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Risk Factors for Severe Rift Valley Fever Infection in Kenya, 2007

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Abstract. A large Rift Valley fever (RVF) outbreak occurred in Kenya from December 2006 to March 2007. We conducted a study to define risk factors associated with infection and severe disease. A total of 861 individuals from 424 households were enrolled. Two hundred and two participants (23%) had serologic evidence of acute RVF infection. Of these, 52 (26%) had severe RVF disease characterized by hemorrhagic manifestations or death. Independent risk factors for acute RVF infection were consuming or handling products from sick animals (odds ratio [OR] = 2.53, 95% confidence interval [CI] = 1.78–3.61, population attributable risk percentage [PAR%] = 19%) and being a herdsperson (OR 1.77, 95% CI = 1.20–2.63, PAR% = 11%). Touching an aborted animal fetus was associated with severe RVF disease (OR = 3.83, 95% CI = 1.68–9.07, PAR% = 14%). Consuming or handling products from sick animals was associated with death (OR = 3.67, 95% CI = 1.07–12.64, PAR% = 47%). Exposures related to animal contact were associated with acute RVF infection, whereas exposures to mosquitoes were not independent risk factors.

INTRODUCTION

Rift Valley fever (RVF) is an acute, febrile, viral disease caused by a phlebovirus in the family *Bunyaviridae*.[1] It affects small domestic ruminants such as cattle, sheep, goats, camels,[2] and humans.[3] Infection with Rift Valley fever virus (RVFV) may cause abortion in pregnant animals, and high mortality in young animals. In humans, RVFV causes an influenza-like illness and occasionally leads to more serious complications.[4,5] At most, 7–8% of patients with RVF develop severe disease including generalized hemorrhagic syndromes, encephalitis, and death.[5,6] 1–20% of patients develop ocular complications, including retinitis, leading to scotomata, and other visual disturbances.[7–9]

Outbreaks of RVF are associated with unusually heavy rainfall, leading to flooding and a synchronous generation of large numbers of infected mosquitoes.[10] Humans acquire RVF through bites from infected mosquitoes and through exposure to blood, body fluids, or tissues of infected animals.[11,12] Direct exposure to infected animals can occur during handling and slaughter or through veterinary and obstetric procedures.[13–15] Laboratory technicians are at risk of acquiring the disease by inhalation of infectious aerosols generated from specimens.[6,16,17] The RVFV was first described in Kenya in 1931 during an epizootic of fatal hepatic necrosis and abortion in sheep.[2] Major epidemics have been noted in Egypt (1977), Kenya (1997–1998), Saudi Arabia (2000–2001), and Yemen (2000–2001).[7,18–20] Until 1977, outbreaks and sporadic infections were described only from Sub-Saharan Africa.[21] The outbreaks in Yemen and Saudi Arabia were the first time that the disease had been recorded outside Africa.[22,23] A study conducted during the 1997–1998 RVF outbreak in Kenya identified contact with animal (particularly sheep) body fluids and sheltering livestock inside the home as specific risk factors for infection with RVFV.[19]

In mid-December 2006, the Ministry of Health in Kenya received reports of fatal cases of a febrile hemorrhagic illness of unknown etiology among people living in Garissa district in its northeastern province, after unusually heavy rains and flooding in the area. The RVFV was isolated and immunoglobulin M (IgM) antibodies to RVFV were detected in clinical specimens from affected patients and animals. During the next 4 months, approximately 700 suspected cases of RVF with 272 confirmed and 120 probable cases were reported in 18 districts within six of eight provinces in Kenya.[24] During this period, RVF outbreaks were reported in Somalia[25] and Tanzania.[26] We carried out an investigation in Kenya to determine risk factors associated with RVF infection, severe illness, and death.

MATERIALS AND METHODS

Study area and population. We conducted a population-based survey and an associated risk factor study in Kilifi district (2°43′S, 40°12′E) of Coast province, Baringo district (0°38′N, 36°0′E) of Rift Valley province, and Garissa district (0°27′S, 39°39′E) of northeastern province (Figure 1) between January and March 2007. These were the three districts most heavily affected during the outbreak. The estimated populations in these districts, based on census data from the Central Bureau of Statistics of Kenya 2007, are Kilifi (678,702), Garissa (440,119), and Baringo (318,712).

Case definition and detection. A case of acute RVF was defined as any person with serologic evidence of recent RVF infection (i.e., IgM antibodies to RVFV or with RVFV nucleic acid detected by reverse transcription-polymerase chain reaction [RT-PCR]), including serosurvey participants. A case of severe RVF disease was defined as any person who met the acute RVF case definition who reported hemorrhagic symptoms (i.e., epistaxis, gingival bleeding, melena, hematemesis, or hemoptysis), was found to have hemorrhagic manifestations (i.e., skin purpura). This included persons identified either during the serosurvey or during outbreak surveillance,[24] who met the probable or confirmed RVF case definition used for this outbreak.[27] A probable case was defined as any patient with unexplained fever and bleeding manifestations. Probable cases had no specimen available either because 1) they died before a specimen could be obtained, 2) they did not have

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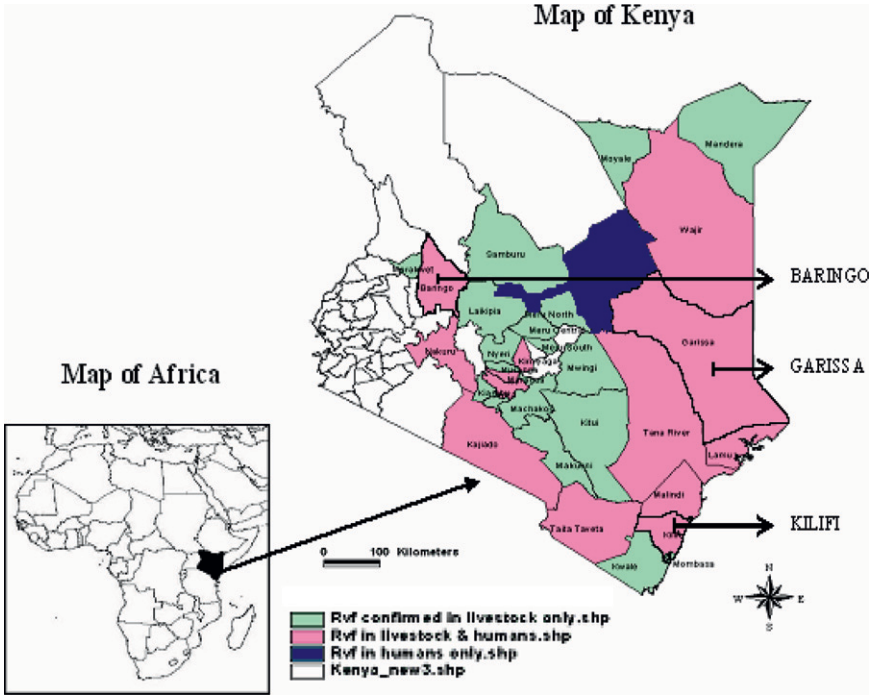

FIGURE 1. Map of Kenya showing areas affected by Rift Valley fever infection in humans and animals, 2007. The names and locations of the three study sites for the risk factor study are identified by arrows.

access to health care during their acute illness, or 3) they were at hospitals where staff was not able to collect specimens and information.[24] All consenting participants meeting the above case definition were enrolled in the study. For those who died before the survey or were too critically ill to be interviewed, a consenting close relative, who lived with the case-patient during the period before and during onset of illness or death, served as proxy and responded to a standardized questionnaire.

Enrollment of survey participants. Residents were systematically selected from the three districts most affected by the outbreak (Garissa, Kilifi, and Baringo). Line lists of reported probable and confirmed cases were obtained from the respective Ministry of Health district surveillance teams and used to identify geographical units (usually villages) where clustering of cases occurred within these three districts. Active case detection was carried out in villages with known probable or confirmed cases. In each village with at least two cases, village elders (Garissa and Baringo) or Global Positioning System (GPS) mapping (in Kilifi) were used to enumerate all households. A household was defined as any group of people who consumed food prepared in the same pot. Households were selected from these lists using a random number table.

Methods for selection of participants in the survey varied slightly in each of the three districts. According to the line lists, 161 villages were affected within these three districts (Garissa 62, Baringo 52, and Kilifi 47); 129 villages had > 1 case. Of these affected villages with > 1 case, the 55 (Garissa 19, Baringo 11, Kilifi 25) villages with the highest numbers of probable or confirmed RVF cases or deaths were enrolled in the study. In Garissa and Baringo districts, the village chief or elder compiled an enumerated list of all the households in their village. A random number generator was used to select a simple random sample of 20 households per village. The selected households were visited until 25 participants were enrolled. In Kilifi, a GPS map of all households (generated by Wellcome Trust-KEMRI, Kilifi) within one square mile of each case was used to randomly select a household as a starting point; every other household along the road from that household was then visited until 25 participants were enrolled.

To enable assessment of risk factors for severe disease and for death, we enrolled the randomly identified survey participants from the selected villages in addition to the probable and confirmed cases identified through outbreak surveillance and active case detection from the same villages.

Field procedures. In selected households, a standardized questionnaire was administered to all consenting adults greater than 14 years of age and one randomly selected person 5–14 years of age. We systematically selected both children and adults to ascertain whether there were age-specific risk factors. A separate questionnaire about possible household level exposures was administered to the household head. Local health workers fluent in English, Kiswahili, Kalenjin, and Somali were trained to administer the questionnaires in the appropriate local language spoken by the respondent in the three districts. The questionnaires collected demographics (age, sex, occupation, and travel), clinical information, and information on exposures likely associated with risk for contracting RVF. Exposures of interest included contact with animals, where animals were sheltered, proximity to water sources, and mosquito risk reduction behaviors. Proxy interviews were used to obtain information on persons who had died before the study period. Interviews were conducted by Ministry of Health staff and residents of the Kenya Field Epidemiology and Laboratory Training Program (FELTP).[28]

Laboratory procedures. At least 5 mL of blood was collected from consenting participants and kept in cool boxes before and during transporting the specimens to the hospital laboratory (in Garissa or Kilifi and Baringo). At the

laboratory, sera were separated after centrifugation at 2000 × *g* for 10 min and then decanted into 1.8 mL sterile cryo tubes. Sera were kept in a −20°C freezer until transported to the KEMRI/CDC laboratory in Nairobi in cool boxes. Serum specimens were tested for the presence of RVFV-specific IgM and IgG antibodies using a sandwich enzyme-linked immunosorbent assay (ELISA, as described previously).[29] Briefly, goat antiserum against human μ-chain of IgM (ICN Pharmaceuticals, Costa Mesa, CA) was diluted 1:500 and used to coat plates overnight. After washing and blocking, test and control serum diluted 1:400 in diluent buffer were added to wells in quadruplicates and the plates incubated at 37°C for 1 hour. After washing, RVFV antigen diluted 1:400 was added to two wells and mock antigens to the other two wells of each sample on the plate. After incubation at 37°C for 1 hour and washing, mouse anti-RVFV antibody diluted 1:2,000 was added to each well followed by horseradish peroxidase conjugated goat anti-mouse IgG diluted 1:10,000 (H + L chain; Zymed Laboratories, San Francisco, CA). Immunoreactivity was detected using 2, 2′-azino di-ethyl-benzothiazoline-sulfonic acid as peroxidase substrate (Kirkegaard and Perry Laboratories, Gaithersburg, MD) at room temperature and the optical density (OD) read at 405 nm. The mean OD readings were converted into a percentage of high-positive control serum (PP) value using the equation: (mean net OD of test sample/mean net OD of high-positive control) × 100.[29] One-step real-time RT-PCR using the portable Lightcycler 2.0 system (Roche Molecular, Mannheim, Germany), as described by Drosten[30] was used to show RFV-specific nucleic acid. Briefly, the one-step RT-PCR used the AmpliTaq gold *Taq*-polymerase (Applied Biosystems, Foster City, CA) in 5′-nuclease assays. The primers used were 5′-AAAGGAACAATGGACTCTGGTCA-3′ forward and 5′-CACTTCTTACTACCATGTCCTCCAAT-3′ for reverse that amplified a 94 nucleotide fragment from the G2 gene of the virus. The 5′ nuclease probe was 5′-AAAGCTTTGATATCTCTCAGTGCCCCAA-3′ labeled with 6-carboxyfluorescein at the 5′ end and with 6-carboxy-N,N,N,N-tetramethylrhodamine at the 3′ end. The cycling profile included a reverse transcription step performed at 50°C for 30 minutes followed by pre-incubation at 95°C for 15 minutes. The 45 cycles were then run at 95°C for 5 seconds, and annealing and extension at 57°C for 35 seconds. Fluorescence was read at the combined annealing-extension step at 57°C.[30]

Sample size calculation. The study was powered to assess risk factors associated with severe RVF among infected persons. We sought a sample size to provide 80% power (with Type I error = 5%) to detect a risk factor with an odds ratio (OR) of 3.5. Thus, we aimed to enroll 72 non-severe infections to be detected by the survey to compare with 36 cases of severe disease (among cases identified during disease surveillance from villages where the survey was conducted), assuming 30% of non-severe cases and 60% of severe cases were exposed to the factor of interest. Assuming a seroprevalence for acute infection (IgM antibodies) of 15%,[19] this would require sampling of 1,080 persons.

Ethical considerations. Informed written consent was obtained from adults ≥ 18 years of age and from a parent or primary guardian of subjects less than 18 years of age, and from proxies. Because the investigation was conducted as part of an urgent public health response to the epidemic, the Kenya Ministry of Health approved the project as non-research, not requiring approval by an ethics committee.

Data analysis. Data were entered, edited, and analyzed using Epi Info version 3.4.3 (CDC, Atlanta, GA) and SAS 9.1 (SAS Institute, Cary, NC) software. For the purposes of analysis, we excluded participants who had RVFV IgG antibodies with no detectable IgM antibodies (thus, lacking evidence of acute infection). Although the timing of infection for these participants could not be precisely determined, it was likely to be remote. Remote infection would likely convey immunity rendering exposures for these individuals not meaningful for the purposes of assessing risk factors for acute infection.

Bivariable analyses using χ^2 tests were performed to calculate ORs and 95% confidence intervals (CI). Variables with a P value ≤ 0.05 during bivariable analysis were included in the multivariable model. Unconditional logistic regression with stepwise backward elimination was used to obtain the final model.

During bivariable and multivariable analyses of risk factors associated with acute RVF infection, persons with evidence of acute RVF infection were compared with persons with no evidence of recent or past RVF infection (i.e., neither IgM nor IgG antibodies to RVFV). For analyses of risk factors for severe disease, persons who died and met the probable or confirmed RVF case definition or had hemorrhagic manifestations with laboratory evidence of acute RVF infection were compared with persons meeting the acute RVF case definition who survived and did not report hemorrhagic manifestations. For the analysis of risk factors for death, persons who died were compared with all others with evidence of acute infection with RVFV (Table 1).

The population attributable risk percent (PAR%) was calculated for variables, which were statistically significant ($P \leq 0.05$) during multivariable analysis. The PAR% was calculated by subtracting the incidence rate of disease in the unexposed (1_0) from the incidence rate of disease in the total study

Table 1

Comparison groups with their corresponding sample sizes used during the three types of analyses for risk factors associated with Rift Valley fever (RVF)*

Analysis type	Comparison groups	Participants no.
1. Risk factors associated with acute RVF infection	a. Participants with evidence of acute RVF infection (met probable case definitions or had IgM antibodies or RVF nucleic acid detected by RT-PCR	202
	b. Participants with no evidence of acute RVF infection (no IgM antibodies detected and RT-PCR negative)	659
2. Risk factors associated with severe RVF disease among persons with acute RVF infection	a. Participants who died or reported hemorrhagic manifestation	52
	b. Persons who survived who had no hemorrhagic manifestations	150
3. Risk factors associated with death among persons with acute RVF infection	a. Participants who died	12
	b. Participants who survived	190

* RT-PCR = reverse transcription-polymerase chain reaction.

population (exposed and unexposed) (I_T) and then dividing the difference by the incidence rate of disease in the total study population (exposed and non exposed) (I_T) and multiplying the result by 100% (i.e., PAR% = $(I_T - 1_0/I_T) \times 100\%$).[31]

RESULTS

Detection of cases. There were 1,042 participants from whom sera and laboratory results were available. Of these, 181 participants who had RVFV IgG antibodies with no detectable IgM antibodies were excluded from the final analysis (see Methods). Thus, our analyses are based on data from 861 persons in 424 households. Among the 861 study participants, 202 (23%) (95% CI = 21–27%) had evidence of acute RVF. Seventy-two of the 202 persons (36%) were cases identified by surveillance and were used to identify villages for sampling purposes; these participants (or proxies) were interviewed during the risk factor study (see Methods). Among these 72 cases, 34 (47%) (95% CI = 35–59%) had severe RVF disease, whereas 38 (53%) (95% CI = 41–64%) had non-severe RVF illness. Seven hundred eighty-nine people, who were not already known to be cases by surveillance and active case detection, were enrolled in the survey as part of the systematic random survey. Of these 789 survey participants, 130 (17%) had evidence of acute RVF infection. Thus, a total of 202 acute RVF cases were identified for analysis. Of these 202 acute RVF cases, 52 (26%) (95% CI = 20–32%) persons had severe RVF disease characterized by hemorrhagic manifestations or death; 12 cases died. Eighteen cases with severe RVF disease were identified during the systematic random sampling.

One-third of participants in Baringo district, 30% of participants in Garissa district, and 16% of participants in Kilifi district had evidence of acute RVF infection (Table 2) increased with age. Proportion of persons with evidence of acute RVF increased with rising age-group (i.e., 19% of persons less than 14 years of age, 23% of persons 15–29 years, 25% of persons 30–49 years, and 26% of persons greater than 50 years of age). The proportion of participants with acute RVF infection was highest among herdspersons (35%), housewives (24%), and farmers (23%) (Table 2). Among participants with evidence of acute RVF infection, Baringo district had the highest prevalence of severe disease (34%; 95% CI = 22–48%), whereas Kilifi district had the lowest (17%; 95% CI = 9–28%) (Table 3). Overall, slightly more males had evidence of acute RVF than females, which was statistically significant in bivariable analysis but not during multivariate analysis (Table 4).

Factors associated with acute Rift Valley fever infection and severe disease. Twelve exposures were associated with acute RVF infection during bivariable analyses and were included in the multivariable model (Table 4). These factors included animal contact (consuming or handling products from sick animals, consuming raw milk, milking, skinning, slaughtering, sleeping with animal herds, touching blood, and caring for animals during birthing), socio-demographic factors (male gender and herdsperson occupation), proximity to water sources, and having a flooded home. Traveling outside the district and behaviors to reduce contact with mosquitoes, including having a bed net, using repellents, indoor residual spraying in the home, wearing clothes covering the arms and legs at dawn and dusk, and spraying animals with insecticides, were not associated with acute RVF infection and were not included in the model. Exposure variables found to be independently associated with acute RVF infection in the multivariable model were consuming or handling products from sick animals (Table 4). "Consuming or handling products" was asked as one question; thus, it was not possible to separate these potential risk factors.

Four factors were associated with severe disease versus nonsevere RVF disease during bivariable analyses and were included in the multivariable model. These included animal contact/herding animals (OR = 2.04; 95% CI = 1.06–3.92), caring for animals during birthing (OR = 2.80; 95% CI = 1.30–6.03) and touching an aborted animal fetus (OR = 3.83; 95% CI = 1.62–9.07), and being a herdsperson (OR = 2.22; 95% CI = 1.12–4.37). In the multivariable model, only touching an

TABLE 2

Demographic characteristics of persons with evidence of acute Rift Valley fever (RVF) infection during the Rift Valley Fever survey in 2006–2007 in Kenya*

Characteristic	Acute RVF/number of survey participants	(%)	95% CI
District			
Baringo	56/168	(33)	26–41
Garissa	76/254	(30)	24–36
Kilifi	70/439	(16)	13–20
Total	202/861	(23)	21–27
Gender			
Male	108/399	(27)	23–32
Female	92/444	(21)	17–25
Age group in years			
≤ 14	22/114	(19)	13–28
15–29	78/335	(23)	19–28
30–49	58/236	(25)	19–31
≥ 50	37/142	(26)	19–34
Occupation			
Herdsperson	53/150	(35)	28–44
Housewife	52/219	(24)	18–30
Farmer	31/134	(23)	16–31
Student	35/180	(19)	14–26
Formal employment	21/135	(16)	10–23

*CI = confidence interval.

TABLE 3

Demographic characteristics of participants with severe Rift Valley fever (RVF) disease among participants with evidence of acute Rift Valley fever infection in 2006–2007 in Kenya*

Characteristic	Number with severe disease/number with acute RVF infection	Proportion of those with acute RVF with severe disease (%)	95% CI
District			
Baringo	19/56	(34)	22–48
Garissa	21/76	(28)	18–39
Kilifi	12/70	(17)	9–28
Total	52/202	(26)	20–32
Gender			
Male	32/108	(30)	21–39
Female	20/92	(22)	14–32
Age group in years			
≤ 14	8/22	(36)	17–32
15–29	19/78	(24)	15–35
30–49	16/58	(28)	17–41
≥ 50	9/37	(24)	12–41
Occupation			
Herdsperson	20/53	(38)	25–52
House wife	13/52	(25)	14–39
Farmer	6/31	(19)	8–38
Student	9/35	(26)	13–43
Formal Employment	4/21	(19)	5–42

*CI = confidence interval.

TABLE 4
Risk factors associated with acute Rift Valley fever (RVF) infection during bivariable and multivariable analysis*

Exposure	Bivariable comparisons			Multivariable model
	Acute RVF $N = 202$	Controls $N = 659$	OR (95% CI)	Adjusted OR (95% CI)
Consumed or handled products from sick animals	75 (37)	117 (18)	2.74 (1.93–3.88)	2.53 (1.78–3.61); $P < 0.0001$
Herdsperson	53 (26)	97 (15)	2.06 (1.41–3.01)	1.77 (1.20–2.63); $P = 0.0042$
Slaughtered animals	50 (25)	89 (14)	2.11 (1.43–3.11)	NS
Skinned animals	51 (25)	88 (13)	2.19 (1.49–3.23)	NS
Slept outside with herd	33 (16)	60 (9)	1.95 (1.23–3.08)	NS
Milked animals	74 (37)	44 (22)	2.07 (1.47–2.91)	NS
Contact with animal blood	62 (31)	114 (17)	2.12 (1.48–3.04)	NS
Cared for animals during bathing	34 (17)	55 (8)	2.22 (1.40–3.52)	NS
Consumed raw milk	57 (28)	123 (19)	1.71 (1.19–2.46)	NS
Water source within 100 m of home†	141 (70)	403 (61)	1.47 (1.05–2.06)	NS
Male	108 (54)	291 (45)	1.42 (1.03–1.95)	NS
House flooded in previous month	95 (51)	247 (39)	1.57 (1.13–2.18)	NS

NB: +Animal refers to cow, sheep, or goat.
* OR = odds ratio; CI = confidence interval; NS = not significant.
† Water sources include dams, streams and rivers, standing water, empty water collection containers, or animal watering trough.

aborted animal fetus remained significantly associated with severe disease (OR = 3.83, 95% CI = 1.68–9.07; PAR% = 14%; $P = 0.002$). Proximity to water sources or other exposures associated with mosquito contact were not significantly associated with severe RVF disease.

The only exposure variable significantly associated with death among individuals with acute RVFV infection during bivariable analysis was consuming or handling products from sick animals (OR = 3.67, 95% CI = 1.07–12.64; PAR% = 47%; $P = 0.039$); with only one bivariable risk factor identified, multivariable analysis was not done for this outcome.

DISCUSSION

Although there have been a number of studies of risk factors for RVF infection and illness, this is the first published study to focus on risk factors associated with severe RVF disease and death. A potentially important finding was that consuming or handling products from sick animals was significantly associated with acute RVF infection, severe illness, and death. Mosquito-related exposures were difficult to quantify and were not associated with infection or severe disease in the multivariable analysis. During bivariable analysis, contact with animals (cows, sheep, or goats) was significantly associated with acute infection with RVFV and with severe RVF disease. In our study, similar to studies conducted during previous RVF outbreaks,[13–15,19] exposures associated with animal contact, including consuming or handling products from sick animals (milk, meat, or blood) and being a herdsperson were significantly associated with acute RVFV infection. In the current study, these exposures were also associated with severe disease in the bivariable model. However, contact with an aborted animal fetus was the only independent factor (in the multivariable model) associated with increased likelihood of severe RVF disease. It is possible that aborted fetuses contain high quantities of RVFV, increasing the risk either through direct secretions or aerosolizing of virus after touching the animal. Touching an aborted fetus was also shown to be a risk factor for infection during a study of sporadically occurring RVF during a non-epidemic period.[32]

Previous studies have shown that certain types of exposures to animals and their secretions (through slaughtering or sick animals) were associated with infection with RVFV, and transmission is also felt to occur by bites from infected mosquitoes.[11,12] Because most RVF infections are subclinical,[33] we set out to determine whether specific factors were associated with severe disease. It is likely that exposure to infected animals and their secretions provide greater opportunities for infection with large inoculum of RVFV. This contrasts with the presumably much smaller inoculum of virus likely associated with one or more bites from infected mosquitoes. Previous studies of other infections in animals have documented that the probability of severe disease is determined by the size of the inoculum, the route of inoculation, and the frequency of naturally occurring immunizing inoculations (infections that do not cause symptoms but do induce protective immunity).[34] In humans, there are a variety of diseases for which inoculum affects clinical presentation and outcome including hepatitis B,[35] leishmaniasis,[36] hemolytic uremic syndrome caused by verocytotoxin-producing *Escherichia coli*,[37] leptospirosis,[38] and yellow fever.[39]

Exposures to infected mosquitoes might be sufficient to stimulate immunity, but perhaps more rarely to lead to severe outcomes (like mortality). Consistent with this notion are data showing that while the highest prevalence for acute RVF infection during this outbreak was in Baringo District, the case-fatality ratio was lowest there.[24] In Baringo District, mosquito densities were higher than in Garissa and Kilifi,[40] and the proportion of cases involved with occupations linked with animal care practices were lower.[24] However, an important limitation in reaching this conclusion is that enhanced surveillance in Baringo district, based on lessons learned in Garissa district and Kilifi district (where RVF occurred a few months earlier) may have led to more complete detection of cases in Baringo. This limitation may also be responsible for the greater proportion of acute infections associated with severe disease in Baringo when compared with Kilifi District.

The association of acute RVF infection and consuming or handling products from sick animals has been documented in other studies.[6,19,41,42] Previous studies have also reported high-risk occupations for RVF infection, including abattoir workers,[43] veterinary personnel,[44] herdspersons,[45] and farmers.[46] However, earlier studies have not focused on factors associated with severe disease or death among persons infected

with RVF virus; thus, the findings of this study linking consuming or handling products from sick animals to death will provide further impetus to focus on minimizing the potential for these exposures during future RVF outbreaks. The differences between districts in terms of access to health care or hospitals, active case finding and modalities of supportive care available and provided to RVF patients, not studied during this investigation, need to be considered during future studies.

The PAR% quantifies the contribution of a risk factor to the outcome of interest. The PAR% for death among individuals who handled or consumed sick animal products was 47%. This means that 47% of the deaths among individuals acutely infected with RVFV can be attributed to consuming or handling sick animal products, and if this exposure had been eliminated, then 47% of the deaths among the study population could have been prevented. Likewise, the PAR% of consuming or handling sick animal products for acute infection was 19%, suggesting that many mild and severe infections could have been prevented in the study population if consuming or handling products from sick animals had been eliminated.

The high proportion of acute RVF infection and severe disease in males and the association of being male with death during bivariable analysis suggest exposure to a higher dose of infectious virus among males or potential susceptibility of males to RVF infection and disease. However, unlike the RVF outbreak in Northeastern Kenya in 1997–1998[19] and a recent study in northeastern Kenya of risk factors for sporadically occurring RVF during a non-epidemic period,[32] gender was not an independent risk factor for infection in our study. Association of male gender with acute RVF infection in bivariable analysis was likely related to the occupation of herding, predominantly performed by males, which involves increased animal-related exposures, such as consuming or handling sick animal products during slaughter, milking, or skinning. Because of their close proximity to animal herds, herdspersons may also be at greater risk of being bitten by mosquitoes that have bitten infected animals.

A high proportion of acute RVF infections were in housewives. This could be related to their handling sick animal products during food preparation procedures. In addition, the findings of our study suggest that younger and older persons may be more susceptible to severe disease and infection, respectively, as evidenced by the high proportion of severe disease among those less than 14 years of age and the high proportion of acute RVF infection among persons greater than 50 years of age.

In addition to the difficulties in assessing mosquito exposures by interview with much precision, limitations of this study included temporal challenges in linking exposures to infection and in case classification. It was not possible to carry out this study prospectively to establish a temporal relationship between exposure and outcome, as both exposure and outcome had occurred by the time the study was initiated. Second, because the outbreak was still ongoing at the time the investigation was conducted, some controls may have been misclassified if they had been exposed and were in a pre- or subclinical stage of the disease and had not yet sero-converted. Of the few clinical infections that have been followed closely for serologic conversion, RVFV-specific IgM antibodies appear around Day 5, peak by Day 30, are absent in 50% of patients by Day 45, and are undetectable at 4 months.[6] We could also have missed people who had been exposed to RVFV > 45 days before having their blood drawn for the survey. They would have been excluded from these analyses because they had IgG antibodies with no IgM antibodies, and it is possible that earlier in the outbreak their exposures resulting in infection were different than later in the outbreak. Finally, during the household interview some relevant family members (e.g., herdsmen or household heads) were in the field grazing livestock or at work; while an attempt was made to revisit the herders or household heads, contact was not always possible. Thus, we may have missed the opportunity to characterize other important exposures, and we may have underestimated the magnitude of the proportion of residents who were infected.

The findings of this study emphasize the potential importance of effective health education campaigns to prevent transmission through handling or consuming infected animals. Pictorial narratives could include messages such as "Do not slaughter, skin, milk, or provide birthing care to sick animals;" "Bury or burn carcasses during an outbreak;" "Boil all milk;" "Wear personal protective equipment -gloves, coveralls, boots, eyewear, and mask when handling sick animal product;" "Avoid contact with infected tissues, blood, milk, meat, and aborted fetuses, or sick animals." During this RVF outbreak several control measures were put in place, which included a ban on raw milk, home slaughter, and animal quarantine; however, slaughter bans and animal quarantine were difficult to enforce because of the critical role of livestock in the livelihoods of residents in many of the affected areas. Another strategy might be to place community health workers, armed with health messages, at points of congregation of high risk individuals, such as watering holes for livestock and market places.

Although mosquitoes may play a role in amplifying and spreading virus among animals, their role in transmission to humans, and especially in causing severe RVF illness, was difficult to evaluate in this study. It was impossible to identify persons bitten by different species of mosquitoes, to detect whether the biting vector had RVFV, and the dose of inocula per bite. Further studies are needed to evaluate the role of mosquitoes and other vectors in transmission of RVFV to humans and animals.

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