MAJOR ARTICLE

Rift Valley Fever Epidemic in Saudi Arabia: Epidemiological, Clinical, and Laboratory Characteristics

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This cohort descriptive study summarizes the epidemiological, clinical, and laboratory characteristics of the Rift Valley fever (RVF) epidemic that occurred in Saudi Arabia from 26 August 2000 through 22 September 2001. A total of 886 cases were reported. Of 834 reported cases for which laboratory results were available, 81.9% were laboratory confirmed, of which 51.1% were positive for only RVF immunoglobulin M, 35.7% were positive for only RVF antigen, and 13.2% were positive for both. The mean age (± standard deviation) was 46.9 ± 19.4 years, and the ratio of male to female patients was 4:1. Clinical and laboratory features included fever (92.6% of patients), nausea (59.4%), vomiting (52.6%), abdominal pain (38.0%), diarrhea (22.1%), jaundice (18.1%), neurological manifestations (17.1%), hemorrhagic manifestations (7.1%), vision loss or scotomas (1.5%), elevated liver enzyme levels (98%), elevated lactate dehydrogenase level (60.2%), thrombocytopenia (38.4%), leukopenia (39.7%), renal impairment or failure (27.8%), elevated creatine kinase level (27.3%), and severe anemia (15.1%). The mortality rate was 13.9%. Bleeding, neurological manifestations, and jaundice were independently associated with a high mortality rate. Patients with leukopenia had significantly a lower mortality rate than did those with a normal or high leukocyte count (2.3% vs. 27.9%; odds ratio, 0.09; 95% confidence interval, 0.01–0.63).

Rift Valley fever (RVF) is an acute zoonotic viral disease that affects ruminant animals and humans [1]. The disease is named after the Rift Valley of East Africa, where the etiologic virus was first isolated in 1930 during an investigation into an epidemic of infection among sheep on a farm in the Rift Valley in Kenya [2]. It was possible to retrospectively identify epizootic outbreaks caused by this virus as far back as 1912 [3]. Since 1930, more than 30 outbreaks of this disease have occurred in Africa [4]. Outbreaks were reported exclusively from sub-Saharan Africa until 1977–1978, when infections in 18,000 persons and 598 deaths were reported in Egypt [5, 6]. In 1987, after dam construction on the Senegal River caused flooding in the lower Senegal River area, a major epidemic, which caused 200 human deaths, occurred for the first time in Mauritania [7]. Another outbreak of RVF occurred in Egypt in 1993, when 41 cases of ocular disease and an estimated 600–1500 infections were reported [8]. The last major outbreak occurred in East Africa (Kenya and Somalia) in 1997–1998 [9]. Epidemics of RVF were limited to the African continent until 2000.

On 11 September 2000, the Ministry of Health (MOH) of the Kingdom of Saudi Arabia (Riyadh) received reports of unexplained severe hepatitis in 7 patients from the Jizan region at the southwestern border of Saudi Arabia. A team from the MOH started inves-

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tigations within 24 h after notification. Clinical manifestations included low-to-moderate–grade fever, abdominal pain, vomiting, diarrhea, and elevated liver enzyme levels progressing to liver failure, encephalopathy or encephalitis, disseminated intravascular coagulation (DIC), renal failure, and, in 5 of the 7 patients, death. An unusual disease with abortion storms and deaths among sheep in the region was also described by the villagers. On the basis of a clinical diagnosis of acute viral hemorrhagic fever in humans and the presence of a concomitant disease in domestic animals with deaths and abortions, the MOH team made a preliminary diagnosis of RVF within 48 h after notification. Serum specimens and a liver biopsy specimen obtained from a patient who died were sent to the Special Pathogens Branch of the Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia, for diagnostic testing. On 15 September 2000, laboratory tests at the CDC confirmed the diagnosis of RVF, using ELISA for RVF virus antigen and RVF IgM detection, RVF RT-PCR, RVF virus isolation, and RVF-specific immunohistochemical testing. Subsequently, the health authorities of the Republic of Yemen realized that a similar, hitherto undiagnosed, disease that was noticed among humans and sheep for several weeks in a northern region of Yemen bordering Jizan region was perhaps also caused by RVF. This was subsequently confirmed to be a simultaneous epidemic of RVF in the Republic of Yemen with the assistance of a team from the World Health Organization (WHO). The present study summarizes the epidemiological, clinical, and laboratory characteristics of this first confirmed occurrence of RVF outside Africa.

METHODS

The regions of the epidemic: Jizan, Asir, and Al-Qunfuda. The Jizan region is located in the southwest of Saudi Arabia, bordering the northwestern region of Yemen (figure 1). The region is inhabited by ~1,025,318 people. It comprises >30 districts and the main city, Jizan, which is a seaport on the Red Sea. The climate is hot and humid most of the year. Most inhabitants work as farmers and raise domestic animals for a livelihood. Electric power is not yet available for the vast majority of the remote villages about which the epidemic centered. Air-conditioning and the use of electric fans are therefore not possible in these areas. As a result, villagers, particularly men, frequently sleep outdoors to avoid the high indoor temperatures and, thus, are intensely exposed to mosquito bites.

Within 3 weeks after the onset of the epidemic in Jizan, the disease appeared on the Tehama Plain of the adjacent region, Asir, and, to a lesser extent, in the Al-Qunfuda area in the Makkah region (figure 1). The Asir region is located northeast of Jizan. The majority of the Asir region consists of the Sarawat Mountains; the area referred to as "the Tehama Plain" is only a narrow coastal strip. The Tehama Plain is considered to be a geographic extension of the Jizan region. The population of Asir is ~1,297,994 people, ~29% of whom live on the Tehama Plain. Al-Qunfuda is a further northward extension of this coastal plain in the Makkah region. The population of Al-Qunfuda is ~55,543 people. The social and environmental conditions in these 3 epidemic areas are similar.

Health care facilities in the epidemic regions. Health care facilities in the areas of the RVF epidemic included 13 hospitals

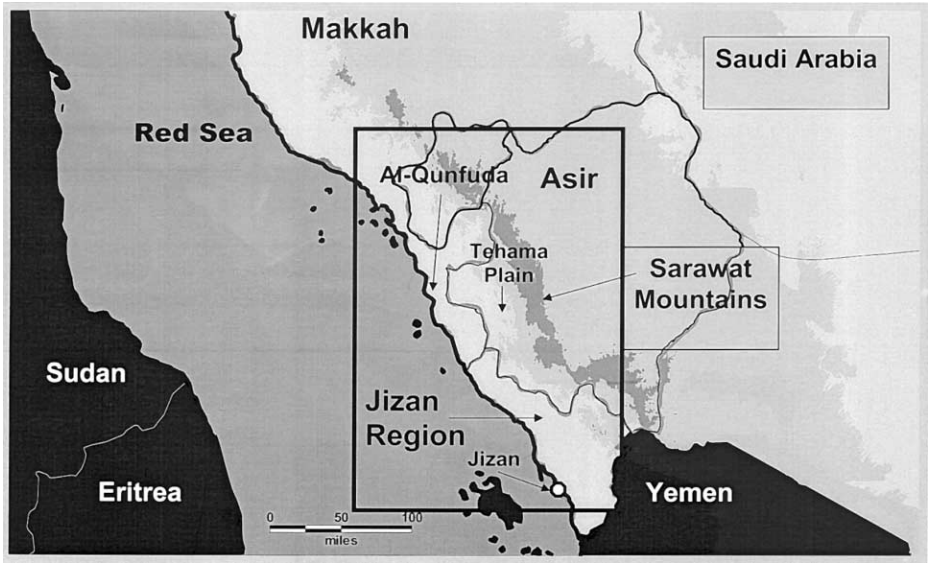

Figure 1. Areas affected by the Rift Valley fever epidemic in Saudi Arabia, 26 August 2000 through 22 September 2001

and 128 primary health care centers (PHCCs) in Jizan, 17 hospitals and 221 PHCCs in Asir, and 1 hospital and 29 PHCCs in Al-Qunfuda.

Case definition. Six categories constituted the case definition formulated and used for detection of suspect cases of RVF. (1) Unexplained febrile illness of >2 days' duration associated with ⩾3-fold elevation in the alanine transferase (ALT), aspartate transferase (AST), or γ-glutamyl transpeptidase level or clinical jaundice; (2) unexplained febrile illness of >2 days' duration associated with features of encephalitis, such as confusion, disorientation, drowsiness, coma, neck stiffness, hemiparesis, paraparesis, or convulsions; (3) unexplained febrile illness of >2 days' duration associated with bleeding, such as ecchymosis, purpura, petechiae, gastrointestinal bleeding (hematemesis, melena, or hematochesia), epistaxis, bleeding from puncture sites, or menorrhagia; (4) unexplained febrile illness of >2 days' duration associated with diarrhea, nausea, vomiting, or abdominal pain and any 1 of the following: hemoglobin concentration of <80 g/L, platelet count of $<100 \times 10^9$ platelets/L, serum creatinine level of >150 μmol/L, or lactate dehydrogenase (LDH) or creatine kinase (CK) enzyme level of >2 times the upper limit of normal; (5) unexplained acute vision loss or scotomas; or (6) unexplained death with a history of fever, lethargy, diarrhea, abdominal pain, nausea, vomiting, or headache in the preceding 2 weeks.

Data collection. Suspected cases were identified through an elaborate preexisting system of PHCCs that referred patients with suspected RVF to district hospitals for medical assessment and hospitalization. Patients presenting or referred to district hospitals with suspected RVF were reviewed at hospital admission, and data were recorded on a standard case report form. Information collected included patient demographic characteristics, risk factors for RVF virus infection, clinical manifestations, and laboratory results. Information related to mortality was obtained from the central operations room in the MOH, which received this information from the epidemic regions on a daily basis.

Specimens obtained. Blood specimens were obtained at admission to the hospital from all hospitalized patients with suspected RVF. Within 24 h after obtainment, specimens were transported in special containers on dry ice to the Central Laboratory in Riyadh, the capital of Saudi Arabia. Initially, specimens were then transported to the CDC for confirmatory testing. Subsequently, a laboratory was established for RVF diagnosis at the Central Laboratory in Riyadh with the assistance of the CDC.

Laboratory confirmation. ELISAs were used to detect RVF virus antigen and specific IgM in patient serum or blood samples using methods described elsewhere [10], as adapted for RVF. The RVF virus antigen detection assay used polyclonal hyperimmune ascitic fluid raised against RVF virus strain Zagazig 501 as the capture antibody and rabbit hyperimmune serum raised against RVF virus Zagazig 501 as the detector antibody. RVF virus–specific IgM antibody was detected by IgM antibody–capture ELISA, with inactivated RVF virus–infected cell slurry prepared as described elsewhere [10]. The first group of cases were also confirmed by isolation and identification of the virus from serum or blood specimens, detection of viral RNA in serum or blood specimens using RT-PCR, and RVF-specific immunohistochemical testing of a liver biopsy specimen using methods described elsewhere [11–13]. Specimens were processed in a laminar flow safety cabinet and treated to inactivate the virus before serological testing (γ irradiation was used in Atlanta, and detergent and heat were used in Riyadh).

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

Data processing. Epi Info, version 6.04b (CDC), was used for data entry and analysis. SPSS, release 7.5.1 (SPSS), was used for multivariate analysis. $P \leqslant .05$ denoted statistical significance.

RESULTS

The date of onset of the first laboratory-confirmed case of RVF in the Jizan region was 26 August 2000, and that of the last case was 22 September 2001. A total of 886 patients with suspected RVF were identified during this epidemic period. Retrospective chart review of patients hospitalized in Jizan region in the preceding 12 months failed to identify any cases of RVF. The date of onset of the first laboratory-confirmed case of RVF in the Asir region was 12 September 2000, and that in the Al-Qunfuda area was 20 September 2000. The dates of onset of the last laboratory-confirmed cases of RVF from these 2 regions were 4 April 2001 and 14 February 2001, respectively. Figure 2 illustrates the epidemic curve of suspected cases of RVF and associated deaths by weekly periods, starting on 26 August 2000 (the date of the onset of the first case) and continuing through 22 September 2001 (the date of the onset of the last case in the epidemic).

Apart from 2 fatal cases that fulfilled only the sixth case definition, all other reported cases fulfilled ⩾2 of the other 5 case definitions. Table 1 shows the sensitivity, specificity, and positive and negative predictive values of the case definitions.

Of 886 reported patients, data from RVF-confirmatory laboratory studies were available for 834 patients, of whom 683 (81.9%) had laboratory-confirmed cases. Of 683 confirmed cases, 354 (51.8%) were reported from Asir, 299 (43.8%) were reported from Jizan, and 30 (4.4%) were reported from Al-Qunfuda. Of the 299 patients who acquired RVF infection in

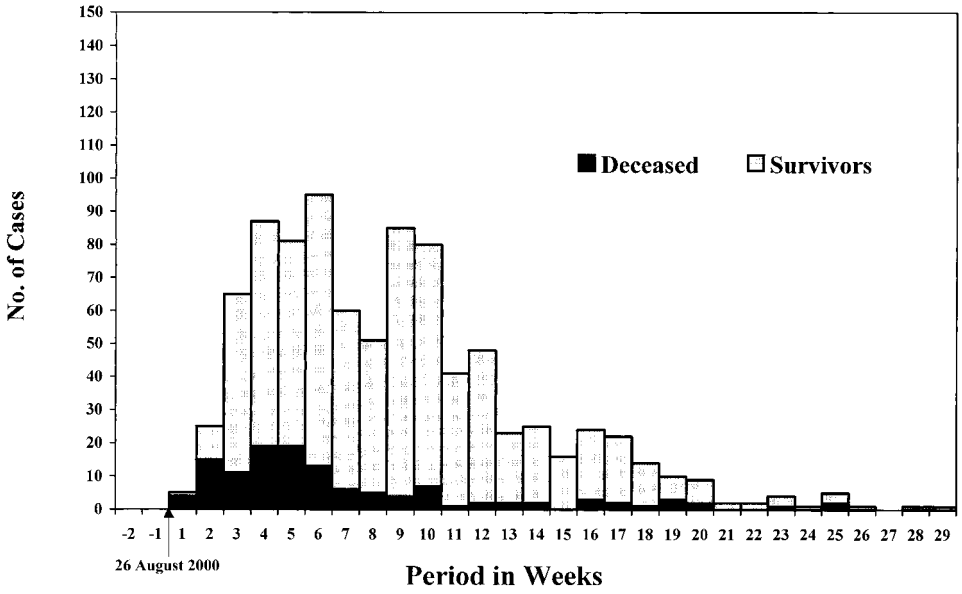

Figure 2. Distribution of 886 cases of Rift Valley fever and deaths, by weekly period, from 26 August 2000 through 22 September 2001. The last 3 cases in the epidemic were reported after week 29, on weeks 32, 43, and 57.

Jizan, 13 received diagnoses outside of this region (5 cases were diagnosed in Riyadh, 3 were diagnosed in Jeddah, 2 were diagnosed in the Eastern Region, 2 were diagnosed in Al-Ahsa, and 1 was diagnosed in Makkah).

Table 2 presents the demographic characteristics of 683 patients with confirmed RVF infection. Of 886 patients with clinically suspected RVF, 3 patients were <10 years of age, but none of these patients had laboratory-confirmed RVF. The disease predominantly affected male patients, with a ratio of male to female patients of 4:1.

Table 3 shows the frequency of patients reporting exposure to mosquitoes and/or animals (mainly sheep and goats), and the frequency of patients reporting animal abortion and animal death. Table 4 presents the clinical features of patients with laboratory-confirmed RVF infection.

Table 5 shows the laboratory characteristics at hospital admission of patients hospitalized with laboratory-confirmed RVF. Of 457 patients with confirmed cases for whom hemoglobin concentrations were available, 69 patients (15.1%) had severe anemia (hemoglobin concentration, <80 g/L) characterized by an abrupt decrease in the hemoglobin concentration and an elevated LDH enzyme level suggesting acute hemolysis. Approximately 45.5% of the patients with severe anemia had evidence of DIC, which was defined as thrombocytopenia (platelet count, $<100 \times 10^9$ platelets/L) associated with prolongation of partial thromboplastin time of >1.2 the control value. Of 450 patients with confirmed cases for whom platelet counts were available, 173 (38.4%) had thrombocytopenia, of whom 37.9% had evidence of DIC. Of 311 patients for whom CK enzyme levels were available, 85 (27.3%) had elevated CK enzyme levels. Tests for myoglobinuria and fractionation of CK, to determine the origin of CK, were not available in the hospitals in the epidemic regions. Approximately 27.3% of patients with high CK enzyme levels had CNS manifestations suggestive

Table 1. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for the first 5 case definitions of Rift Valley fever.

Case definition	Cases fulfilling definition, %	Cases fulfilling the other case definitions, %, by case definition					Sensitivity, %	Specificity, %	PPV, %	NPV, %
		1	2	3	4	5				
1	73.7	NA	17.4	7.2	59.8	1.0	74.7	28.0	82.5	19.5
2	17.7	90.0	NA	31.3	74.5	0.0	17.1	87.3	85.3	19.6
3	7.5	87.8	65.2	NA	87.8	2.4	7.1	94.9	85.4	19.6
4	47.2	93.3	22.0	11.3	NA	1.6	47.0	58.0	83.6	19.4
5	2.2	42.9	0.0	9.1	42.9	NA	2.1	96.4	71.4	18.4

NOTE. For specific case definitions, see Methods. Only 2 cases (0.2%) fulfilled the sixth case definition, and both were laboratory confirmed. Therefore, it was not possible to calculate the sensitivity, specificity, PPV, and NPV for this case definition. NA, not applicable.

Table 2. Demographic characteristics of 683 patients with laboratory-confirmed Rift Valley fever in Saudi Arabia, 26 August 2000 through 22 September 2001.

Characteristic	Value
Age, years[a]	
Mean ± SD	46.9 ± 19.4
Median	50
Age group[a]	
<10 years	0 (0.0)
10–19 years	70 (10.3)
20–29 years	94 (13.8)
30–39 years	72 (10.6)
40–49 years	100 (14.7)
50–59 years	104 (15.2)
60–69 years	134 (19.6)
70–79 years	65 (9.5)
80–89 years	36 (5.3)
⩾90 years	7 (1.0)
Sex	
Male	565 (82.7)
Female	118 (17.3)
Nationality	
Saudi Arabia	594 (87.0)
Yemen	77 (11.3)
Other	12 (1.7)

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

[a] Information was available for 682 patients.

of encephalitis. Shock-induced muscle ischemia was unlikely to be the explanation for the increase in CK enzyme levels, because there was no difference in the frequency of shock between patients with high CK enzyme levels and those with normal CK enzyme levels (9.1% vs. 11.1%; $P = 1.0$). None of the patients with elevated CK enzyme levels had received an intramuscular injection before measurement of the CK enzyme level.

The mean values and ranges of laboratory test values are shown in table 6. Subgroup analysis revealed that the mean laboratory values (±SD) were as follows: for patients with an AST level of >200 U/L, the mean value was 2109 ± 3855 U/L; for those with an ALT level of >200 U/L, the mean value was 1542 ± 2372 U/L; for those with a hemoglobin concentration of <80 g/L, the mean value was 55.7 ± 16.7 g/L; for those with a leukocyte count of $<3.0 \times 10^9$ leukocytes/L, the mean value was $2.0 \pm 0.6 \times 10^9$ leukocytes/L; for those with a platelet count of $<100 \times 10^9$ platelets/L, the mean value was $54.5 \pm 28.1 \times 10^9$ platelets/L; for those with a serum creatinine level of >150 μmol/L, the mean value was 514 ± 317 μmol/L; for those with a LDH enzyme level of >500 U/L, the mean value was 2151 ± 2263 U/L; and for those with a CK enzyme level of >400 U/L, the mean value was 1371 ± 1606 U/L.

Of 683 patients with confirmed RVF infection, 95 (13.9%) died. No confirmed cases of RVF were identified in children <10 years of age. For 682 patients with confirmed cases whose ages were known, the mortality rates, by age group, were as follows: 10–19 years, 15.7% (11 of 70 patients); 20–29 years, 18.1% (17 of 94 patients); 30–39 years, 13.9% (10 of 72 patients); 40–49 years, 9% (9 of 100 patients); 50–59 years, 8.7% (9 of 104 patients); 60–69 years, 10.4% (14 of 134 patients); 70–79 years, 18.5% (12 of 65 patients); 80–89 years, 22.2% (8 of 36 patients); and ⩾90 years, 57.1% (4 of 7 patients). The difference in mortality between the different age groups was statistically significant ($P < .01$). There was no significant difference in mortality between male and female patients (73 [12.9%] of 565 men vs. 22 [18.6%] of 118 women; $P = .1$). The mortality rate for Yemeni citizens (26.0% [20 of 77 patients]) was significantly higher than that for Saudi citizens (12.5% [74 of 594 patients]) or other citizens (8.3% [1 of 12 patients]) ($P < .01$). Sixteen (80%) of 20 Yemeni patients who died were 10–39 years of age.

Table 7 shows the important clinical complications and laboratory derangements that were found to be associated with increased mortality on bivariate analysis. Multivariate logistic regression analysis of 234 cases with complete data showed that only clinical bleeding (OR, 60.2; 95% CI, 3.4–1051.1; $P = .005$), CNS manifestations (OR, 5.5; 95% CI, 1.3–23.5; $P = .02$), and jaundice (OR, 8.3; 95% CI, 1.9–36.2; $P = .005$) were independently associated with high mortality, whereas leukopenia (leukocyte count, $<3 \times 10^9$ leukocytes/L) was found to be an independent predictor of a favorable outcome, compared with normal or high leukocyte counts (mortality rate, 2.3% vs. 27.9%; OR, 0.09; 95% CI, 0.01–0.63; $P = .01$).

Table 3. Risk factors for Rift Valley fever and frequency of animal abortions and deaths reported by 683 patients with laboratory-confirmed disease in Saudi Arabia, 26 August 2000 through 22 September 2001.

Variable	No. (%) of patients
Risk factor[a]	
Exposure to mosquito bites and animals[b]	308 (75.9)
Exposure to mosquito bites only	92 (22.7)
Exposure to animals only[b]	2 (0.5)
None	4 (1.0)
Reported abortion storms in animals[c]	224 (61.7)
Reported extraordinary animal deaths[d]	190 (51.4)

[a] Information was available for 406 patients.
[b] Mainly sheep and goats.
[c] Information was available 363 patients.
[d] Information was available for 370 patients.

Table 4. Clinical features of 683 patients with laboratory-confirmed Rift Valley fever in Saudi Arabia, 26 August 2000 through 22 September 2001.

Variable	*n/N* (%)[a]
Fever	499/539 (92.6)
Nausea	315/530 (59.4)
Vomiting	280/532 (52.6)
Abdominal pain	202/532 (38.0)
Diarrhea	118/530 (22.1)
Jaundice	96/530 (18.1)
CNS manifestations	81/475 (17.1)
Confusion	39/475 (8.2)
Lethargy	36/475 (7.6)
Disorientation	27/475 (5.7)
Vertigo	14/475 (2.9)
Coma	13/475 (2.7)
Tremor	7/475 (1.5)
Amnesia	6/475 (1.3)
Meningism	4/475 (0.8)
Convulsions	3/475 (0.6)
Ataxia	3/475 (0.6)
Chorea	3/475 (0.6)
Hallucinations	2/475 (0.4)
Hemiparesis	1/475 (0.2)
Locked-in syndrome	1/475 (0.2)
Hemorrhagic manifestations	35/494 (7.1)
Hematemesis	18/494 (3.6)
Petechiae	14/494 (2.8)
Bleeding from puncture sites	12/494 (2.4)
Melena	9/494 (1.8)
Purpura	8/494 (1.6)
Gingival bleeding	7/494 (1.4)
Epistaxis	6/494 (1.2)
Conjunctival hemorrhage	6/494 (1.2)
Hematochesia	3/494 (0.6)
Uterine bleeding	2/494 (0.4)
Vision loss or scotomas	10/683 (1.5)
Vision loss	8/683 (1.2)
Scotomas	2/683 (0.3)

[a] No. of patients with feature/no. of patients for whom information was available (%).

DISCUSSION

This epidemic of RVF in southwestern Saudi Arabia coincided with simultaneous occurrences of this disease in Yemen. These epidemics represent the first documented evidence of RVF virus transmission outside of Africa. It is speculated that the RVF virus was introduced into the Arabian peninsula in 1997–1998 during the RVF epidemic in east Africa via introduction of infected imported livestock or via windborne infected mosquitoes, and that climatic conditions have promoted sufficient vector populations to support transmission in Saudi Arabia and Yemen. Two lines of evidence support this speculation. First, the current epidemic began spontaneously in geographically diverse areas in Saudi Arabia and Yemen, suggesting that dissemination of the virus probably occurred before the epidemic period. Second, the genetic sequence of the virus isolated in Saudi Arabia and Yemen is closely related to that of the virus isolated in the 1997–1998 outbreak in east Africa [11]. This virgin-soil epidemic in the Arabian Peninsula emphasizes the threat of the introduction of the virus into other parts of the world.

Acute hepatitis of various degrees of severity was the key manifestation of RVF in this epidemic. Renal failure was a common, previously undescribed complication of RVF occurring in one-quarter of patients. Other complications observed in this epidemic included thrombocytopenia, CNS involvement, severe anemia, hemorrhagic manifestations, and vision loss or scotomas. Nausea, vomiting, abdominal pain, and diarrhea were the most common presenting complaints. This gastroenteritis-like clinical presentation contrasts with the in-

Table 5. Laboratory characteristics at hospital admission of 683 patients hospitalized with laboratory-confirmed Rift Valley fever in Saudi Arabia, 26 August 2000 through 22 September 2001.

Characteristic	*n/N* (%)[a]
Biochemical and hematological laboratory features	
AST level	
>40 U/L	514/528 (97.3)
>200 U/L	373/528 (70.6)
ALT level	
>40 U/L	507/518 (97.9)
>200 U/L	375/518 (72.4)
Hemoglobin concentration of <80 g/L	69/457 (15.1)
Platelet count of $<100 \times 10^9$ platelets/L	173/450 (38.4)
Leukopenia[b]	190/479 (39.7)
Creatinine level of >150 μmol/L	110/397 (27.8)
High LDH level[c]	231/384 (60.2)
High CK level[d]	85/311 (27.3)
Confirmatory laboratory test result	
Positive for antigen or IgM	683/834 (81.9)
Antigen only	244/834 (35.7)
IgM only	349/834 (51.1)
Antigen and IgM	90/834 (13.2)
Negative	151/834 (18.1)

NOTE. ALT, alanine transferase; AST, aspartate transferase; CK, creatine kinase; LDH, lactate dehydrogenase.

[a] No. of patients with characteristic/no. of patients for whom information was available (%).

[b] Leukocyte count, $<3.0 \times 10^9$ leukocytes/L.

[c] LDH level, >500 U/L.

[d] CK level, >400 U/L.

Table 6. Laboratory values at hospital admission for 683 patients hospitalized with laboratory-confirmed Rift Valley fever.

Laboratory value (no. of patients with available results)	Mean ± SD	Median (range)	Normal value
AST, U/L (528)	1526 ± 3363	369 (6–40,560)	0–35
ALT, U/L (518)	1151 ± 2115	364 (4–21,147)	0–35
GGT, U/L (70)	223 ± 254	166 (14–1410)	10–50
Bilirubin, μmol/L (79)	91.8 ± 149.6	45.9 (5.1–929.9)	5.1–17
Hemoglobin, g/L (457)	114 ± 31	120 (14–194)	120–180
Leukocyte count, leukocytes, $\times 10^9$/L (479)	5.7 ± 6.4	3.6 (0.6–52.6)	3.8–10.8
Platelet count, platelets $\times 10^9$/L (450)	128 ± 83	121 (1.0–666)	130–400
Creatinine, μmol/L (396)	208 ± 254	106 (27–1445)	<120
LDH, U/L (384)	1418 ± 1973	660 (58–9577)	100–250
CK, U/L (311)	483 ± 1003	193 (21–12,969)	10–200

NOTE. ALT, alanine transferase; AST, aspartate transferase; CK, creatine kinase; GGT, γ-glutamyl transpeptidase; LDH, lactate dehydrogenase.

fluenza-like illness described in previous RVF epidemics in Africa [1, 4, 14–16]. The disease was notably rare in children <10 years of age, an observation that has been noted elsewhere [17]. The infection in this epidemic appears to have been primarily transmitted by mosquito bites and, to a lesser extent, by direct contact with infected animals, primarily sheep and goats.

Elevated liver enzyme levels, with a ratio of AST level to ALT level of ~1.5–2:1 was the most common laboratory abnormality. Elevated LDH and CK enzyme levels were also commonly observed. Because the facility to fractionate CK to determine its source was not available at the hospitals where patients were admitted, it could only be speculated that, in approximately one-quarter of patients with high CK enzyme levels, the source of this enzyme was the brain, because associated CNS manifestations suggested encephalitis. In the remaining three-quarters of patients with high CK enzyme levels, the source of the enzyme was unknown.

Acute hemolysis was the most likely explanation for the severe anemia observed in 15.1% of patients. Approximately one-half of patients with severe anemia had evidence of DIC, which suggests that microangiopathic destruction was the cause of the hemolysis. In the other one-half, the most likely explanation of the hemolysis was immune-mediated destruction of RBCs. Similarly, only one-third of the patients with thrombocytopenia had evidence of DIC, which suggests consumption as a cause; in the remaining two-thirds, immune-mediated destruction was a possible explanation.

In this epidemic, both antigen and IgM detection assays were

Table 7. Mortality among patients with and without selected complications and laboratory derangements associated with laboratory–confirmed Rift Valley fever.

Complication or laboratory value (no. of patients with available data)	No. (%) of patients with complication		No. (%) of patients without complication		OR (95% CI)	*P*
	Total	Died	Total	Died		
Bleeding manifestations (494)	35	23 (65.7)	459	39 (8.5)	20.6 (8.9–48.4)	<.0001
CNS manifestations (475)	81	43 (53.1)	394	29 (7.4)	14.2 (7.7–26.7)	<.0001
Jaundice (530)	96	44 (45.8)	434	28 (6.5)	12.5 (6.7–25)	<.0001
Creatinine level of >200 μmol/L (396)	88	49 (55.7)	308	16 (5.2)	25 (11.1–50)	<.0001
AST level of >500 U/L (528)	216	58 (26.9)	312	16 (5.1)	6.7 (3.6–12.5)	<.0001
ALT level of >500 U/L (518)	222	63 (28.4)	296	11 (3.7)	10.0 (5.0–20.0)	<.0001
Platelet count of $<100 \times 10^9$ platelets/L (450)	173	54 (31.2)	277	10 (3.6)	12.2 (5.7–26.5)	<.0001
Hemoglobin concentration of <80 g/L (457)	69	24 (34.8)	388	42 (10.8)	4.4 (2.3–8.3)	<.0001
LDH level of >500 U/L (384)	231	57 (24.7)	153	4 (2.6)	12.2 (4.1–41.0)	<.0001
CK level of >400 U/L (311)	85	25 (29.4)	226	30 (13.3)	2.7 (1.4–5.2)	0.001
Leukocyte count of $<3 \times 10^9$ leukocytes/L (479)	190	4 (2.1)	289	63 (21.8)	0.08 (0.02–0.23)	<.0001

NOTE. ALT, alanine transferase; AST, aspartate transferase; CK, creatine kinase; LDH, lactate dehydrogenase.

used to confirm the diagnosis of RVF. Approximately one-third of confirmed cases were only antigen positive, and one-half were only IgM positive; one-eighth were both antigen positive and IgM positive. Therefore, it is essential to use a combination of tests that can detect the virus during the acute stage of the disease (antigen, RT-PCR, and/or viral culture) and during the convalescent period (serological tests for RVF IgM).

The reported case-fatality rate for RVF is generally 1%–3%, but it can be as high as 50% among patients with hemorrhagic manifestations or other complications [18]. The relatively high case-fatality rate in our patients (13.9%) likely reflects the fact that it represented mortality for patients with more-severe infections. True mortality rates can only be derived from population-based seroprevalence studies to determine the true incidence of RVF. The progressively increasing rate of mortality associated with aging in patients aged $\geqslant$60 years may be due to the declining immunity associated with aging. Patients aged 10–39 years also had increased mortality, compared with other age groups. This was perhaps related to more-intense exposure to infected mosquitoes or animals, because patients in this age group were more likely to be involved in farming, fieldwork, and care of animals. The high mortality rate among patients from Yemen is likely associated with late presentation. Most of the Yemeni patients were not legal residents of Saudi Arabia, and, as a result, many of them sought medical advice very late in the course of their illness. In addition, many of them had no shelter and thus had to sleep outdoors, exposing themselves to intense mosquito bites and, thus, higher infective doses of the virus. The observation that most Yemeni patients who died were 10–39 years of age was another factor that contributed to the increased mortality in this age group. Interestingly, patients with leukopenia had a significantly lower mortality rate, compared with those who had leukocyte counts of $\geqslant 3 \times 10^9$ leukocytes/L. To our knowledge, this observation has not been reported with RVF or any other infection.

Many aspects of RVF disease remain to be elucidated. Whether the RVF virus will establish endemicity in the Arabian peninsula, causing low-grade transmission, or recur episodically with transmission-free intervals between the episodes remains to be determined. The pathogenesis of the liver, renal, CNS, retinal, and hematological complications is still unknown. Elucidation of these aspects of the disease may have an important implication on the development of therapeutic interventions to treat the disease or prevent its complications.

In conclusion, this epidemic of RVF in southwestern Saudi Arabia and the neighboring northwestern regions of Yemen represented the first occurrence of this disease outside of Africa and emphasized the potential for the spread of this disease to other parts of the world. Unlike previously described epidemics, detailed clinical and laboratory description of RVF was possible because of the presence of well-structured and developed health care system and facilities in Saudi Arabia.

AUTHOR CONTRIBUTIONS

T.A.M. designed the study, analyzed the data, and wrote the manuscript; T.A.M. was honored and awarded by the King of Saudi Arabia for making the diagnosis of RVF, on the basis of clinical and epidemiological data, within 48 h after notification. Y.A.-M., M.A.-J., and A.M. provided administrative assistance for data collection and critically reviewed the manuscript. A.A.-R. and A.T. participated in data collection and analysis. M.A.-S. and A.A. participated in data collection in the field. A.S.K. oversaw data collection and analysis and critically reviewed the manuscript. T.G.K. oversaw confirmatory laboratory testing for RVF performed at the CDC and the Central Laboratory in Riyadh and critically reviewed the manuscript. O.A.S. supervised all administrative and technical aspects of the study and critically reviewed the manuscript.

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