in other regions of the country and threatens to widen its area of endemicity beyond the peninsula. Human and animal movements, especially those associated with the annual mass gathering event of Hajj (pilgrimage) may facilitate introduction into other continental masses, where it must be differentiated from dengue and other similar arboviral haemorrhagic fevers. In addition to dengue and Kadam viruses, which are known to be endemic in Saudi Arabia, it is thought that other flaviviruses exist in the region, though undetected. Collectively, these viruses present diagnostic challenges that may confound the recognition of clinical cases of Alkhurma haemorrhagic fever. The Saudi Ministry of Health is making concerted efforts to expand the evidence base in order to enhance the diagnostic and preventive protocols used to address the challenge of Alkhurma haemorrhagic fever.

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## 1. Introduction

The emergence and re-emergence of pathogens on a global scale continues to have a great impact on animal and human public health. The impact of such emergence or re-emergence events is magnified where zoonotic pathogens are involved. The emergence of Alkhurma haemorrhagic fever virus (AHFV) in 1995 in the Kingdom of Saudi Arabia ensured that the Kingdom does not remain out of the emerging infectious diseases map. The first AHFV isolate came from an acutely and fatally ill butcher exhibiting viral haemorrhagic fever symptoms [1]. Though the butcher was based in Makkah, where he was occupationally exposed to the suspected virus-carrying sheep, the virus was named after Alkhurma, a small settlement from where the sheep originated. To date, AHFV has been reported from Makkah, Jeddah, Jizan and Najran in the Kingdom of Saudi Arabia (Fig. 1).

## 2. The virus

AHFV has been shown to be a genetic variant of the Kyasanur Forest disease virus (KFDV). It is the first tick-borne haemorrhagic

fever flavivirus to have its whole genome sequenced. Based on the sequence analysis AHFV has an 89% homology with KFDV [2], which belongs to the genus *Flavivirus* of the *Flaviviridae* family (Fig. 2). This genus includes over 70 viruses, a large number of which are arthropod-borne and infect humans and animals [3]. Additional subclassification of the genus puts KFDV, and therefore AHFV, under the mammalian tick-borne virus group together with seven other species (Gadgets Gully, Langat, Louping ill, Omsk haemorrhagic fever, Powassan, Royal Farm and tick-borne encephalitis). Other flaviviruses that have been isolated from clinical (human or vertebrate) or arthropod samples in the Kingdom of Saudi Arabia include the Kadam and dengue viruses.

Local claims of the occurrence of West Nile fever and other tick-borne flaviviruses remain unsubstantiated. AHFV is undoubtedly the most intensely discussed tick-borne pathogen in the local media; additionally, alongside dengue fever, Alkhurma haemorrhagic fever (AHF) constitutes a major public health concern to local health authorities. There is also the fear of the virus being exported elsewhere by home-bound pilgrims returning from the yearly Hajj (pilgrimage) rites.

## 3. Epidemiology

Data from ongoing epidemiological investigations and a retrospective case series [4] strongly incriminate occupational exposure

\* Corresponding author. Tel.: +966 1 2124052; fax: +966 1 2125052.  
E-mail address: [zmemish@yahoo.com](mailto:zmemish@yahoo.com) (Z.A. Memish).



**Fig. 1.** Map of the Kingdom of Saudi Arabia, with regions affected with Alkhurma haemorrhagic fever virus represented by red dots. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of the article.)

to AHFV as a risk factor in developing illness. At-risk occupations include livestock herdsman and live-animal retailers. Housewives and young girls/women generally involved in preparing meat at home before cooking have also been shown to be at risk. Other risk factors include living in neighbourhoods with livestock, tick bites and drinking unpasteurised milk [4]. There have been fears of nosocomial transmission of AHFV within hospital settings and community-based human-to-human transmission. However, to date no such cases have been documented [5]. This distinguishes it from Crimean–Congo haemorrhagic fever, another tick-borne viral haemorrhagic disease with known nosocomial transmission risk [6,7].

#### 4. Animal hosts

AHFV is a zoonotic disease and clinical cases have been epidemiologically linked to exposure to livestock (camels and sheep). However, AHFV has yet to be isolated from such animals. Similarly, neither antibodies nor AHFV RNA have been detected in non-human vertebrates. This is because of the lack of studies in livestock. Additionally, studies are lacking in small animals that may serve as reservoirs of AHFV; small animals, including wild cats, hedgehogs and a variety of burrowing reptiles, can serve as hosts or blood-meal sources for the immature and mature stages of putative soft and hard tick vectors. In an attempt to trace back a recent clinical case involving a camel herdsman, the camel sera tested negative for AHFV RNA by real-time quantitative reverse transcription polymerase chain reaction (RT-qPCR). Since serology was not done the situation remained inconclusive, as it could not be ascertained that the camel sera had been collected post-viraemia or that the camels that may have been viraemic had not been sold or moved elsewhere.

It is expected that future broad-based studies will reveal the range of animal hosts of this tick-borne pathogen. It remains to be confirmed whether AHFV has the same virulent characteristics in monkeys or other primates as have been observed with KFDV in India [8]. While deaths or acute illnesses may be occurring in monkeys and baboons found in the Makkah region, active surveillance for AHFV infection in these animals has not been carried out.

#### 5. Vectors

Despite the limited research efforts committed to AHFV, there is a large body of evidence that indicates that this virus is a tick-borne flavivirus. Several phylogenetic studies have indicated that it belongs to the mammalian tick-borne group in the *Flavivirus* genus [2,4,9,10]. However, studies are lacking that give details on which tick species are the main vectors for AHFV and how these species interact with their various biotypes to give rise to zoonotic transmission. The first detection of AHFV was in the soft tick *Ornithodoros savignyi*, when viral RNA was detected in ticks collected in the eastern part of Jeddah from land used by beef camels to rest [10]. AHFV has also been detected in *Hyalomma dromedarii* ticks taken from camels in Jeddah [personal communication, Z. Memish]. Other potential tick vectors of AHFV and other tick-borne viruses are endemic in various parts of the Kingdom [11].

One study has hypothesized the mosquito-borne nature of AHFV [12]. Interestingly, data on the characterization and phylogenetic analysis of the viruses reportedly isolated remain unavailable to date. Published studies on experimentally or naturally infected mosquitoes are also lacking.

It is true that clinical cases of AHF have been documented in areas with high mosquito densities and exposure to mosquitoes. However, the data available on the virology of AHFV strongly

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