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# Alkhumra (Alkhurma) virus outbreak in Najran, Saudi Arabia: Epidemiological, clinical, and Laboratory characteristics

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## KEYWORDS

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 Najran;  
 Saudi Arabia

**Summary** *Objective:* After its first appearance in Alkhumra district of Jeddah in 1994–1995, and then in Makkah in 2001–2003, the new hemorrhagic fever virus, known as *Alkhumra* (misnamed as Alkhurma) virus (*ALKV*), has subsequently been reported from Najran, in the south border of Saudi Arabia.

*Methods:* This is a descriptive cohort study summarizing the epidemiological, clinical, and laboratory characteristics of *ALKV* infected patients diagnosed in Najran from 1 August 2003 through 31 December 2009.

*Results:* A total of 148 suspected cases were reported, of which 78 (52.7%) cases were laboratory confirmed; 2 cases in 2003, 1 case in 2004, 4 cases in 2005, 1 case in 2007, 12 cases in 2008, and 58 cases in 2009. The cases were reported year round but 64.1% (50/78) of them occurred in the summer time. Twenty-five (32.1%) cases occurred as clusters in 5 families. The virus seemed to be transmitted from livestock animals to humans by direct contact with these animals and likely by mosquito bites. Ticks did not seem to be involved in the transmission of infection from animals to humans. Clinical and laboratory features included fever (100%), headache (85.9%), malaise (85.9%), arthralgia (83.3%), anorexia (82.1%), myalgia (82.1%), backache (71.8%), nausea and vomiting (71.8%), chills (60.3%), retro-orbital pain (55.1%), diarrhea (51.3%), abdominal pain (48.7%), hemorrhagic manifestations (25.6%), central nervous

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system manifestations (23.1%), leucopenia (87.7%), elevated liver enzymes (85.7%), prolonged partial thromboplastin time (52.6%), thrombocytopenia (46.2%), elevated creatine kinase level (45.7%), and elevated lactate dehydrogenase (25.0%).

**Conclusion:** *ALKV* infection has now been recognized outside its original boundaries in Saudi Arabia which may herald its identification in other countries.

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## Introduction

Alkhumra virus (*ALKV*) infection is a new viral hemorrhagic fever (VHF) that has been identified only in Saudi Arabia. It was first isolated in 1995 from 6 patients living in Alkhumra district in Jeddah.<sup>1,2</sup> In 2001–2003, Madani re-identified the disease and described 20 confirmed cases in the holy city of Makkah, 75 km far from Alkhumra, and proposed the name "Alkhumra" be given to the virus after the geographic location from which it was originally isolated.<sup>3</sup> Subsequently, cases have been sporadically reported from Najran, a region in the south of Saudi Arabia, since 2003. Since 2008, there has been a sharp increase in the number of reported cases from Najran region and the outbreak is currently still active. This descriptive cohort study summarizes the epidemiological, clinical, and laboratory characteristics of *ALKV* infection diagnosed in Najran from 1 August 2003, when the first case of this infection was reported, through 31 December 2009.

## Patients and methods

### Najran, the outbreak region

Najran is a province of Saudi Arabia, located in the south of the country along the border with Yemen (Fig. 1). It is the fourth largest province of the country's 13 provinces with an area of 360,000 km<sup>2</sup>. Its capital is Najran city. The region is inhabited by approximately 620,000 people. The climate is hot during the summer months with an average of 32° C. Temperatures in winter drop to an average of 6° C. It is rainy in the mountainous areas. It is mainly an agricultural province with most inhabitants working as farmers and herders of domestic animals for a livelihood. Most of the houses of people living in the various districts in Najran are widely separated from each other with distances in between ranging from 50 to 500 m. Extended families often live together in the same house. Animals are often kept in the back-yards of houses. Najran province contains three geographical regions: first, the flat region which lies in the middle of Najran, second, the north western mountainous region, and third, the eastern sandy region which is a part of the Empty Quarter (Rub Al-khali). Health care facilities in Najran province include 8 hospitals and 60 primary health care centers.

### Case definition

After the identification of the first 4 cases of *ALKV* infection in Makkah in 2001, a case definition was formulated for surveillance of this disease in Saudi Arabia.<sup>3</sup> *ALKV* infection was suspected if a patient had an acute febrile illness of at least 2 days duration and at least 2 of the following 4 clinical or laboratory criteria: (1) at least 3-fold elevation of alanine

transferase (ALT), or aspartate transferase (AsT), or clinical jaundice; (2) features of encephalitis such as confusion, disorientation, drowsiness, coma, neck stiffness, hemiparesis, paraparesis, or convulsions; (3) hemorrhagic manifestations such as ecchymosis, purpura, petechiae, gastrointestinal bleeding (hematemesis, melena, hematochesia), epistaxis, bleeding from puncture sites, or menorrhagia; (4) platelet count  $<100 \times 10^9/L$ , or lactate dehydrogenase (LDH) or creatine phosphokinase (CK) enzyme  $>2$  times upper normal level ( $>500$  and  $>400$  U/L, respectively).

### Data collection

Patients presenting or referred to Najran hospitals with suspected *ALKV* infection were reviewed on admission, and data recorded on a standard case report form. Information collected included patient demographics, risk factors for *ALKV* infection, clinical manifestations, laboratory results, complications, and outcome. Additionally, the research team visited the houses of patients to assess the environmental factors that may contribute to transmission of infection such as livestock animals, mosquitoes, and ticks, and to assess the health of livestock animals kept by patients.

### Specimens obtained

Blood specimens were obtained from all patients hospitalized with suspected *ALKV* infection within 4 days of hospitalization. The specimens were transported in IATA compliant containers on dry ice to the Ministry of Health Central Laboratory in Riyadh, the capital of Saudi Arabia and to the Special Infectious Agents Unit, a biosafety level 3 virology laboratory, at King Fahd Medical Research Centre, King Abdulaziz University, Jeddah, Saudi Arabia.

### Laboratory confirmation

Blood specimens collected within 14 days of onset of illness were tested for *ALKV* RNA using the one-step real-time RT-PCR (Tib Molbiol, Berlin, Germany) designed and developed based on *ALKV* sequence published by Charrel et al.<sup>4</sup> The real-time RT-PCR test was performed using the portable Light Cycler 2.0 system (Roche Molecular, Mannheim, Germany) and the AmpliTaq Gold Taq 21 polymerase (Applied Biosystems, Foster City, California) in 5'-nuclease assays. When collected at least 7 and 14 days after onset of illness, blood specimens were tested for anti-*ALKV* immunoglobulin M (IgM), and immunoglobulin G (IgG), respectively.

Blood specimens were also tested for *Rift Valley fever* (RVF) and *Dengue* PCR (when collected within 14 days), IgM (when collected at least 7 days after onset), and, IgG (when collected at least 14 days after onset), using previously described methods.<sup>5–11</sup> The ELISA systems



**Figure 1** Map of Saudi Arabia showing the two provinces where *Alkhumra* virus infection is identified, Makkah province which includes Jeddah city (where Alkhumra district is located) and the holy city of Makkah, and Najran city.

used to detect *Dengue* IgM and IgG antibodies were *Dengue* group-specific, employing a common antigen for *Dengue* virus serotypes 1, 2, 3, and 4 (PanBio Ply Ltd, Australia). Anti-ALKV IgM antibody titers were determined by IgM antibody-capture ELISA, with an inactivated ALKV virus-infected cell slurry prepared using the same procedures previously described.<sup>5,6</sup> Anti-ALKV IgG antibody titers were determined by using ALKV virus-infected cell antigens in an ELISA format as described.<sup>5,6</sup>

### Treatment

All patients received supportive care with intravenous fluids and, when indicated, ionotropic support, transfusion of blood and fresh frozen plasma, mechanical ventilation, and antimicrobial therapy for secondary bacterial or fungal infections. No specific antiviral medication was used for therapy.

### Veterinary assessment of livestock

Many people living in Najran kept sheep and goats and sometimes camels in the back-yards of their houses. Additionally, there were 5 abattoirs and marketplaces in Najran city. All animals kept in the back-yards of the houses of ALKV

infection-confirmed human cases as well as some randomly selected animals in the 5 abattoirs and marketplaces were clinically examined by one of the authors (E.M.E.A, a professor of veterinary medicine and arbovirology) and the relevant epidemiological data was collected from the owners.

### Mosquito and tick survey

Mosquitoes and ticks were collected over a two-week period from 10 to 24 March, 2009, to determine the prevalent species. Mosquitoes were collected using Black Hole mosquito traps designed to attract mosquitoes by ultraviolet light and generation of odor and carbon dioxide via a photocatalysis process with titanium oxide. The trap had a large fan that sucked mosquitoes into a collection basket. The traps were placed around randomly selected houses and animal pens of patients with confirmed ALKV infection in Najran. Ticks were collected from premises of livestock animals kept by patients with confirmed ALKV infection.

### Data processing

The Statistical Package for Social Science (SPSS) program (Release 15.0, 2006) was used for data entry and analysis.

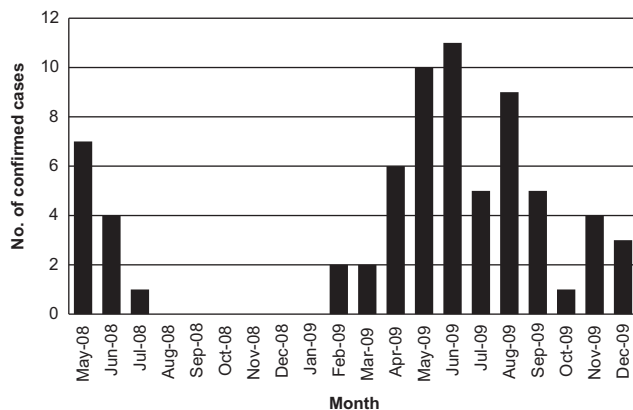


**Results**

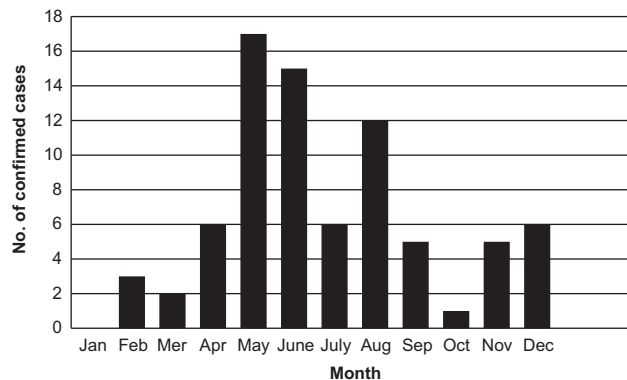
From 1 August 2003, to 31 December 2009, a total of 148 cases fulfilled the clinical case definition of *ALKV* infection, of which 78 (52.7%) cases were laboratory confirmed; 2 cases in 2003, 1 case in 2004, 4 cases in 2005, 1 case in 2007, 12 cases in 2008, and 58 cases in 2009. All 148 cases had negative tests for *RVF* and *Dengue* IgM, IgG and PCR. The 78 *ALKV*-confirmed cases were identified from 23 districts in Najran, namely, Almeshaalaa (16 cases), Alghuwaila (10 cases), Albalad (8 cases), Aljerba (7 cases), Dahdha (5 cases), Rair (5 cases), Althayba (4 cases), Aldheyafa (3 cases), Alhadan (3 cases), Alkhaledeyah (2 cases), Aloraaisa (2 cases), Alshorfa (2 cases), and one case each from Abulsaud, Aldhaiqa, Alfaisalyah, Almohammadyah, Almoonja, Alqabel, Beer Askar, Hai Alfahd Aljanoobi, Thajar, Wadi Reeman, and Yadama. Fig. 2 illustrates the epidemic curve of *ALKV*-confirmed cases by monthly periods for 2008–2009 (70 cases). Cases were reported year round but 50 (64.1%) cases occurred in the summer time from May to August. Fig. 3 shows the cumulative number of confirmed cases of *ALKV* infection diagnosed from 2003 to 2009 by month of onset (total 78 cases).

Sixty-nine (88.5%) patients were diagnosed as in-patients following hospitalization for acute febrile illness and 9 (11.5%) patients were identified by contact tracing. Of the 69 hospitalized patients, the duration of illness prior to presentation to the hospital ranged from 1 to 10 days with a mean of 4.9 ( $\pm 2.1$ ) days. The hospital stay ranged from 1 to 19 days with a mean of 6.2 ( $\pm 3.3$ ) days.

Table 1 summarizes the demographic characteristics and possible risk factors for acquiring *ALKV* among the laboratory-confirmed cases. The 21.8% of patients who reported no direct contact with livestock animals and who reported mosquito bites as the only risk factor, had livestock animals living in the vicinity to their homes. Twenty-five (32.1%) cases occurred as clusters of infections in the same household in 5 families: family A, 4 patients with date of onset of their illness occurring in the period of 11–29 December, 2005; family B, 5 patients in the period of 18–31 May, 2008; family C, 5 patients in the period of 27 May–24 June, 2008; family D, 4 patients in the period of 28 February–20 April, 2009; family E, 7 patients in the period of 1–20 May,



**Figure 2** Confirmed cases of *Alkhumra* virus infection diagnosed in 2008–2009 by month of onset (total, 70 cases).



**Figure 3** Cumulative number of confirmed cases of *Alkhumra* virus infection diagnosed from 2003 to 2009 by month of onset (total, 78 cases).

2009. None of the patients had signs of tick bites. Of the three patients who recalled tick bites, two patients were also exposed to animals and the third one was also exposed to mosquitoes. None of the patients who had contact with animals reported animal abortion, disease, or death.

Table 2 shows the clinical features and complications of the 78 patients with laboratory-confirmed *ALKV* infection. The temperature on admission ranged from 37.1 to 40.6° C with a mean of 38.8 ( $\pm 0.8$ )°C. Two of the 78 (2.6%) patients had a biphasic illness with an initial febrile period of 9 and 10 days, respectively, followed by an afebrile period of 2 and 3 days, followed by a second short febrile period of 2 days. Table 3 shows the laboratory characteristics on admission, and Table 4, the mean values and range of laboratory results on admission, of the 78 patients with laboratory-confirmed *ALKV* infection. Serum creatinine was available for 5 patients only; three of them had a normal level, one had slightly elevated serum creatinine (152  $\mu\text{mol/L}$ ), and the 5th patient had acute renal failure with a serum creatinine of 692  $\mu\text{mol/L}$ . The remaining 73 patients, who did not have serum creatinine measured, likely had a normal creatinine level as there was no clinical or biochemical indication to justify serum creatinine testing by their attending physicians.

Of the 78 patients with laboratory-confirmed *ALKV* infection, 70 (89.7%) patients had positive *ALKV* PCR tests, 3–13 days after onset of illness with a mean of 6.4 ( $\pm 2.0$ ) days (Table 5). Of 38 (48.7%) patients who had IgM tests, 10 (26.3%) patients were positive for IgM, 5–39 days after onset of illness with a mean of 14.7 ( $\pm 10.3$ ) days. Two of the 10 patients with positive IgM were also PCR-positive at 5 and 8 days of illness. Of 148 patients with suspected *ALKV* infection, 5 patients had IgG tests as their blood samples were obtained only 14 or more days after onset of their illness (Table 5). Only one of these 5 patients was positive for IgG 19 days after the onset of his illness. Convalescent serum to test for a rising IgG titer was not obtained because the patient was not available for testing after discharge from the hospital. The patient's positive IgG result was considered to be due to a past infection with the virus.

The vast majority (81.7%) of patients with confirmed *ALKV* infection kept livestock, mainly sheep and goats, in the back-yards of their houses. Some of these animals were kept in these premises for more than five years to

**Table 1** Demographic characteristics and risk factors for 78 patients with laboratory-confirmed *Alkhumra* virus infection in Najran, Saudi Arabia from 2003 to 2009.

Characteristic	Value
Age, Mean $\pm$ SD, range (year)	30.1 ( $\pm$ 16.5), 4–85
Age groups (year)	
<10	5 (6.4)
10 to <20	17 (21.8)
20 to <30	26 (33.3)
30 to <40	11 (14.1)
40 to <50	8 (10.3)
50 to <60	6 (7.7)
$\geq$ 60	5 (6.4)
Gender	
Male	49 (62.8)
Female	29 (37.2)
Nationality	
Saudi Arabia	46 (59.0)
Yemen	24 (30.8)
Bangladesh	3 (3.8)
Egypt	2 (2.6)
India	2 (2.6)
Syria	1 (1.3)
Occupation	
Students	22 (28.2)
Housewife	19 (24.4)
Self-employed	8 (10.3)
Other <sup>a</sup>	28 (37.3)
Cases occurring as clusters in families <sup>b</sup>	25 (32.1)
Risk Factors	
Direct contact with animals and mosquito bites	46 (58.9)
Mosquito bites as the only possible risk factor	17 (21.8)
Animal contact as the only possible risk factor	14 (17.9)
History of tick bites <sup>c</sup>	3 (3.8)
Drinking raw milk	37 (47.4)
Living or working in close proximity to livestock animals (sheep, goat & camels) in Najran	60 (76.9)
Home animals	49/60 (81.7)
Livestock marketplace	5/60 (8.3)
Restaurant kitchens where animals are slaughtered	3/60 (5.0)
Abattoir	2/60 (3.3)
Farm	1/60 (1.7)
Species of animals contacted	
Sheep and goat	33/60 (55.0)
Sheep, goat and camel	27/60 (45.0)
Types of contact with livestock animals	
Milking and feeding the animals	35/60 (58.3)
Slaughtering and butchering	20/60 (33.3)
Touching live animals	4/60 (6.7)
Handling raw meat	1 (1.7)
Number of patients reporting abortion storms, disease, or extraordinary deaths among animals	0
Number of patients reporting rat infestation of the house or the immediate surroundings	1 (1.3)

Data are no. (%) of patients, unless otherwise indicated.

<sup>a</sup> Includes laborer in restaurant kitchen (3 patients), office employee (3 patients), retired employee (3 patients), unemployed (3 patients), butcher (2 patients), livestock trader (2 patients), preschool children (2 patients), soldier (2 patients), teacher (2 patients), and one each of car trader, carpenter, driver, farmer, shepherd, tailor, and welder.

<sup>b</sup> See text under "Results" section for details.

<sup>c</sup> Two of these three patients with history of tick bites were also exposed to animals and the third one was exposed to mosquitoes.

**Table 2** Clinical features and complications in 78 patients with laboratory-confirmed *Alkhumra* virus infection in Najran, Saudi Arabia from 2003 to 2009.

Variable	Number of patients (%)
<b>Clinical features</b>	
Fever	78 (100)
Headache	67 (85.9)
Malaise	67 (85.9)
Arthralgia	65 (83.3)
Anorexia	64 (82.1)
Myalgia	64 (82.1)
Backache	56 (71.8)
Nausea and vomiting	56 (71.8)
Chills	47 (60.3)
Retro-orbital pain	43 (55.1)
Diarrhea	40 (51.3)
Abdominal pain	38 (48.7)
<b>Hemorrhagic manifestations</b>	
Epistaxis	9 (11.5)
Bleeding from the gum	8 (10.3)
Haematemesis	5 (6.4)
Melena	2 (2.6)
Fresh bleeding per rectum	1 (1.3)
Purpura	1 (1.3)
Vaginal bleeding	1 (1.3)
<b>Central nervous system manifestations</b>	
Altered sensorium	17 (21.8)
Confusion	8 (10.7)
Disorientation	7 (9.3)
Neck stiffness	7 (9.3)
Coma	4 (5.1)
Convulsions	4 (5.1)
Hallucination	3 (3.8)
Photophobia	1 (1.3)
Tremor	1 (1.3)
Cough	7 (9.0)
Sore throat	5 (6.4)
Cervical lymphadenopathy	1 (1.3)
Jaundice	1 (1.3)
Conjunctival injection	0
Dizziness	0
Rash	0
Visual loss or scotomas	0
<b>Complications<sup>a</sup></b>	
Encephalitis	10 (12.8)
Admission to intensive care unit	6 (7.7)
Gastrointestinal bleeding	6 (7.7)
Fulminant hepatitis	4 (5.1)
Disseminated intravascular coagulation	3 (3.8)
Mechanical ventilation	2 (2.6)
Acute renal failure	1 (1.3)
Respiratory failure	1 (1.3)
Vegetative state post encephalitis	1 (1.3)
<b>Mortality</b>	<b>1 (1.3)</b>

<sup>a</sup> Some patients had more than one complication, hence total number adds up to >11 patients.

**Table 3** Laboratory characteristics on admission of 78 patients hospitalized with laboratory-confirmed *Alkhumra* virus infection in Najran, Saudi Arabia from 2003 to 2009.

Variable	n/N (%) <sup>a</sup>
AsT > 40 U/L	54/63 (85.7)
ALT > 40 U/L	43/64 (67.2)
AsT > 200 U/L	20/63 (31.7)
ALT > 200 U/L	12/64 (18.8)
Bilirubin >17 $\mu$ mol/L	5/39 (12.8)
Hemoglobin <110 g/L	5/62 (8.1)
Platelets < 100 $\times$ 10 <sup>9</sup> /L	30/65 (46.2)
INR > 1.2	5/21 (23.8)
PTT > 45 s	10/19 (52.6)
Leukopenia <3.0 $\times$ 10 <sup>9</sup> /L	57/65 (87.7)
High CK > 400 U/L	21/46 (45.7)
High LDH > 500 U/L	9/36 (25.0)

ALT, alanine transferase; AsT, aspartate transferase; CK, creatine phosphokinase; INR, international normalized ratio; LDH, lactate dehydrogenase; PTT, partial thromboplastin time; SD, standard deviation.

<sup>a</sup> No. of patients with characteristic/no. of patients for whom information was available (%).

supply their owners with milk and meat. These small flocks consisted of adults and young lambs and kids. Most of the flocks consisted of females with a few males for breeding. The back-yards, in which these animals were kept, were pens open to the atmosphere, a situation that enabled flying biting arthropods to feed freely on these animals. No insect repellents were applied on these animals to prevent arthropod biting.

Livestock at Najran abattoirs and animal marketplaces were clinically examined and the relevant epidemiological data was collected from the owners. The animals consisted of adult camels, sheep, and goats, of various breeds. The goats were of the local southern breed. The sheep were of the local Herfy and Niaami breeds as well as foreign breeds, namely Sawakni (from Sudan) and Barbari (from Somalia). The camels were of the local breeds with some imported Somali and Sudanese breeds. All livestock animal species examined were healthy and showed no signs suggestive of arboviral infections such as abortions, stillbirths, teratogenesis of the neonates, icterus, or nasal discharge.

A total of 946 mosquitoes were collected, of which 936 (98.9%) mosquitoes were *Culex* species, 8 (0.8%) mosquitoes were *Anopheles* species, and 2 (0.2%) mosquitoes were *Culiseta* species. A total of 208 ticks were collected, of which 205 (98.6%) ticks were *Hyalomma* species, and 3 (1.4%) ticks were *Ornithodoros savignyi*.

## Discussion

Viruses that cause hemorrhagic fever belong to four viral families: *Arenaviridae*, which include *Lassa*, *Junin*, *Machupo*, *Guanarito*, and *Sabia* viruses; *Bunyaviridae*, which include *RVF*, *Crimean Congo hemorrhagic fever (CCHF)*, and the *Hantavirus*; *Filoviridae*, which include *Marburg* and the *Ebola* viruses; and *Flaviviridae*, which include *Yellow fever*, *Dengue*, *Omsk hemorrhagic fever (OHF)*, *Kyasanur Forest*

**Table 4** Mean values and range of laboratory results on admission for 78 patients hospitalized with laboratory-confirmed *Alkhumra* virus infection in Najran, Saudi Arabia from 2003 to 2009.

Laboratory test	n <sup>a</sup>	Mean ± SD	Range	Normal
AsT (U/L)	63	375 ± 661	17–2900	0–35
ALT (U/L)	64	165 ± 217	11–917	0–35
ALP (U/L)	53	113 ± 115	25–590	40–120
Bilirubin (μmol/L)	28	47 ± 153	2.0–763.0	5.1–17
Hemoglobin (g/L)	62	132 ± 18	93–178	120–180
Leukocytes × 10 <sup>9</sup> /L	66	2.1 ± 0.8	0.8–4.7	3.8–10.8
Platelets × 10 <sup>9</sup> /L	66	103 ± 48	11–262	130–400
LDH (U/L)	36	706 ± 1115	74–4844	100–250
CK (U/L)	47	1448 ± 2589	30–12945	10–200
INR	20	1.2 ± 0.4	1.0–2.7	0.9–1.2
PTT (s)	19	47 ± 8	35–66.2	25–35

ALT, alanine transferase; AsT, aspartate transferase; ALP, alkaline phosphatase; CK, creatine phosphokinase; INR, international normalized ratio; LDH, lactate dehydrogenase; PTT, partial thromboplastin time; SD, standard deviation.

<sup>a</sup> n, Number of patients for whom results were available.

disease (KFD), and *Alkhumra* viruses. Most hemorrhagic fever viruses are zoonotic, with the possible exception of the four *Dengue* viruses, which continually circulate among humans.<sup>12</sup> Many VHF viruses are vector-borne (*RVF*, *CCHF*, *Yellow fever*, *Dengue*, *OHF*, *KFD*, and *ALKV*), while others are not (*Lassa*, *Junin*, *Machupo*, *Guanarito*, *Sabia*, *Hantavirus*, *Marburg*, and *Ebola* viruses).

*ALKV* is the fourth VHF identified in Saudi Arabia; the other three are *CCHF*, *Dengue* fever, and *RVF*. Three of the four VHF diseases identified in Saudi Arabia, namely *ALKV*, *CCHF*, and *Dengue*, were confined to Makkah and Jeddah which are 80 km apart in the Western Province. Occurrence of *ALKV* and *CCHF* in these two cities is most likely related to the importation of large numbers of livestock into Makkah city through the seaport, Jeddah, for the Hajj seasons. Alkhumra district, located in the southern part of the seaport Jeddah, has long been the holding site for the imported livestock animals before their dispatch to Jeddah, Makkah, and other regions in the southwestern provinces. Most of these animals are imported from African countries and Australia.

Unfortunately, *Alkhumra* virus was misnamed as “Alkhurma” virus in many scientific publications due to a typographical error where the “m” and “r” were transpositioned.<sup>4,13–17</sup> The new word “Alkhurma” is the name of a small Saudi city that is 280 km far from “Alkhumra” district located in the south of the seaport

Jeddah where the original cases were identified.<sup>3</sup> The first publication that committed this typographical error clearly stated, however, that the virus was first isolated from Jeddah (where Alkhumra and not Alkhurma is).<sup>4</sup> Livestock marketplaces and slaughter houses, the characteristic environmental risk factors for acquiring *ALKV* infection, have long been located in Alkhumra district in Jeddah. All cases of this virus identified so far have been from Alkhumra/Jeddah, Makkah and lately from Najran. None of *ALKV* cases, including the first case identified in 1994, was reported from Alkhurma city as confirmed by the Ministry of Health.<sup>3</sup>

The identification of *ALKV* in Najran is the first reported occurrence of this disease outside Jeddah and Makkah. There are several possibilities to explain this outbreak in Najran. Firstly, the virus could have been introduced to Makkah and Jeddah (pilgrimage areas), Najran (agricultural area), and perhaps other, as yet unidentified, places in Saudi Arabia, via livestock animals from neighbouring African countries or Yemen where the virus may not have yet been identified. *RVF* is, likewise, believed to have been introduced to Saudi Arabia from east Africa in 1997–1998 leading eventually to the *RVF* epidemic in the southwestern regions of Saudi Arabia in 2000–2001.<sup>18</sup> The second possibility is that the virus could have been introduced to Najran via livestock animals brought from Makkah and Jeddah. The third possibility is that the virus is endemic in many areas of the country, three of which (Jeddah, Makkah, and Najran)

**Table 5** Confirmatory laboratory results for 148 patients hospitalized with suspected *Alkhumra* virus infection in Najran, Saudi Arabia from 2003 to 2009.

Test	Number of patients tested	Number of patients who were positive for the test (%)	Days between onset of illness and collection of blood sample for the test (range, mean ± standard deviation)
PCR	148 (100)	70 (47.3)	3–13, 6.4 ± 2.0
IgM	38 (25.7)	10 (26.3) <sup>a</sup>	5–39, 14.7 ± 10.3
IgG	5 (3.4%)	1 (20) <sup>b</sup>	19

<sup>a</sup> Two of the 10 patients with positive IgM were also PCR-positive at 5 and 8 days of illness.

<sup>b</sup> This IgG-positive patient was negative for PCR and IgM.



have thus far been identified and the remaining areas are yet to be identified.

As illustrated in Fig. 2, most of *ALKV* infections occurred in the summer months (May to August). Similarly, most cases of the non-zoonotic mosquito-borne *Dengue* arbovirus that has caused an outbreak in Jeddah since 2004, have occurred in the summer months between May and August (2010, unpublished data from the Ministry of Health). Interestingly, all *Culicoides*-transmitted arboviral diseases reported in animals in Saudi Arabia such as *Bluetongue*, *Akabane*, *Bovine Ephemeral Fever*, *African Horse Sickness*, and *Epizootic Hemorrhagic Disease of Deer*, have occurred during the summer months as well.<sup>19–24</sup> Studies in Saudi Arabia assessing the seasonality and abundance of *Culicoides* also showed that the summer time between May and September constituted the peak abundance and activity of these arthropods.<sup>25</sup> Whether *Culicoides* play any role in the transmission cycle of *ALKV* in animals remains unknown, however. In light of this, it seems that there is a strong link between the breeding season of the flying arthropods (summer months) and *ALKV* cases in Najran. It is known that some of the flying arthropods are on-the-wing year round, which could explain the occurrence of the disease at a low level of frequency outside the summer months.

The epidemiological, clinical, and laboratory characteristics of Najran outbreak of *ALKV* infection described herein are similar to those of the outbreak that occurred in Makkah in 2001–2003.<sup>3</sup> Few noteworthy differences between Najran and Makkah outbreaks include the fact that the proportion of females reported in Najran outbreak was higher than that in Makkah (38% versus 10%), 5 children <10 years of age were reported in Najran outbreak whereas none were reported in Makkah, more patients in Najran reported similar illness in the family compared to patients in Makkah outbreak (25% versus 5%), and the mortality in Najran was notably lower than that in Makkah outbreak (1.3% versus 25%). The first three salient differences are most likely due to the difference in the style of living between the two localities. Najran is a rural area where closely related families and their extended members usually live together in big houses with back-yards to keep sheep and goats. All family members including women and older children usually share the responsibility of feeding and milking the animals and cleaning their premises. The notably low mortality observed in Najran outbreak may be secondary to an established endemicity of *ALKV* in this region with some protective immunity among humans developing as a result of frequent exposure to the virus. This is supported by the limited annual incidence of *ALKV* in Najran between 2003 and 2007 prior to the outbreak in 2008–2009.

The epidemiological data of our study suggested that direct contact with livestock animals and/or mosquito bites were likely the primary risk factors for acquiring *ALKV* infection. Fifty-nine percent of the patients had both animal contact and mosquito bites as possible risk factors, 21.8% of the patients had mosquito bites as the only possible risk factor, and 17.9% of the patients had contact with animals as the only possible risk factor for acquiring *ALKV* infection. The one-fifth of patients who reported no direct contact with livestock animals and who reported mosquito bites as the only risk factor, had livestock animals living in the vicinity to their homes. Therefore, we speculate that the virus was likely transmitted from these apparently

asymptomatically-infected livestock animals to the human beings living in the same vicinity by mosquitoes. The speculated possibility of mosquito-borne transmission of *ALKV* is further supported epidemiologically by the finding that one-third (32.1%) of patients lived in the same household. This clustering of cases among one-third of patients may also raise the possibility of human to human transmission. Almost half of the patients had history of drinking raw milk, but all of them were also exposed directly to animals and/or mosquito bites. A case control study would normally be an ideal design to determine the actual risk factors for acquiring infections. However, for this particular *ALKV* outbreak, a case control study would perhaps be of limited value because of the fact that almost all the population in Najran live in the same social and environmental conditions including proximity to animals and exposure to mosquitoes. Biological studies to confirm the vector-ability of mosquitoes or ticks and the susceptibility of livestock and other animals to *ALKV* infection are more appropriate to define the true risk factors and mode of transmission of *ALKV*.

Due to the close phylogenetic similarity between *ALKV* and *KFD* virus, it could be argued that ticks may play an important role in the transmission cycle of *ALKV*.<sup>13</sup> This argument is further supported by a PCR-based detection of a virus closely related to *ALKV* from one *Ornithodoros savignyi* (sand tampan) tick out of 124 ticks collected from camels and camel resting places in Jeddah, Saudi Arabia.<sup>14</sup> Additionally, this species of ticks was identified in Najran accounting for 1.4% of all ticks collected. However, as previously suggested by Madani, our study reaffirms that ticks do not seem to play an important role in the transmission of *ALKV* from animals to humans, although, their role as a reservoir of the virus in its ecologic niche is conceivably possible.<sup>3</sup> In this study, only 3 patients reported tick bites, two of them were also exposed to animals and the third one was also exposed to mosquito bites. Of note is that the bite of the *O. savignyi* tick is so painful and ferocious to be forgotten as described by Mans and Neitz.<sup>29</sup> None of the patients confirmed to have *ALKV* infection in this study or the previous ones including the three patients who reported tick bites in this study recalled such a painful and memorable encounter with ticks. The speculated mosquito-borne nature of *ALKV*, as indicated epidemiologically, is supported by the fact that several mosquito-borne flaviviruses have been isolated from ticks, e.g., *Saint Louis encephalitis* virus and *West Nile virus*; yet, ticks were not confirmed to be biological vectors of such infections.<sup>14,26,27</sup> Additionally, even though most *ALKV*-closely related viruses are known to be associated with ticks, in at least one instance, the *Powassan* virus, there is some evidence that the virus is also found in different species of mosquitoes including *Culex*.<sup>14,28</sup> *Culex* species, the predominant mosquito species in Najran, has been confirmed to be a competent vector of many viruses in the three distinct families of mosquito-borne arboviruses, namely *Bunyaviridae*, such as *RVF* virus, *Togaviridae*, such as *Western Equine Encephalomyelitis*, as well as *Flaviviridae*, such as *Japanese Encephalitis Virus*, *Murray Valley Encephalitis Virus*, *Kunjin Virus*, *Saint Louis Encephalitis Virus*, and *West Nile Virus*.<sup>30–34</sup> However, the importance of isolating *Powassan* virus from mosquitoes remains to be elucidated as it could have been due to intake of viremic blood from an animal or human source.

In summary, ALKV is a novel hemorrhagic fever flavivirus that is reported only from Saudi Arabia. It was originally reported from Jeddah in 1994, and then from Makkah in 2001–2003, and most recently from Najran from 2003 to date. Acute febrile flu-like illness, hepatitis, hemorrhagic manifestations, and, less commonly, encephalitis are the main clinical features. The virus seemed to be transmitted from livestock animals (sheep, goats, or camels) to humans by direct contact with these animals or the mosquito bites. However, ALKV vector-ability of mosquitoes needs to be confirmed with biological studies. Tick bites did not seem to be associated with transmission of infection from animals to humans. However, the exact role of arthropods such as ticks, mosquitoes, and *Culicoides*, and animals such as sheep, goats, camels, and other mammals in the transmission and maintenance of the virus remains to be elucidated.

### Conflict of interest

The authors declare that they have no conflicts of interest.

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### Appendix. Supplementary material

Supplementary data related to this article can be found online at [doi:10.1016/j.jinf.2010.09.032](https://doi.org/10.1016/j.jinf.2010.09.032).

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