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Rift Valley fever seropositivity in humans and domestic ruminants and associated risk factors in Sengerema, Ilala, and Rufiji districts, Tanzania

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ABSTRACT

Objectives: Data on Rift Valley fever virus (RVFV) prevalence in urban settings and pastoral areas of Tanzania are scarce. We performed a cross-sectional study of RVFV seroprevalence and determinants in humans and animals from Ilala, Rufiji, and Sengerema districts of Tanzania.

Methods: Blood samples from the study participants were tested for anti-RVFV immunoglobulin G (IgG) antibodies using an enzyme-linked immunosorbent assay. Logistic regression was used to determine association between exposure risk practices and RVFV seropositivity.

Results: The study involved 664 humans, 361 cattle, 394 goats, and 242 sheep. The overall anti-RVFV IgG seroprevalence in humans and animals was 2.1% (95% confidence interval [CI] 0.01-0.04) and 9.5% (n = 95, 95% CI 0.08-0.12), respectively. Seroprevalence in humans in Rufiji, Ilala, and Sengerema was 3.0% (n = 225, 95% CI 0.01-0.06), 1.8% (n = 230, 95% CI-0.005- 0.04), and 1.4% (n = 209, 95% CI 0.01-0.04), respectively ($P > 0.05$). Seroprevalence in animals in Sengerema, Rufiji, and Ilala was 12.1% (n = 40, 95% CI 0.09-0.16), 11.1% (n = 37, 95% CI 0.08-0.15), and 5.4% (n = 18, 95% CI 0.03-0.08), respectively ($P = 0.006$). Handling of carcasses increased the odds of RVFV seropositivity 12-fold (odds ratio 11.84, 95% CI 1.97-71.16).

Conclusion: The study confirms previous occurrence of RVFV in multiple species in the study districts. Animal handling practices appear to be essential determinants of seropositivity.

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Background

Rift Valley fever (RVF) is a zoonotic disease caused by RVF virus (RVFV). Tanzania experienced 10 RVF outbreaks between 1930 and 2007 (Sindato et al., 2014). RVFV can be transmitted to humans by handling of animal tissue during slaughtering or butchering; assisting with animal births; conducting veterinary procedures; consuming unpasteurized milk; or disposing of carcasses or fetuses (Hartman, 2017; Msimang et al., 2019). Human infections from the bites of infected mosquitoes (most commonly *Aedes* and *Culex* spp.) have also been reported (Kwaśnik et al., 2021).

Most previous RVF studies in Tanzania concentrated in the Rift Valley and central regions where traditional cattle keeping is practiced (Tarimo et al., 2008; Mohamed et al., 2010; Sindato et al., 2014; Wensman et al., 2015; Ahmed et al., 2018; Matiko et al., 2018; Budodo et al., 2020). There is scant information on the prevalence of and risk factors for RVF in urban settings and new pastoral farming areas in Tanzania. The emergence of RVFV in new areas has been associated with animal trade and movement (Abdo-Salem et al., 2011; El-Harrak et al., 2011; Carroll et al., 2011). Therefore, it is essential to study RVFV burden in areas where livestock traditionally was not kept, but that now host large herds of cattle. This might provide evidence-informed interventions and surveillance strategies to improve decision making on livestock development and disease control and to reduce risk of zoonosis. This study was conducted to assess the seroprevalence and associated risk determinants of RVF in humans and domestic ruminants (cattle, sheep, and goats) in three different districts of Tanzania.

Materials and methods

Study setting and design

This cross-sectional study was carried out in Sengerema, Rufiji, and Ilala districts of Tanzania (Figure 1) in March 2020. The districts were selected to include an area with traditional livestock keeping (Sengerema), a nonlivestock-keeping district with recently introduced cattle (Rufiji), and an urban district with the largest cattle auction market and largest abattoir in the country (Ilala).

Sengerema District is located southwest of Lake Victoria at latitude 2-3°S and longitude 31-45°E. The district experiences a short rainy season in October-December and a long rainy season in February-May. The average temperature range is 21–23°C. The average annual rainfall range is 900-1,200 mm.

Rufiji District is located in the eastern part of the country, at latitude 7.47-8.03°S and longitude 38.62-39.17°E. The district lies on the Rufiji River valley, which is characterized by a flood plain that defines its ecology, settlement pattern, and economic activities. The district experiences a short rainy season in September-October and a long rainy season in February-May. Livestock keeping in Rufiji was introduced in the early 2000s, when the district began receiving pastoralists from different areas of Tanzania (Mwilawa, 2003; Komba and Mahonge, 2020).

Ilala is an urban district located at latitude 6-7°S and longitude 39-40°E. The district consists of a large lowland area and a small upland zone. The lowland area constitutes the urban part of the district, whereas the upland area is predominantly agricultural and rural in character. The district is humid, with a temperature range of 26-35°C and annual rainfall of 1,000–3,600 mm. The rains are bimodal; the short rainy season is October-December and the long rainy season is March-May.

In Sengerema and Rufiji, we consulted with the district veterinary, medical, vector surveillance, and livestock field officers and the local people to identify two wards (one urban and one rural) perceived to be at highest risk of mosquito activity. The selection criteria included the presence of ecological features/terrain suitable for mosquito breeding and survival, susceptibility to flooding, and high concentration/density of humans and domestic ruminants. In each district we selected two wards with the highest number of these ecological characteristics. In Ilala, Vingunguti Ward (in which the largest abattoir in Tanzania is located) and Pugu Ward (in which the largest livestock market of Dar es Salaam is located) were selected for the study.

Human sampling

For each district, a sample size of 230 humans aged ≥1 year old was targeted from the selected wards, with 100 from the community (households), 100 from primary healthcare facilities, and 30 from the largest animal slaughtering facility. At community level, a simple random sampling was used to select households from the sampling frame obtained from the village office. Once selected, all eligible members of households (but not more than five members per household, to avoid oversampling from a single household) were invited to take part in the study. At the animal slaughtering facilities, we adopted a simple random selection approach using the sampling frame of workers obtained from slaughter facility authorities. We sampled workers and other individuals conducting regular activities, including vendors of animal products and accompanying children. We complemented this approach with a respondent-driven approach to optimize sampling, especially for the targeted subjects not in the register of the animal slaughtering facility. For the healthcare facility–based sampling, outpatients were recruited on first-come, first-enrolled basis regardless of health condition until the targeted sample size had been achieved. After measuring the axillary body temperature using a digital clinical thermometer, a phlebotomist collected blood samples (5 ml from individuals aged ≥18 years old and 2 ml from those aged <18 years old) by venipuncture using standard sterile technique.

Animal sampling

For each district, a sample size of 330 domestic ruminants (cattle, sheep and goats) aged >6 months was targeted. The three species were equally represented in the sample. In each of the selected villages in Rufiji and Sengerema, from the list of livestock keepers obtained from the village office we randomly selected a minimum of 10 herds keeping at least one of the three domestic ruminants. All eligible animals in the selected herd were sampled, but sampling was limited to a maximum of 30 animals per herd to avoid oversampling from a single herd. In Ilala, all animals sampled were from the abattoir and livestock market. Additional sampling from the abattoir was also conducted in Sengerema; in Rufiji no animals were sampled from the abattoir. From each animal, a veterinarian collected 5 ml of blood.

Data collection

A semistructured questionnaire uploaded in the AfyaData app (Karimuribo et al., 2017) on smartphones was used to collect data from adult individuals (≥18 years old). The data collected were those related to sociodemographic characteristics and to animal and nonanimal behavioral risk practices (based on a recall period of 12 months before the interview date).

Animal data collected included species, age, sex, fever on sampling day, and history of abortion in the 12 months before sampling. For the animals sampled from slaughtering facilities, the information about history of abortion was limited to only the period in which the stock owner had kept the animal, i.e., between purchase and slaughtering time. In the absence of exact birth records,

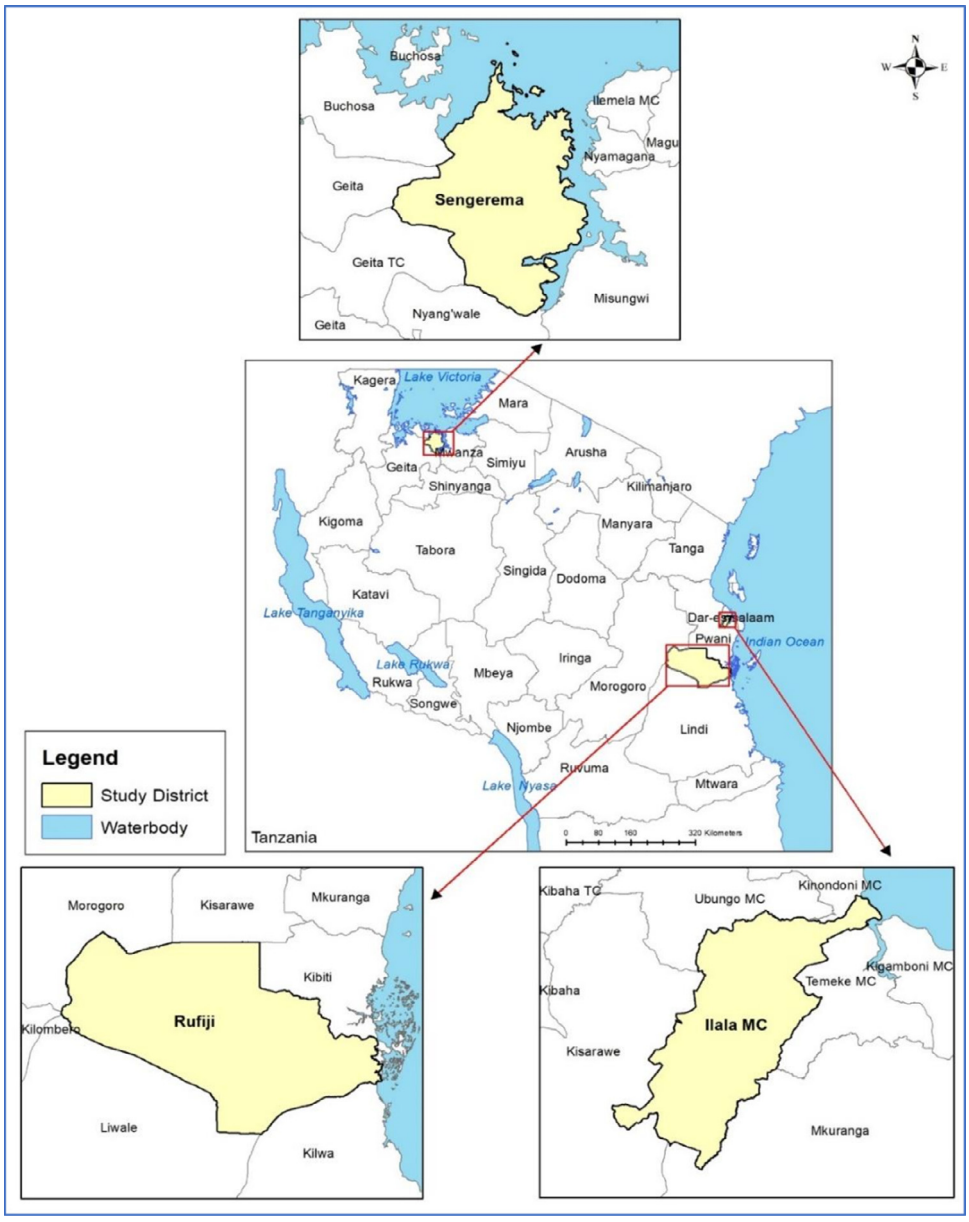

Figure 1. Geographical distribution of the study districts.

the animal's age was identified through a combination of information provided by the farmer's recall and information obtained from the dentition technique (Herzog et al., 2019). The collected data were submitted daily to a server located at Sokoine University of Agriculture.

Sample storage and laboratory examination

The collected human and animal blood samples were kept in a cool box with ice packs before separating the serum from whole coagulated blood by centrifugation into labeled 1.8-ml cryovials. The samples were stored at −196°C in liquid nitrogen containers in the field and transported to the Sokoine University of Agriculture laboratory, where they were kept in a freezer at −80°C until laboratory analysis. Serum samples were examined for the presence of immunoglobulin G (IgG) antibodies against RVFV using the commercial ID Screen® RVFV Competiton Multi-species enzyme-linked immunosorbent assay (IDvet, Innovative Diagnostics, Grabels, France), according to the manufacturer's instructions. The diagnostic sensitivity of the test in domestic ruminants (cattle, sheep, and goats) has been reported to be 85-100%, and specificity has been reported to be 100% (Kim et al., 2012; Kortekaas et al., 2013; de Bronsvoort et al., 2019; Lubisi et al., 2019; Pedarrieu et al., 2021). A preliminary evaluation found its sensitivity and specificity in human samples to be 100% (Comtet et al., 2010).

Data analysis

The epidemiological data were downloaded from the server, matched with laboratory results in Microsoft Excel based on individual identification numbers, and imported into STATA 13.1 (StataCorp, College Station, TX, USA) for analysis. The potential behavioral risk practices and demographic variables were analyzed for their association with RVFV seropositivity using a multivariable logistic regression model. A binary variable describing RVFV status was created and given a value of "1" (positive) when anti-RVFV IgG was detected and "o" (negative) when it was not detected. The Spearman rank-order correlation was run to assess the relation-

ship and direction of the association between RVFV seropositivity in animals and humans (Zar, 1972; Altman, 1990). The discriminatory ability of the final model (the discriminatory accuracy of the combination of risk factors) was assessed using receiver operating characteristic (ROC) curves and quantified using the area under the curve (AUC) (Pepe, 2003; Royston and Altman, 2010). To measure the ability of the model to correctly classify individuals with or without evidence of exposure to RVFV (i.e., with or without antibodies specific to RVFV), the AUC was constructed by plotting the true positive fraction (TPF) (i.e., sensitivity) against the false positive fraction (FPF) (i.e., 1 − specificity) for the outcome of interest. For a dichotomous risk factor (exposed or not exposed), the TPF expresses the probability of being exposed to the risk factor when the RVF occurs, and the FPF indicates the probability of being exposed to the risk factor when the RVF does not occur. The AUC values are 0-1, where a value of 0 indicates a perfectly inaccurate prediction and a value of 1 reflects a perfectly accurate prediction. A value of 0.5 suggests no discrimination, 0.7-0.8 is considered moderate prediction accuracy, >0.8-0.9 is considered excellent prediction accuracy, and >0.9 is considered outstanding prediction accuracy (Hosmer and Lemeshow, 2000).

Ethical considerations

This study received ethical approval from the Tanzania Medical Research Coordinating Committee of the National Institute for Medical Research (Ref. No. NIMR/HQ/R.8a/Vol. IX/2688). The study protocol, study objectives, and procedures of participation were explained to study participants. During the recruitment of participants, approval from parents/guardians was sought for their children to participate in the study. Additional assent was sought from children before their participation. Informed consent was sought from each adult participant. Participant identity was masked by use of coded identity numbers in place of names.

Results

Sociodemographic characteristics

A total of 664 individuals (Sengerema = 209, Ilala = 225, Rufiji = 230) were enrolled in the study. More than one-half of participants (58.3%) were recruited from healthcare facilities, one-third (33.4%) from households, and 8.0% from animal slaughtering facilities. Two-thirds of the study participants (66.1%) were female. Overall, participants were aged 2-95 years (median age 30 years, interquartile range [IQR] 22-41). The median ages of female and male participants were 30 (IQR 23-39) and 30 (IQR 20-47), respectively. A total of 96 participants (14.5%) were students or children younger than school-age. About one-half of participants (52.1%) had attained a primary level of education, and almost one-third (29.2%) had no formal education. Eleven percent and 7.5% had attained secondary and post-secondary education, respectively. Of the 568 participants who reported their primary source of income, one-half (50.2%) were involved in crop agriculture, over one-third (35.0%) in formal employment, 12.5% in petty trading, and 2.1% in livestock keeping. A total of 41 individuals were keeping at least one of the domestic ruminants (Table 1).

Characteristics of the study animals

A total of 997 animals comprising cattle (361), goats (394), and sheep (242) were sampled from Ilala (334), Rufiji (332), and Sengerema (331). Overall, two-thirds (65.0%) were sampled from herds and one-third (35.0%) from slaughtering and livestock market facilities. A majority of the animals (92.3%, n = 920) were aged ≥1 year and almost two-thirds were female (63.5%, n = 633). Of the 470 female animals aged ≥1 year, 26 (2.61%) had a history of abortion in the previous 12 months. Ninety-nine animals (9.9%) had fever on the day of sampling; sheep were the most likely to have fever (17.8%, n = 43), followed by goats (11.7%, n = 46), and then cattle (2.8%, n = 10) ($P = 0.001$).

RVFV seroprevalence in humans and animals

Overall, the seroprevalence of IgG specific to RVFV in humans was 2.1% (14/664). The district-specific seroprevalence was 3.0% in Rufiji (n = 225), 1.8% in Ilala (n = 230), and 1.4% in Sengerema (n = 209) ($P > 0.05$). The overall RVFV seroprevalence in animals was 9.5% (n = 95). The species-specific seroprevalence was 18.6% (n = 67), 6.1% (n = 16) and 3.1% (n = 12) in cattle, sheep, and goats, respectively ($P = 0.001$). Highest RVFV seroprevalence in animals was recorded in Sengerema (12.1%, n = 40) and Rufiji (11.1%, n = 37) and lowest was recorded in Ilala (5.4%, n = 18) ($P = 0.006$). The highest RVFV seroprevalence in cattle was recorded in Rufiji (24.8%, n = 26) and Sengerema (24.8%, n = 36) ($P = 0.001$). The highest RVFV seroprevalence in goats and sheep was recorded in Rufiji (5.5%, n = 8, $P > 0.05$) and Ilala (9.9%, n = 18, $P = 0.05$), respectively (Table 2).

Human behavioral risk practices and RVFV seropositivity

Results of multivariable logistic regression suggested that individuals who reported having split a carcass had almost 11-fold higher odds of seropositivity compared with those who did not report this practice (OR 10.84, 95% CI 1.97-71.16). Individuals who reported sleeping under mosquito net had 79% reduced risk of seropositivity (OR 0.21, 95% CI 03-0.88). Individuals from Rufiji (OR 8.23, 95% CI 1.18-57.02) and Ilala (OR 2.36, 95% CI 0.30-18.78) had higher odds of seropositivity compared with those from Sengerema. Individuals who reported having flowerpots at home had three-fold increased odds of seropositivity (OR 3.13, 95% CI 0.75-13.13). Open water containers at home were associated with more than two-fold increased odds of seropositivity (OR 2.5, 95% CI 0.55-11.53). The assessment of the predictive accuracy of the final multivariable model based on the AUC derived from the ROC analysis (AUC = 0.80) suggested that the model provided a moderate degree of discrimination.

Seropositivity in domestic ruminants (9.5%) was generally five-fold higher than in humans (2.1%), suggesting that there was one case in humans for every five cases in domestic ruminants. For specific animal species, seropositivity in cattle (18.6%) was almost nine-fold that in humans; in sheep, it was three times (6.1%) higher than in humans; and in goats, it was two-fold lower (3.1%) than in humans. At the district level, seropositivity in Rufiji was eight times higher in cattle (24.8%) than in humans (3.0%); seropositivity in Sengerema was seven times higher in cattle (24.8%) than in humans (1.4%); and in Ilala it was more than two-fold higher in cattle (4.5%) than in humans (1.8%). Seropositivity in Rufiji was 1.8 times higher in goats (5.5%) than in humans (3.0%); in Ilala, it was similar in goats and humans (1.8%); and in Sengerema it was lower in goats (1.5%) than in humans (3.4%). Seropositivity in Ilala was almost six times higher in sheep (9.9%) than in humans (1.8%); in Rufiji it was 1.3 times higher in sheep (3.8%) than in humans (3.0%); and in Sengerema it was 1.1 times higher in sheep (3.9%) than in humans (3.4%).

Factors associated with RVFV seropositivity in animals

The multivariable logistic regression model suggested that compared with the animals sampled from Ilala, those from Rufiji (OR 2.51, 95% CI 1.38-4.57) and Sengerema (OR 2.28, 95%CI 1.25-4.13)

Table 1
Sociodemographic characteristics of the participants by district

Variable	Response	Ilala (n=225)	Rufiji (n=230)	Sengerema (n=209)	Total (N=664)	*P*-value
Age	<28	86 (38.2%)	131 (57.0%)	57 (27.3%)	274 (41.3%)	<0.001
	28-40	93 (41.3%)	58 (25.2%)	67 (32.1%)	218 (32.8%)	
	>41	46 (20.4%)	41 (32.1%)	85 (40.7%)	172 (29.9%)	
Sex	Female	168 (74.7%)	168 (73.0%)	103 (49.3%)	439 (66.1%)	<0.001
	Male	57 (25.3%)	62 (27.0%)	106 (50.7%)	225 (33.9%)	
Education level	None	21 (9.3%)	81 (35.2%)	92 (44.0%)	194 (29.2%)	<0.001
	Primary	115 (51.1%)	126 (54.8%)	105 (50.2%)	346 (52.1%)	
	Secondary	50 (22.2%)	14 (6.1%)	10 (4.8%)	74 (11.1%)	
	Tertiary	39 (17.3%)	9 (3.9%)	2 (1.0%)	50 (7.5%)	
Main source of income[a]	Crop agriculture	4 (2.0%)	126 (75.5%)	155 (78.3%)	285 (50.2%)	<0.001
	Livestock keeping	2 (1.0%)	0 (0.0%)	10 (5.1)	12 (2.1%)	
	Petty trading	60 (29.6%)	6 (3.6%)	6 (3.0%)	72 (12.7%)	
	Employment	137 (67.5%)	35 (21.0%)	27 (13.6%)	199 (35.0%)	
Keep animals[b]	Yes	2 (1.0%)	3 (1.7%)	36 (17.7%)	41 (7.0%)	<0.001
	No	206 (99.0%)	171 (98.3%)	167 (82.3%)	544 (93.0%)	

[a] A total of 568 respondents reported their main source of income.
[b] Only adults aged ≥18 years (n = 544) are included.

Table 2
Distribution of RVFV seropositivity in humans and animals by district

Species		Ilala	Rufiji	Sengerema	Total	*P*-value
Humans	No. tested	225	230	209	664	>0.05
	No. (%) positive	4 (1.8)	7 (3.0)	1 (1.4)	14 (2.1)	
Cattle	No. tested	111	105	145	361	<0.001
	No. (%) positive	5 (4.5)	26 (24.8)	36 (24.8)	67 (18.6)	
Goats	No. tested	111	148	135	394	>0.05
	No. (%) positive	2 (1.8)	8 (5.4)	2 (1.5)	12 (3.1)	
Sheep	No. tested	111	80	51	242	>0.05
	No. (%) positive	11 (9.9)	3 (3.8)	2 (3.9)	16 (6.1)	
All ruminants	No. tested	333	333	331	997	0.006
	No. (%) positive	18 (5.4)	37 (11.1)	40 (12.1)	95 (9.53)	

RVFV, Rift Valley fever virus.

had significantly higher odds of seropositivity. Compared with cattle, goats (OR 0.13, 95% CI 0.07-0.25) and sheep (OR 0.34, 95% CI 0.19-0.61) had lower odds of seropositivity. The assessment of the predictive accuracy of the final multivariable model based on the AUC derived from the ROC analysis (AUC = 0.75) suggested that the model provided a moderate degree of discrimination.

Association of RVFV seropositivity between animals and humans

The strong positive correlations of the variables were observed between combined animal seropositivity percentages and human seropositivity percentages (Rho = 0.904) and between cattle seropositivity percentages and human seropositivity percentages (Rho = 0.867). There was a weak positive correlation between goat and human seropositivity percentages (Rho = 0.167). A negative correlation was observed between sheep and human seropositivity percentages (Rho = −0.893). There was a negative correlation between sheep and goat seropositivity percentages (Rho = −0.448) and between sheep and cattle seropositivity percentages (Rho = −0.997). A weak correlation was observed between cattle and goat seropositivity percentages (Rho = 0.440) (Figure 2).

Discussion

Our study adopted a One Health approach to concurrently investigate the seroprevalence of RVFV in humans and domestic ruminants based on detection of IgG specific to the RVFV. We also investigated human behavioral exposure risk practices and their association with RVFV seropositivity. In addition, we assessed the relation between RVFV seropositivity in animals and humans. We conducted this study during the interepidemic period in the three districts with limited information regarding RVF in animals and humans.

There are several notable findings from our study. First, this study found evidence of RVFV seropositivity in 14 of 664 humans, of whom four were born after 2007 (the year in which Tanzania reported the last RVF outbreak). Although RVF outbreak has not been reported in Tanzania since then, detection of antibodies specific to RVFV among individuals born after 2007 suggests that the virus has been circulating at cryptic levels or that mild outbreaks may have faded out unidentified, especially in the absence of regular surveillance. Within Tanzania, similar low prevalence of RVF in humans has recently been reported in Moshi, Mvomero, Kalambo, Kondoa, and Kinondoni (Rugarabamu et al., 2021; Kumalija et al., 2021) whereas higher prevalence rates have been reported in Mbeya, Mvomero, and Ukerewe (Budodo et al., 2020; Rugarabamu et al., 2021).

Second, Rufiji and Ilala had higher rates of seropositivity in humans than did Sengerema, which could be due in part to differences in ecological features, human and animal population density, and animal and nonanimal exposure practices that provide a permissive environment for mosquito breeding. It is likely that these districts are unknown hotspots or disease endemic areas that require further study to establish disease transmission dynamics.

Third, our study shows that those working in animal slaughtering facilities were at highest risk. Previous studies have reported an association between animal exposure practices and human RVFV activity (Kumalija et al., 2021; Rugarabamu et al., 2021). The animal exposure practices mainly related to slaughtering of animals observed in our study have been reported previously in Uganda (Nyakarahuka et al., 2018) and Tanzania (Kumalija et al., 2021).

Fourth, seroprevalence among domestic ruminants was higher in cattle than in sheep and goats. The facts that the animal prod-

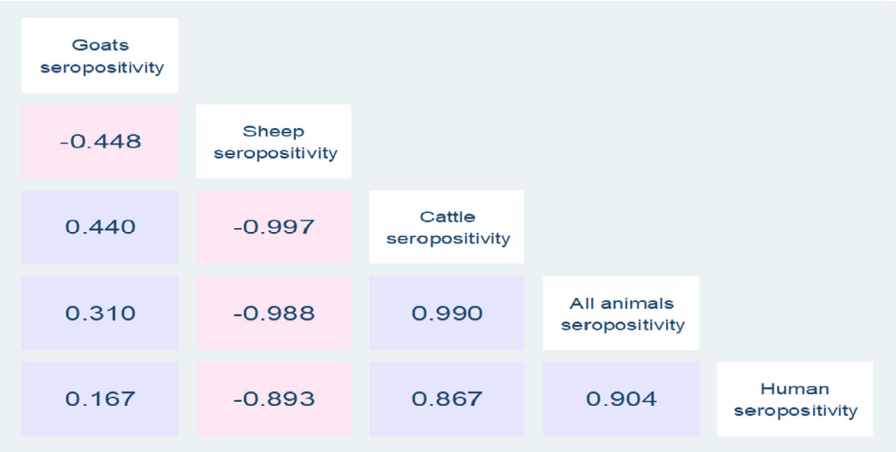

Figure 2. Heatmap matrix plot of pairwise correlations between RVFV seropositivity percentages in animals and humans. Positive correlations (Rho >0) are shown in blue and negative correlations (Rho <0) in pink.

ucts consumed frequently by humans in the study areas are those of cattle origin and that the slaughtering of cattle involves more people than the slaughtering of sheep and goats suggest that the cattle-human contact structure may increase the likelihood of infection of humans relative to the risk resulting from sheep or goats.

Fifth, our results suggest that there was one seropositive human for every five seropositive domestic ruminants, every nine seropositive cattle, and every three seropositive sheep. This observation is consistent with the hypothesis that human risk of RVFV is a function of the disease occurrence in animals, and the transmission dynamics depend on both the affected animal species and human-animal contact structure (Gerdes, 2004; Mohamed et al., 2010; Nguku et al., 2010; Ikegami and Makino, 2011; Sindato et al., 2014). A multispecies framework has been suggested as an essential habitat for the maintenance and persistence of the virus (Haydon et al., 2002), which accords with our observed significant positive correlation between seropositivity in multiple domestic ruminant species and seropositivity in humans. A strong association between seropositivity in humans and animals suggests that it is critical to carry out targeted One Health surveillance, prevention, and control measures against the disease.

Our findings should be viewed in light of several limitations. Based on the study's cross-sectional nature, it is not easy to establish the exact period of past exposure in animals or humans. Our focus was on IgG detection to estimate past exposure. Therefore, we cannot confirm the status of active infection in the subjects at sampling time. The presence of antibodies against RVFV may be a result of antibody persistence in the host following initial exposure or may represent a cumulative effect from repeated exposure. Based on the fact that human life span is generally longer than that of animals, it is plausible that humans have experienced a longer time of exposure than animals. We interpret the association of IgG seropositivity between animals and humans with caution because the exposure observed in the sampled humans may not necessarily have originated from the sampled animals. In our study, the unit of analysis was a district, and animal and human samples were not necessarily collected from the same households. Therefore, an attempt to extrapolate the results to a higher spatial resolution should be made with caution.

Conclusion

We have reported antibodies specific to RVFV in humans and domestic ruminants during the interepidemic period in the three districts with limited data on disease transmission dynamics. We found a high prevalence of potentially high-risk animal- and nonanimal-related behavioral practices among the sampled human population. We found a significant positive correlation between seropositivity in humans and animals. Participation in animal slaughtering was the primary route of past exposure to RVFV infection.

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Declarations of competing interest

The authors have no conflicts of interest to declare.

Author contributions

LEG, CS, SFR, AZ, and RK conceptualized the idea. CS, PKT, and TM conducted the investigation. CS and LEG performed data analyses. LEG, CS, SFR, AZ, FN, RK, CS, PKT and TM performed interpretation and writing of the first and subsequent versions of the manuscript. All authors contributed to intellectual content and finalizing the manuscript and have read and agreed to the submitted version of the manuscript.

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