Saudi Journal of Biological Sciences 29 (2022) 1900–1910

Contents lists available at ScienceDirect

Saudi Journal of Biological Sciences

journal homepage: www.sciencedirect.com

Review

Human Alkhumra hemorrhagic Fever: Emergence, history and epidemiological and clinical profiles

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ARTICLE INFO

Article history:
Received 18 January 2021
Revised 3 October 2021
Accepted 14 October 2021
Available online 22 October 2021

Keywords:
Alkhumra hemorrhagic fever virus
Flaviviruses
Infectious diseases
Saudi Arabia

ABSTRACT

Alkhumra hemorrhagic fever (AHF) is a severe, often fatal hemorrhagic disease in humans. It is caused by Alkhumra hemorrhagic fever virus (AHFV), a newly described flavivirus first isolated in 1995 in Alkhumra district, south of Jeddah City, Saudi Arabia. It is transmitted from infected livestock animals to humans by direct contact with infected animals or by tick bites. In the recent past, the incidence of AHF has increased, with a total of 604 confirmed cases have been reported in Saudi Arabia between 1995 and 2020. Yet, no specific treatment or control strategies have been developed and implemented against this infection. Hence, the likelihood of increased prevalence or the occurrence of outbreaks is high, particularly in the absence of appropriate prevention and control strategies. This narrative review presents an overview of the current knowledge and future concerns about AHF globally.

Contents

Abbreviations: AHF, Alkhumra hemorrhagic fever; AHFV, Alkhumra hemorrhagic fever virus; DENV, dengue fever virus; CFV, chikungunya fever virus; YFV, yellow fever virus; KFDV, Kyasanur Forest disease virus; RVFV, Rift Valley fever virus; OHFV, Omsk hemorrhagic fever virus; CCHFV, Crimean-Congo Hemorrhagic fever virus; ICTV, International Committee on Taxonomy of Viruses.

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Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

https://doi.org/10.1016/j.sjbs.2021.10.031
1319-562X/

1. Introduction

Viral hemorrhagic fevers (VHF) are a group of acute febrile illnesses characterized by systemic involvement, including generalized bleeding in cases of severe infection (Ippolito et al., 2012). Patients with VHF manifest combinations of malaise, prostration, generalized signs of coagulation abnormalities and increased vascular permeability. Although the more severely ill patients suffer from bleeding, this does not result in a life-threatening loss of blood volume (Jahrling et al., 2012). Viral hemorrhagic fevers are caused by a number of viruses belonging to different families, including *Flaviviridae*, *Bunyaviridae*, *Arenaviridae* and *Filoviridae* (Bray and Schaechter, 2009). Those in the *Flaviviridae* family include dengue fever virus (DENV), chikungunya fever virus (CFV), yellow fever virus (YFV), Alkhumra hemorrhagic fever virus (AHFV), Kyasanur Forest disease virus (KFDV) and Omsk hemorrhagic fever virus (OHFV), and all these viruses belong to the genus *Flavivirus*. These flaviviruses are single-stranded RNA viruses that can infect humans through contact with infected animal reservoirs or through arthropod vectors (Zakham et al., 2017).

Alkhumra hemorrhagic fever virus was misnamed ‘‘Alkhurma” virus in many scientific publications due to a typographical error where the letters ‘m’ and ‘r’ were transposed (Madani et al., 2012). The International Committee on Taxonomy of Viruses (ICTV) has corrected this mistake recently and approved the name ‘‘Alkhumra” as the correct name of the virus (Pletnev et al., 2011). This novel flavivirus discovered in Saudi Arabia in the mid-1990 s was identified as the cause of hemorrhagic fever among cattle owners, shepherd and butchers (Madani et al., 2014a). Since then, several cases of Alkhumra hemorrhagic fever (AHF), with case-fatality rates of up to 30%, have been documented in western and southern Saudi Arabia (Qattan et al., 1996; Charrel et al., 2007; Alzahrani et al., 2010). Alkhumra hemorrhagic fever virus (AHFV) belongs to the genus *Flavivirus* and is described as having close similarity with KFDV (Mahdi et al., 2011; Bhatia et al., 2020). Knowledge gaps in respect of AHF include the mode of transmission from the natural reservoir to livestock animals and humans, the role of ticks as vectors and reservoirs of the virus, the pathophysiology of human infection, and the type of immunity that develops post exposure.

To date, no specific treatment or prevention and control strategies have been developed against this infection. Thus, major outbreaks of AHF among at-risk communities are anticipated (Fareez et al., 2013). Hence, accessible studies on AHFV and AHF were reviewed to summarize the available important evidence regarding one of the emerging zoonotic viral diseases in the Arabian Peninsula and its effect on humans and livestock animals.

2. Literature search

2.1. Search strategy

To identify the relevant literature, Web of Science, Scopus, Google Scholar and PubMed databases were searched for available pertinent publications without time restriction, i.e., from the earliest to most recent (31 December 2020). The search process was undertaken using MeSH terms alone or in combination: ‘‘Alkhurma hemorrhagic fever” OR ‘‘Alkhurma hemorrhagic fever virus” OR ‘‘Alkhurma virus” OR ‘‘Alkhumra hemorrhagic fever” OR ‘‘Alkhumra hemorrhagic fever virus” OR ‘‘Alkhumra virus”. The search terms included the two names of the virus (i.e., Alkhurma and Alkhumra). Moreover, the search was extended to include relevant data from the World Health Organization and national vector-borne disease control reports. Furthermore, additional literature was identified through manual searches of references listed in articles identified by the initial screening. The search process was confined to English-language publications.

After the initial screening of the aforementioned databases, the titles and abstracts of the identified records were screened to obtain the full text of the relevant articles. Then, the bibliographic details (authors, title, full source, document type and addresses) of the identified articles were downloaded and stored in a file. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines in conducting this study and reporting the results (Moher et al., 2015).

2.2. Inclusion ***criteria***

After removing duplicated records, papers were included in the review if they met the following criteria: (1) Study design: populations and/or health facilities-based surveys, epidemiological descriptive studies, cross-sectional, case–control studies, retrospective studies and case reports; (2) Sources: published in peer-reviewed journals or public reports; (3) Language: full text or abstract in English; and (4) Timeframe: published before January 01, 2021.

2.3. Exclusion criteria

The exclusion criteria were as follows: (1) Study design: studies without data such as in-silico studies; and (2) papers in languages other than English.

2.4. Search **results**

Fig. 1 displays the PRISMA-based diagram of the study selection process, including the inclusion and exclusion criteria and the number of studies identified at each stage. A total of 1087 potentially relevant research papers were identified. Among these, 240 studies met the inclusion criteria and their full texts were extracted and assessed for eligibility. Overall, 62 studies/reports were found eligible for this review; the majority of these studies were carried out in the Arabian Peninsula region, mainly in Saudi Arabia (n = 40), and the remaining studies (n = 22) were conducted in the rest of the world. Twenty-seven studies were experimental research studies; three were book chapters, three were papers for conferences, seven were systematic reviews and *meta*-analyses and 22 were case reports and annual public health reports. The majority of the 62 studies were published after 2010.

Overall, 604 confirmed cases of AHF have been reported in Saudi Arabia since 1995 (Zaki, 1997; Charrel et al., 2005; Alzahrani et al., 2010; Memish et al., 2014; MOH, 2020; Madani and Abuelzein, 2021) (Table 1). The cases were confirmed as AHFV-positive by either identification of viruses by molecular assays or detection of IgM by ELISA serological assay. These cases were reported in six locations (within three regions namely Makkah, Najran and Jazan), with Najran Region was the most affected region harboring 74.3% (449/604) of the confirmed cases followed by Jeddah (11.8%; 71/604) and Makkah (11.6%; 70/604) while only two cases (0.3%) were reported in Jazan (Memish et al., 2014; MOH, 2020; Madani and Abuelzein, 2021). Interestingly, three cases were recently reported in Alqunfudha governorate of Makkah Region in

Table 1
Distribution of confirmed cases of AHF reported in Saudi Arabia since 1995 according to location, year and nationality.

	N	%
Location		
Makkah*	70	11.6
Jeddah*	71	11.8
Taif*	9	1.5
Alqunfudha*	3	0.5
Najran	449	74.3
Jazan	2	0.3
Year		
1994–2000	16	2.6
2001–2005	28	4.6
2006–2010	154	25.5
2011–2015	340	56.3
2016–2020	66	10.9
Nationality		
Saudi	351	58.1
Non-Saudi	253	41.9
Total	604	100.0

* All are within Makkah Region.

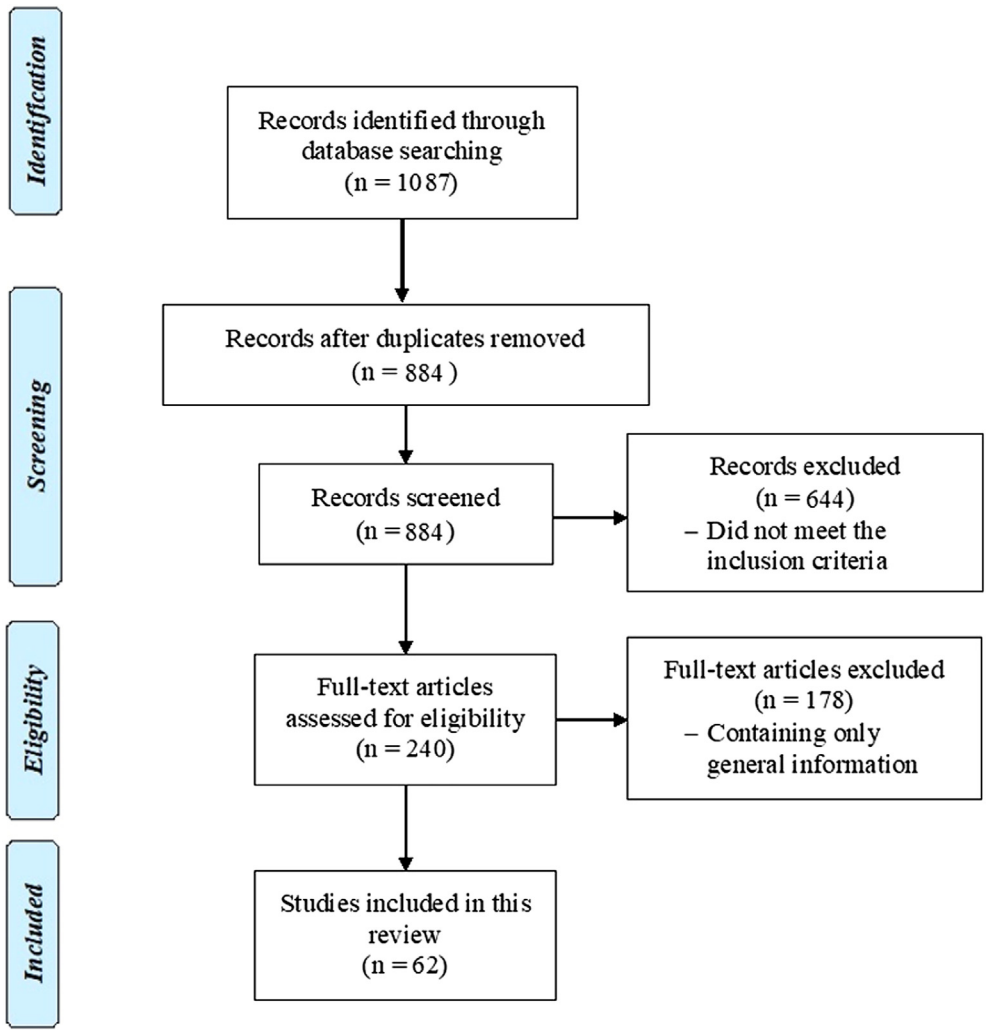

Fig. 1. Flow diagram of studies selection process using PRISMA guidelines.

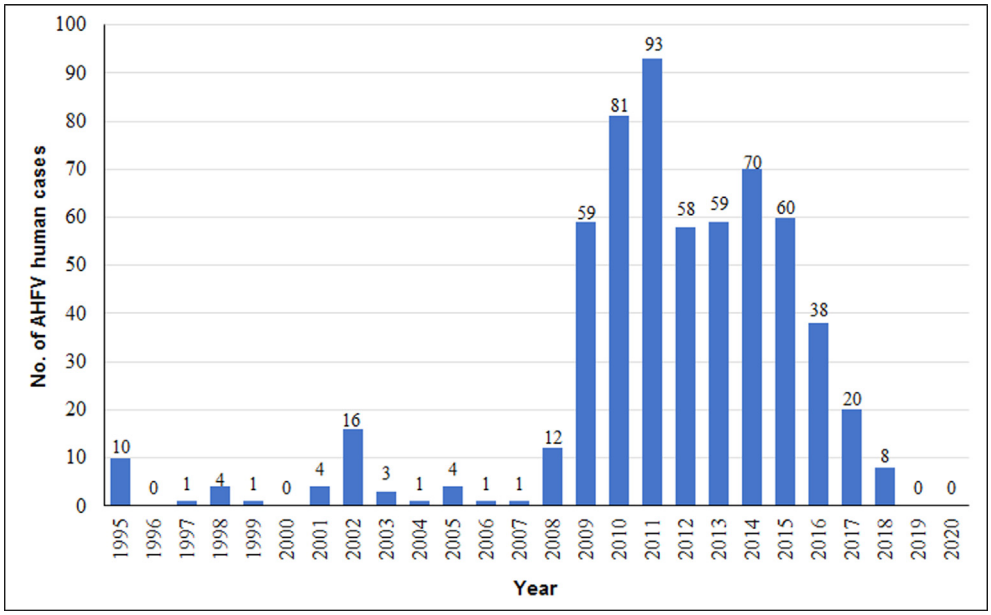

Fig. 2. Distribution of annual human AHFV cases reported in Saudi Arabia between 1995 and 2020.

April 2017 represented a new location for AHFV infection within Saudi Arabia (Madani and Abuelzein, 2021). With regards to nationality, over half (58.1%; 351/604) of these cases were Saudis and 41.9% (253/604) were non-Saudis, with majority of the non-Saudis were from Egypt and Yemen who were involved in the livestock industry and worked as butchers, shepherds, and abattoir workers (Memish et al., 2014; MOH, 2020). Moreover, the number of confirmed cases increased over time; with the majority (93 cases) of the confirmed cases were reported in 2011, with the number of confirmed cases peaks in July and December (Charrel et al., 2005; Alzahrani et al., 2010; Memish et al., 2014). After 2011, the trend decreased gradually with only 8 cases were reported in 2018 while no cases were reported in 2019 and 2020 (MOH, 2020) (Fig. 2).

3. Molecular characteristics of AHFV

Alkhumra hemorrhagic fever virus (AHFV) belongs to the genus *Flavivirus* of the *Flaviviridae* family. The AHFV comprised of a single positive sense RNA, the genome ranges from 10,685 to 10,749 nucleotides that encode a single open reading frame (ORF), known as a polyprotein [Madani et al., 2014b; Ul-Rahman, 2019). A single polyprotein composed of three structural proteins, namely the capsid/core (C), pre-membrane (prM) and envelop (E) proteins, and seven non-structural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B and NS5) (Charrel et al., 2001; Ul-Rahman et al., 2019). The complete coding sequence of an AHFV prototype strain 1176 (GenBank accession no. AF331718) revealed that the RNA of this strain had 10,685 nucleotides that encode a single 3,416 amino-acid polyprotein (Charrel et al., 2001). Interestingly, the whole genome sequencing was performed on an AHFV strain isolated from a patient in Najran, Saudi Arabia and the sequence analysis revealed different number of nucleotides; the RNA of this strain had 10,546 nucleotides; however, the phylogenetic analysis showed 99% shared sequence identity with other 18 AHFV strains previously reported in Makkah and Jeddah (Madani et al., 2014b). Overall, based on molecular characteristics of AHFV's polyprotein, genetic distances, envelope protein and evolutionary relationships, the virus was recognised belongs to the TBFV group.

4. History and evolution of AHFV

The genus *Flavivirus* includes more than 70 recognized viruses, with about half of them are important human emerging/re-emerging pathogens responsible for fever, encephalitis or hemorrhagic fever (Kuno et al., 1998). Those emerging/re-emerging flaviviruses include DENV, Zika virus (ZIKV), YFV, West Nile encephalitis virus (WNEV), Japanese encephalitis virus (JEV), and tick-borne encephalitis virus (Grard et al., 2007). The flaviviruses differ from other viruses belong to other genera of the *Flaviviridae* family in their antigenic, epidemiological, and ecological characteristics. However, within the genus *Flavivirus*, flaviviruses share a complex antigenic relationship; and therefore, majority of these viruses including the YFV, the prototype of this group, were serologically divided into eight antigenic serocomplexes using cross-neutralization with polyclonal antisera (Calisher et al., 1989). Nevertheless, some viruses including the YFV could not be assigned to any complexes as well as some new flaviviruses that have been identified but their relationship with the other flaviviruses has not been fully determined (Kuno et al., 1998). Hence, better criteria for classification were established through molecular genetic classification. Previous studies demonstrated that the genus *Flavivirus* represented a monophyletic lineage that was divided into three clusters: the tick-borne flaviviruses group (TBFV), the mosquito-borne flaviviruses group (MBFV) and the no-known vector flaviviruses (NKV) group (Kuno et al., 1998; Grard et al., 2007) (see the phylogenetic tree in Fig. 3).

Furthermore, the TBFV includes at least 12 viruses that share a common ancestor within the genus Flavivirus and are divided into three groups (see the phylogenetic tree in Fig. 3). The first group is the mammalian TBFV (m-TBFV) which includes six important humans and animal pathogens, namely KFDV and OHFV that cause hemorrhagic fever in humans, and Langat virus (LGTV), Louping ill virus (LIV), Powassan virus (POWV), and Tick-borne encephalitis virus (TBEV) that are all encephalitic viruses (Grard et al., 2007; Harima et al., 2021). The group also includes three other viruses that are not known to be human pathogens: Gadgets Gully virus (GGYV), Karshi virus (KSIV) and Royal Farm virus (RFV) (Grard et al., 2007). The second group is the seabird TBFV group (s-TBFV) which includes Tyuleniy virus (TYUV), Saumarez Reef

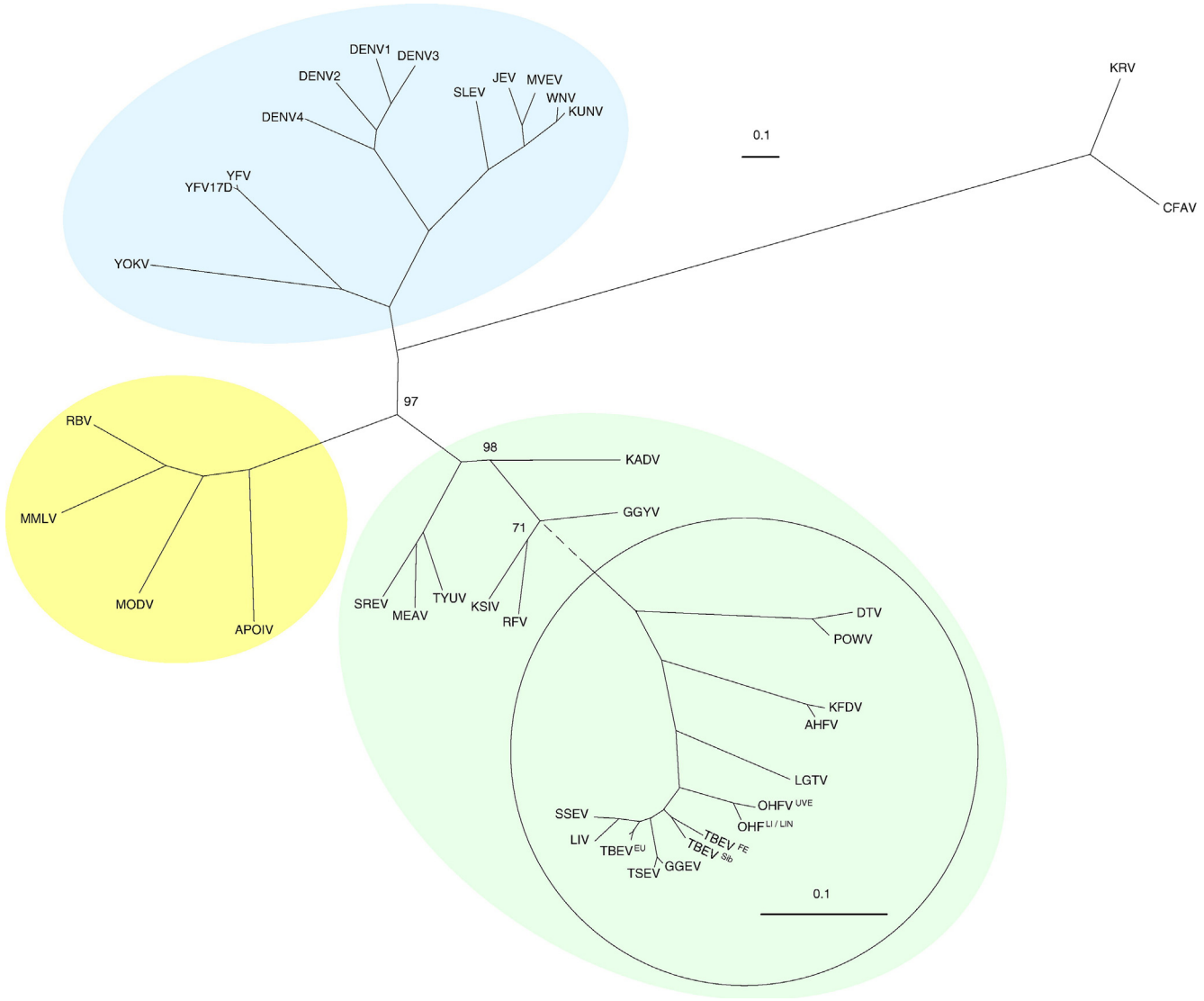

Fig. 3. A phylogenetic tree based on complete flavivirus amino acid sequences and the maximum likelihood method. All branchings were supported by quartet puzzling frequencies at 99% or 100% except at the forks where a value is indicated. The tick-borne flavivirus group is highlighted in green, the mosquito-borne flavivirus group in blue and the no-known vector flavivirus group in yellow. To improve the legibility of the tree, the distal part of the TBFV branch is presented with a 3.5 × magnification. Reprinted from Virology, 361(1), Grard G, Moureau G, Charrel RN, Lemasson JJ, Gonzalez JP, Gallian P, Gritsun TS, Holmes EC, Gould EA, de Lamballerie X, Genetic characterization of tick-borne flaviviruses: new insights into evolution, pathogenetic determinants and taxonomy, pp 80–92, Copyright (2007), with permission from Elsevier.

virus (SREV) and Meaban virus (MEAV). The third group includes a single virus, Kadam virus (KADV) (Harima et al., 2021). Interestingly, a closely related hemorrhagic virus has unexpectedly reported from a butcher in Alkhumra district of Jeddah, Saudi Arabia in 1995 (Zaki, 1997). Full genome sequencing and phylogenetic studies using the NS5 sequence have recognised it as a novel virus, Alkhumra hemorrhagic fever virus (AHFV), with a 89–92% nucleotide sequence homology with KFDV (Zaki, 1997; Ul-Rahman et al., 2019). It is concluded that both viruses are likely to be descendants from a common ancestor and represent two genetic subtypes of the same virus species. Thus, currently AHFV is included in the m-TBFV group as a subtype of KFDV, with the latter is the prototype of this species (Harima et al., 2021).

The KFDV was discovered in the late 1950′s in Karnataka, India. Given its emergence decades after KFDV and its high sequence homology with KFDV, it has been speculated that AHFV might have arose following an introduction of KFDV to Saudi Arabia from India (Charrel et al., 2001; Dodd et al., 2011). Indeed, some previous studies suggested a key role for the migratory birds in the spread of the KFDV from India to Yunnan Province, China (Wang et al., 2009). Similarly, Hoffman et al. (2018) reported AHFV RNA in immature Hyalomma rufipes ticks collected in Turkey and Greece from migratory birds that arrive Europe and Asia Minor from sub-Saharan and eastern Africa. Thus, it has been speculated that both KFDV and AHFV originated in Africa and then KFDV spread to India and AHFV to Saudi Arabia (Dodd et al., 2011; Hoffman et al., 2018). Another hypothesis also suggested that AHFV has been introduced to Saudi Arabia through millions of animals transported annually from Africa to Saudi Arabia to be slaughtered during the Hajj seasons (Charrel and Gould, 2011).

5. Controversy on virus designation

Based on official reports by the Ministry of Health, Kingdom of Saudi Arabia, the first six cases of the disease in 1994–1995 were

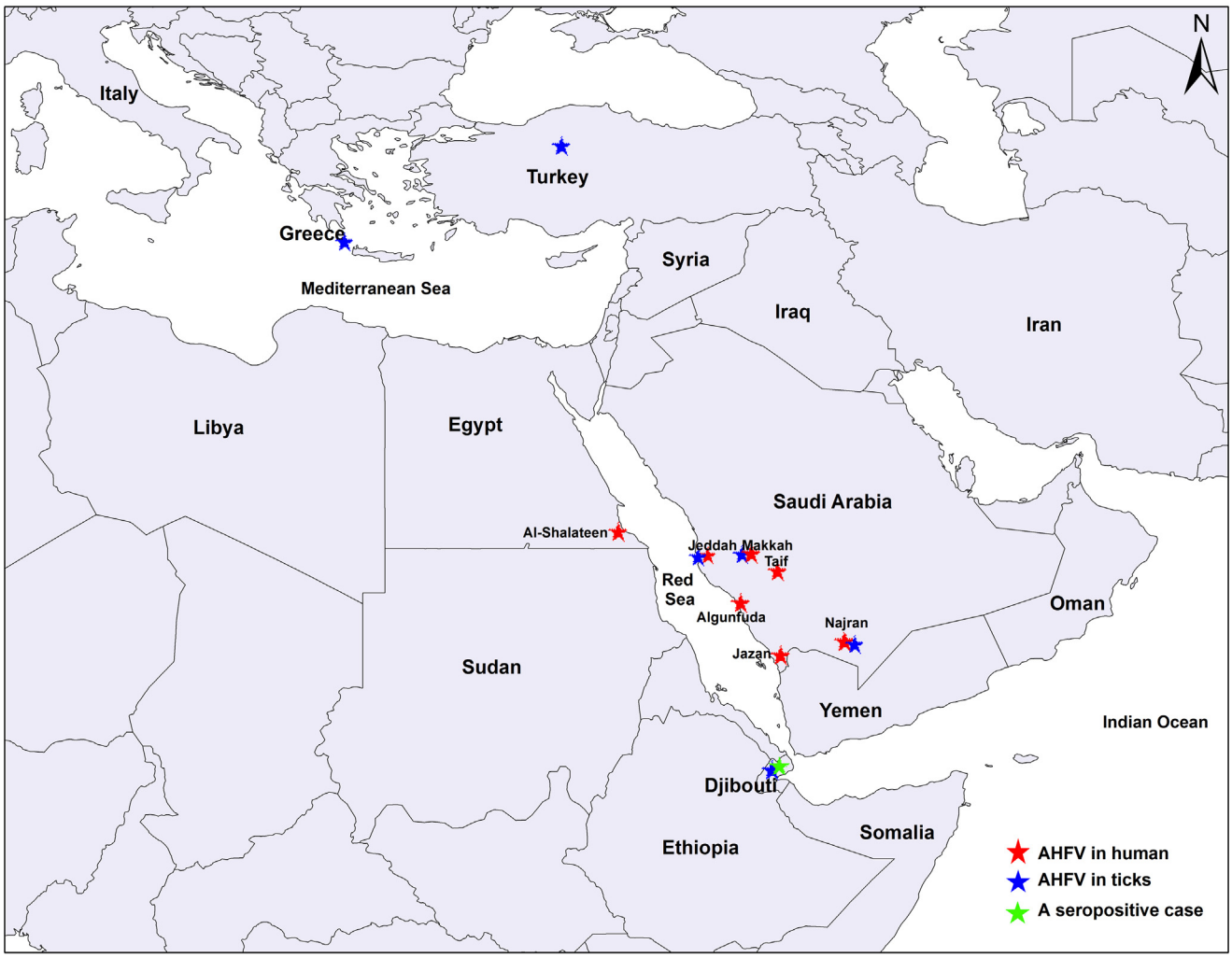

Fig. 4. A map showing the distribution of Alkhumra hemorrhagic fever virus reported in humans and ticks. The map was created using the Esri ArcGIS 10.7 software.

certainly from Alkhumra district, southern Jeddah City (Zaki, 1997; Madani, 2005). Alkhumra district has long been the location of livestock markets and slaughterhouses, ideal environmental conditions that favor the transmission of AHFV (Madani et al., 2011; Bhatia et al., 2020). The cases were originally misdiagnosed as Crimean-Congo hemorrhagic fever virus (CCHFV) (Bunyaviridae family) (Alzahrani et al., 2010). However, due to the high sequence homology with KFDV, the infections were considered to have been caused by a distinct variant of KFDV (Dodd et al., 2011; Ul-Rahman et al., 2019). Subsequently, the virus was reidentified by Madani in February 2001 in which it was referred to as Alkhumra virus (ALKV) for the first time (Madani, 2005; Madani et al., 2011). In 2001, the Ministry of Health alerted all health sectors throughout the country about this new virus and its potential as a fatal infection.

With regard to the name, there are no standard rules for the naming of newly discovered viruses and other biological pathogens. However, arboviruses are commonly named after the geographical location where they were first discovered or where the index case came from, or after the disease main symptom or the vector, following ICTV codes. In the case of the Alkhumra *sive* Alkhurma virus, the debate on its designation has been ongoing for a while (Charrel et al., 2006). Moreover, it should be remembered that the debate is not merely about the naming of a distinct virus species, but also about its initial description as a mere genotype or variant of KFDV (Zaki, 1997; Alzahrani et al., 2012).

6. Epidemiology of AHFV

The geographical range of AHFV is from endemic area in the west of Saudi Arabia but may include southwest Egypt and the east coast of Africa, Djibouti (Fig. 4). Between November and December 1995, AHFV was first isolated in Jeddah, Saudi Arabia from six butchers presented at Dr Suliman Fakeeh Hospital with dengue-like fever or fatal hemorrhagic fever signs and symptoms (Zaki, 1997). In addition, the author demonstrated that four more patients who worked with sheep and had similar clinical presentations to the six butchers were found to be seropositive for AHFV. That was the first time that a flavivirus tick-borne closely related to KFDV was confirmed in this region. It was identified as zoonotic viral infection as this area is mostly associated with camel and sheep ticks (Zaki, 1997).

The virus RNA was also detected in sand tampan ticks, *Ornithodoros savignyi* (Audouin), and camel ticks, *Hyalomma dromedarii*, collected in western Saudi Arabia (Charrel et al., 2007; Mahdi et al., 2011). The spread of viruses such as AHFV can be serious if they transmit among non-immune populations. However, genomic mining of AHFV provides a powerful tool for the design of new strategies that can be focused on various regions of the genome in case of spread (Ruiz-Aymá et al., 2016).

Between 2003 and 2007, eight sporadic confirmed cases of AHFV infection were reported in Najran Region, southern Saudi Arabia along the border with Yemen (Madani et al., 2011). After

2007, 70 confirmed cases of AHFV infection were reported, again in Najran Region, in a large outbreak that occurred in 2008–2009 (Madani et al., 2011). Memish and his research team conducted a seroprevalence study to assess exposure to AHFV, CCHFV, Rift Valley fever virus (RVFV) and DENV among 1026 soldiers from military units based in different Saudi Arabian regions who were deployed to Jazan Region (Memish et al., 2011). The study reported a relatively high seroprevalence of AHFV (13 cases; 1.3%,), with most AHFV-seropositive individuals were from Tabuk and Eastern regions; thus, the study indicated a wider geographical distribution and endemicity of AHFV than previously concluded (Memish et al., 2011). In agreement with a previous study conducted in Najran Region during the period 2006–2009 (Madani et al., 2011), seropositive status was found to be significantly correlated with mild or asymptomatic infection and none of the AHFV-seropositive individuals had a history of severe illness (Madani et al., 2011; Memish et al., 2011). Hence, a better understanding of the ecology, natural history and epidemiology of this viral infections is urgently needed to evaluate the possible risks to public health in Saudi Arabia, and in other potentially endemic areas.

Jazan region, the location of the Memish study (Memish et al., 2011), is an entry point to Saudi Arabia that experiences heavy human and animal traffic, particularly during the annual Hajj pilgrimage as well as through illegal cross-border migration. The region is endemic for many tropical infectious diseases such as leishmaniasis, malaria and dengue fever (Abass et al., 2020; Al-Mekhlafi et al., 2021; Alshabi et al., 2021). Moreover, the 2000–2001 RVF outbreak in Saudi Arabia was restricted to Jazan region, with more than 880 confirmed RVF cases and a case-fatality rate of up to 14% (Balkhy and Memish, 2003). While epidemiological studies on AHFV have focused on the western region of Saudi Arabia, specifically Makkah Region, where cases were first reported and outbreaks were characterized by high morbidity and mortality rates (Madani, 2005), a few studies conducted in Najran and Jazan regions confirmed the extension of the geographical range of the disease to the southern region of the country, where only subclinical infections had been described before that (Alzahrani et al., 2010; Memish et al., 2010).

Previous studies have also suggested a wider geographical distribution for AHFV, with infections reported beyond Saudi Arabia. For instance, in 2010, the virus was isolated from two Italian travelers who had returned home from southern Egypt, near the border with Sudan (Carletti et al., 2010). During their separated visits to Egypt, the travelers have visited a camel and dromedary market in Al-Shalateen, a touristic village in southern Egypt, and have experienced tick bites. Few days after returning to Italy, they were hospitalized with high fever, shaking chills, anorexia, malaise, nausea and vomiting, and blurred vision (Carletti et al., 2010). The diagnosis of AHFV infection was confirmed based on sequence and phylogenetic analyses. Interestingly, another two Italian travelers who had visited the same area in southern Egypt have been diagnosed with AHFV upon returning home (Ravanini et al., 2011; Musso et al., 2015).

Moreover, a study in Djibouti reported the presence of AHFV, for the first time in the Horn of Africa, in Amblyomma lepidum ticks collected from cattle imported from Somalia, Ethiopia and other parts of Africa (Horton et al., 2016). Another study on the detection of arboviruses in humans in Djibouti found only one case positive for the AHFV antibody in a 13-year-old girl who lived nearby an abattoir (Andayi et al., 2014). Furthermore, AHFV was identified in immature Hyalomma rufipes ticks infesting migratory birds caught in the North Mediterranean Basin, specifically in Turkey and Greece (Hoffman et al., 2018). These findings imply that the virus has a wide geographical range and that there might be other AHFV infections that have been underreported (CDC, 2014; Tambo and El-Dessouky, 2018a, 2018b).

Overall, the prevalence of AHFV within various tick populations as well as the role of animals and livestock in the transmission of the virus are not well known (Bhatia et al., 2020; CDC, 2014). Hence, further research on AHFV is required to develop and improve public health measures against the disease. All of these studies give a picture of the spread and the possibility of an African origin for the disease (Dodd et al., 2011). Furthermore, these findings can be linked to the well-known geographical distribution of the potential tick vectors, *O. savignyi* and *H. dromedarii* (Charrel et al., 2007; Mahdi et al., 2011).

7. Mode of transmission

Although AHFV is classified as a zoonotic virus and its potential tick hosts (the hard tick H. dromedarii and the soft tick O. savignyi) are mainly found in the Middle East, North and East Africa, and India (Mans and Neitz, 2004; Perveen et al., 2020), the mode of AHFV transmission is not well understood. Previous studies have suggested that humans can acquire the infection through tick bites or through direct contact with crushed infected ticks (Charrel et al., 2007; CDC, 2014). Although livestock may provide blood meals for ticks, no animal reservoirs have been reported for AHFV (Bhatia et al., 2020). However, close contact with livestock or domestic animals may be associated with an increased risk of AHF in humans (Memish et al., 2012; Musso et al., 2015; Bhatia et al., 2020). Moreover, transmission of AHFV through consuming raw or undercooked meat or raw dairy products (milk and cheese) has not been reported, although some tick-borne flaviviruses can be transmitted to humans via this route (Ilic et al., 2020). Likewise, two previous studies suggested a role for mosquitoes in the transmission of AHFV (Madani, 2005; Charrel et al., 2006); however, data to support this hypothesis are not available. Yet, human-to-human transmission of AHF is not known (Bhatia et al., 2020).

Tick-borne flaviviruses are usually transmitted by hard ticks; however, Alkhumra viral RNA has been detected in soft ticks (*O. savignyi*) collected at a camel resting place in Jeddah, Saudi Arabia (Charrel et al., 2007). Moreover, AHFV RNA has also been detected in Amblyomma lepidum ticks collected from cattle in Djibouti (Horton et al., 2016). Also, interestingly, AHFV RNA has been detected in immature *Hyalomma rufipes* ticks infesting northward migratory birds en route from sub-Saharan and eastern Africa to Europe (Greece, Italy, Spain) and Turkey (Hoffman et al., 2018). Until 2007, only serological and simple molecular data were suggestive of tick-associated AHFV transmission. Then, Charrel et al. (2007) provided the first evidence that the tick is the primary vector in AHFV infection. This evidence was supported by a complete sequence of AHFV isolated from tick, which was collected from Jeddah, that showed 99.7% homology with the known human AHFV strain 1176 (Charrel et al., 2007). Although AHFV virus replication in ticks has not yet been described, studies in endemic areas including Saudi Arabia and Djibouti have found a link between the *Ornithodoros* ticks and tick-borne diseases (Hoogstraal et al., 1981; Mahdi et al., 2011; Horton et al., 2016).

Despite the notable phylogenetic similarity between AHFV and KFDV, epidemiological studies have not revealed an important role for ticks in the zoonotic transmission of AHFV from animals to humans. Nonetheless, it is plausible that ticks act as a vector for transmitting AHFV among animals and as a reservoir of the virus (Madani et al., 2011; Bhatia et al., 2020). Previous studies have also suggested an association between the seasonal pattern of AHFV (March–July) and the peak activity of ticks at the beginning of March (Charrel et al., 2005; Alzahrani et al., 2010). However, a recent study on the seasonal population dynamics of *H. dromedarii* on camels in the UAE demonstrated high prevalence and continu-

ous presence of the ticks on camels and/or at camels resting places during the entire year regardless of the weather fluctuations (Perveen et al., 2020).

On the other hand, a previous study, which reported a total of 37 cases of AHF in Makkah Region between 2001 and 2002, suggested that mosquito bites and/or direct contact with infected sheep are modes of transmission (Madani, 2005). However, as yet, AHFV has not been detected by serological testing of or virus isolation from mosquitoes. In the same vein, a previous study conducted in Najran Region found no significant difference in the history of mosquito bites between an AHFV and a control group, and concluded that mosquitoes are not important in the transmission of AHFV (Alzahrani et al., 2010). However, the study design (i.e., case–control) might not be appropriate for drawing such a conclusion, particularly for Najran Region where the whole population have high exposure to mosquitoes. Therefore, further field studies to explore the presence of AHFV in various arthropod vector species are required to gain insights into the potential involvement of arthropod vectors in AHFV transmission. In addition, experimental studies are essential to confirm the ability of AHFV to infect laboratory-reared vectors and to disseminate the virus to animal hosts (Madani et al., 2012).

The potential role of rodents, shrews and other vertebrates in the transmission of AHFV is yet to be explained. Interestingly, a previous animal-model study demonstrated that AHFV has less morbidity and mortality in the mouse model (Dodd et al., 2014). However, more studies are needed to confirm viral genome detection and replication in other vertebrate populations to enable better understanding of the animal-to-animal, animal-to-human and human-to-human transmission possibilities.

8. The Hajj and risk of exposure

The Hajj is the annual Islamic pilgrimage to Mecca (also called Makkah), Saudi Arabia from the 8th of Dhul-Hijjah to the 13th day of the same month; the 12th month of the lunar Islamic year. Any healthy Muslim adult is obliged to perform Hajj once in his/her life subject to financial and physical capability. About two to three million pilgrims perform Hajj every year; one third of them are local residents of Saudi Arabia and two thirds come from other countries. During the Hajj, animals have to be sacrificed at a particular time, therefore for this Hajj practice every year the Saudi government needs to import more than three million head of cattle and sheep and neighboring countries. These animals either to have personal slaughtered animal as a traditional practice, or by modern streamline slaughterhouse as Saudi government ordered (Memish et al., 2012). In addition, more than 10,000 international abattoir workers are needed for this event, which is supervised by the Saudi government in accordance with high-quality public health guidelines. In a recent study that employed serological and molecular methods to determine the risk of some zoonotic infections among permanent slaughterhouse workers during the Hajj, AHFV was detected only in one worker (Almasri et al.,2019). Despite the limited results of this study, the potential risk of widespread transmission of infectious infections including AHFV remains high.

9. Pathogenesis of AHFV

Overall, there is a dearth of data on the pathogenesis of AHFV. The first animal-model study to investigate the pathogenicity of AHFV was conducted by Dodd et.al. (2014). Although the study demonstrated that both AHFV and KFDV infect the mice liver, kidney, gastrointestinal tract and brain, less lethal and viral loads of AHFV were observed as compared to KFDV (Dodd et al., 2014). Histopathological examination of the brains of AHFV-infected rats confirmed the development of meningoencephalitis, though inflammatory infiltration was patchy with no necrosis seen (Madani et al., 2014a). Moreover, the study showed that pathological changes in the brains of AHFV-infected rats were similar to those described by Holbrook et al. (2005) in their study on the brains of Powassan virus-infected mice. However, necrosis in the form of acute neuronal injury, edema and karyorrhexis was observed in some areas of the cerebrum of Powassan virus-infected mice (Holbrook et al., 2005). On the other hand, patchy meningoencephalitis with some evidence of perivascular cuffing without necrosis was observed in the brains of OHFV-infected mice (Holbrook et al., 2005). By contrast, in a BALB/c mouse model, a previous study found that AHFV infection did not cause a clinically evident disease; the virus was detected in a range of visceral tissues where it only caused subclinical or mild histopathologic changes and induced a proinflammatory cytokine response in the spleen and kidney (Sawatsky et al., 2014). In a recent animal model that utilized mice lacking the type I interferon receptor ($IFNAR^{-/-}$), Bhatia et al. (2021) demonstrated that AHFV-induced pathology was mainly observed in the spleen, liver, heart, and lymph nodes while no pathological changes were found in the lungs, kidney or brain.

Viral hemorrhagic fevers encompass a diverse group of human and animal systemic febrile illnesses in which fever and hemorrhage are caused by a taxonomically varied range of viruses (Hidalgo et al. 2017). Although replication of the causative viruses in infected cells of target tissues or organs can directly contribute to the pathological manifestations of VHF, the disease seems to be caused by dysregulation of the innate immune response (Basler, 2017). Due to sporadic and unexpected outbreaks of VHF caused by certain viral infections such as AHFV, KFDV and OHFV, clinical and epidemiological data on those VHF are scarce (Jahrling et al., 2012; Bhatia et al., 2020).

10. Clinical manifestation

After the initial identification of AHFV in Alkhumra district, a total of 37 suspected cases were reported between 2001 and 2003 in the district, of which 20 were laboratory confirmed (Madani, 2005). Among those 20 confirmed patients, 11 had hemorrhagic manifestations and five of them died (Alzahrani et al., 2010). This reflects a high case-fatality rate for this infection. Mortality in hospitalized patients can be as high as 30%, which makes AHFV one of the most deadly flaviviruses (Charrel et al., 2007; Alzahrani et al., 2010). The clinical picture of AHF is extremely severe. Based on the AHFV-confirmed cases, the disease presents at first with nonspecific acute flu-like symptoms such as fever, general malaise, headache, *retro*-orbital pain, joint pain, anorexia, vomiting and diarrhea (Alzahrani et al., 2010; Madani et al., 2011; Memish et al., 2014). Moreover, thrombocytopenia, leucopenia and elevated serum liver enzymes, as well as severe neurologic and hemorrhagic symptoms are also developed in a sizable proportion of cases; encephalitis and hemorrhagic manifestations have been found to occur in 20% and 55% of cases, respectively (Madani et al., 2011). In addition, asymptomatic and mild cases have also been reported (Alzahrani et al., 2010; ECDC, 2010).

11. Diagnosis

Differential diagnosis of AHF includes CCHF, RVF and Lassa fever, which occur in similar geographical areas, as well as KFDV (Tambo and El-Dessouky, 2018a; Tambo et al., 2018b). Due to similarities between these infections, clinical diagnosis might be difficult. However, suspected cases can be confirmed by laboratory diagnosis that can be done in the early stage of the illness based

on either molecular or serological assays. The first line of testing for AHFV infection is RT-qPCR which rely on the amplification of the NS5 region of the viral genome isolated from patients' blood samples (Memish et al., 2014; Bhatia et al., 2020). Moreover, serological diagnosis of AHF is done by IgG and IgM testing using enzyme-linked immunosorbent assay (Madani et al., 2011; Memish et al., 2011). Kinetics of antibody responses following AHF has not been well established yet; however, previous studies suggested antibody kinetics similar to those for KFDV (Bhatia et al., 2020). In general, AHFV-specific IgG and IgM antibodies appeared in human serum at almost the same time after symptom onset (5–8 days), but IgM persisted for a longer period (4 months) compared to IgM which persisted for about 3 months (Yadav et al., 2019; Bhatia et al., 2020). Overall, the current available AHF diagnostics are limited and poorly enforced; hence, there is an urgent need for the development of innovative new diagnostic assays including point-of-care tests and evaluation of their performance in outbreak settings.

12. Treatment and case management

Similar to other arboviral infections, no standard specific antiviral drugs are available to treat AHF. However, patients receive supportive therapy, which consists of maintenance of proper hydration and circulation, maintenance of oxygen status and blood pressure, and treatment for any related complications (Bhatia et al., 2020). Hence, drug screening systems should be developed to enable the identification of new and repurposed drugs for subclinical and clinical AHFV infections.

13. Prevention and control

To date, licensed vaccines exist for five flaviviruses (YFV, DENV, JEV, KFDV and TBEV), and several others have been evaluated in preclinical and clinical studies. Given that no specific treatments or prophylaxis or vaccines are also currently available for AHFV, preventive measures and increased awareness among targeted populations are the only measures against the disease. Health education on the virus and its transmission is essential. Tick-infested areas should be avoided, tick repellents for human skin and tick collars and acaricides for animals should be used, and close contact with livestock and domestic animals should be avoided (Memish et al., 2012; Bhatia et al., 2020). Moreover, periodic serologic screening of workers in farms and/or slaughterhouses and regular inspection of animals should be considered (Al-Tawfiq and Memish, 2017). In addition, a program of active surveillance of livestock and domestic animals, especially when abnormal patterns of morbidity or mortality occur, is highly recommended (Memish et al., 2012). Furthermore, tick surveillance has been suggested as an important and essential component of the tick-borne diseases control programmes (Hoffman et al. 2018; Eisen and Paddock, 2021)

14. Conclusions

Due to natural and human-made conditions such as the massive increase in globalization and connectivity, urbanization, climate change and increased human–animal contact, the incidence of emerging and reemerging infectious diseases has increased rapidly and frequently with significant human and economic costs. Public awareness of the health risk that viral infections pose to human health has improved in the last few decades, which have witnessed a number of VHF epidemics and outbreaks caused by emerging and reemerging viruses such as Ebola virus, KFDV, OHFV, CCHFV, DENV and AHFV (Holbrook et al., 2012). Diseases caused by these viruses were grouped together with other unrelated viral infections and collectively named as VHF as they have common, severe clinical manifestations characterized by a notable tendency to fatal hemorrhage. The pathogenesis of some of these diseases such as AHF and KFD is still not very well understood. Thus, better clinical and epidemiological classification of these diseases is needed. The eradication and elimination of some infectious diseases such as poliomyelitis and smallpox raised the hope that more life-threatening infectious diseases could also be eradicated. However, this hope may soon fade away due to outbreaks of various new infectious diseases such as Marburg disease, Lassa fever, Ebola viruses, and most recently Coronavirus disease (COVID-19).

Although AHFV was first isolated and identified in the mid-1990s and the incidence of infection has notably increased in the recent past, no specific antivirals, vaccines or prevention and control strategies have been developed yet. Thus, the likelihood of major AHF outbreaks cannot be dismissed if appropriate and effective containment strategies are not adopted.

15. Research involving human participants and/or animals

Not applicable.

Informed consent

Not applicable.

Ethical approval

Not applicable.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors would like to thank the Deanship of Scientific Research, Jazan University. This review is part of the Research Groups funding programme (Vector-Borne Diseases Research Group, Grant no. RG-2-1) of Jazan University.

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