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Original Article

Seroprevalence of leptospirosis among hospitalized febrile patients in Unguja Island

Ally Abdullah Ally[1], Athumani Msalale Lupindu[1], Robert Machang'u[2], Abdul Selemani Katakweba[3,4]

Abstract

Background: Leptospirosis is one of the neglected causes of febrile illness and death in developing countries, including Tanzania. The study aims to determine the seroprevalence of leptospirosis among hospitalized febrile patients in Unguja Island.

Methods: A cross-sectional study was carried out in the three selected hospitals in Unguja Island between January and March 2022. A total of 402 participants with febrile illness were enrolled in the study, and blood samples were collected for sera preparation. Microscopic agglutination test (MAT) was used to detect antibodies against five Leptospira serovars, including Sokoine, Lora, Pomona, Grippotyphosa, and Hebdomadis. All sera samples reacted with MAT titers≥1:160 were counted as positive, MAT titers ranging from 1:20 to 1:80 were counted as exposed to Leptospira bacteria while the absence of agglutination was regarded as negative. The data was analyzed using SPSS version 26, 2019. Descriptive and logistic regression was performed, and p≤0.05 was considered statistically significant.

Results: The mean age of study participants was 29.62 ±16.34, with a range of 0 days to 80 years. Most of them were females (64.2%) and unemployed (67.9%). The overall seroprevalence of leptospirosis was 7.7% (95% CI: 5.3-10.8). Females were 1.016 times higher likelihood to have leptospirosis (AOR = 1.016, 95% CI: 0.47-2.185, p = 0.968). Participants aged 18-35 were 2.093 times more likely to be infected with leptospirosis (AOR= 2.093, 95% CI: 0.835-5.250, p = 0.115). Participants who were unemployed (AOR = 1.169, 95% CI: 0.522-2.615, p = 0.704) revealed a significantly higher likelihood of being infected with leptospirosis. The predominant Leptospira serovars circulating among febrile patients were Sokoine 44 (10.9%), Lora 25 (6.2%), Grippotyphosa 20 (5.0%), Pomona 10 (2.5%), and Hebdomadis 9 (2.2%).

Conclusion: Leptospirosis is a public health threat among febrile patients in Unguja Island; therefore, it's important to be considered in the differential diagnosis of non-malaria febrile patients for early prevention and control strategies.

Keywords: Seroprevalence, Leptospirosis, Febrile Patients, Malaria, Unguja Island, Tanzania

Background

Leptospirosis is a neglected tropical zoonotic disease of public health importance caused by pathogenic spirochete bacteria that belong to the genus Leptospira [1-3]. The disease is distributed worldwide, particularly in tropical and subtropical regions, with over 1,000,000 cases reported annually and close to 60,000 deaths [4]. Rodents are considered the most important disease reservoirs in humans due to their existence in various environments [5]. Animals such as pigs, goats, cattle, and dogs act as carriers and can transmit Leptospira infection to humans throughout their entire lifetime if left untreated [6-8]. Humans may be infected by Leptospira bacteria through either direct contact with the urine of infected animals or indirectly through polluted environments such as water and soil. The bacteria can penetrate the human body via open wounds and abrasions in the skin or through mucous membranes such as the mouth, nose, and eyes [5,9,10,11]. Furthermore, the disease is one of the neglected causes of febrile illness and deaths in most African countries because of inadequate knowledge of the disease among healthcare workers and citizens and a lack of diagnostic resources [12,13]. Infected patients with this disease can

*Correspondence: ally.abdullah.ally@gmail.com
[1]Department of Veterinary Medicine and Public Health, Sokoine University of Agriculture, P. O. Box 3015, Chuo Kikuu, Morogoro, Tanzania

Full list of author information is available at the end of the article

develop acute, subacute, or chronic conditions. In acute and subacute stages, infected humans develop a range of symptoms such as fever, severe headache, chills, muscle, and joint pains, nausea, vomiting, diarrhea, and jaundice that are undifferentiated from other febrile illnesses such as malaria, brucellosis, yellow and dengue fevers [1,9,14]. In chronic conditions, the patients are associated with health complications, such as kidney dysfunctions, liver impairment, and hemorrhagic pulmonary syndrome [15]. The incubation period of leptospirosis usually ranges from 5–14 days but has also been reported to be up to 30 days [9,16].

In July 2022, Tanzania experienced re-emerging leptospirosis in the southern part (Lindi). Twenty confirmed cases and three deaths associated with symptoms of nasal bleeds, fever, headaches, and fatigue were reported [17]. Lack of diagnostic equipment and knowledge among healthcare workers on leptospirosis has led to misdiagnosis in favor of malaria due to the similarities in clinical symptoms [12,18]. Malaria prevalence has been maintained below 1% in Zanzibar for many years since 2013, but a clear understanding of the origin of fever among non-malaria febrile patients remains a big challenge [18,19]. Even though malaria and leptospirosis have common clinical symptoms and Leptospira bacteria being reported as a public health concern among non-malaria febrile patients [18], understanding the prevalence of leptospirosis and circulation serovars among febrile patients is important as far as the epidemiology of leptospirosis in concerned. Hence, the present study aimed to determine the Leptospira serovars circulating among febrile patients in Unguja Island, Seroprevalence, Leptospirosis, Febrile Patients, Malaria, Unguja Island, Tanzania.

Methods

Study Area

The study was conducted on Unguja Island, the main island of Zanzibar, an archipelago situated off the eastern coast of Tanzania mainland (6° 08′ 26.00" S, 39° 20′ 11.57" E). Unguja Island comprises three regions: Mjini Magharibi, Kaskazini Unguja, and Kusini Unguja. The health system of Zanzibar is classified into primary, secondary, and tertiary levels for providing healthcare services to the communities and ensuring that communities access good health services at the primary level within or less than 5 km of the nearest public health facility [20]. Hence, three purposively selected public hospitals at the tertiary level were involved in the study, including Mnazi Mmoja Referral Hospital located at Mjini Magharibi, Kivunge District Hospital situated at Kaskazini Unguja, and Makunduchi District Hospital located at Kusini Unguja (Figure 1). These hospitals were selected because they are the only public hospitals available in Unguja with advanced diagnostic facilities.

Study design and sample size determination

A cross-sectional study was conducted from January to March 2022, involving patients of all ages with febrile illness. The estimated population size of people living on Unguja Island was 1,346,332 and was projected to equal 71.2% of the total population of the Zanzibar Islands [21]. Therefore, the sample size of participants who enrolled in the study was estimated using a formula for the known population described by [22]: n = N/ (1+Ne2) with a 95% confidence level, where n = estimated sample size, N = known population size and e= level of precision (0.05). Therefore, the estimated sample size of the study participants was 399.8 people, almost 400 participants, and each hospital involved 134 study participants.

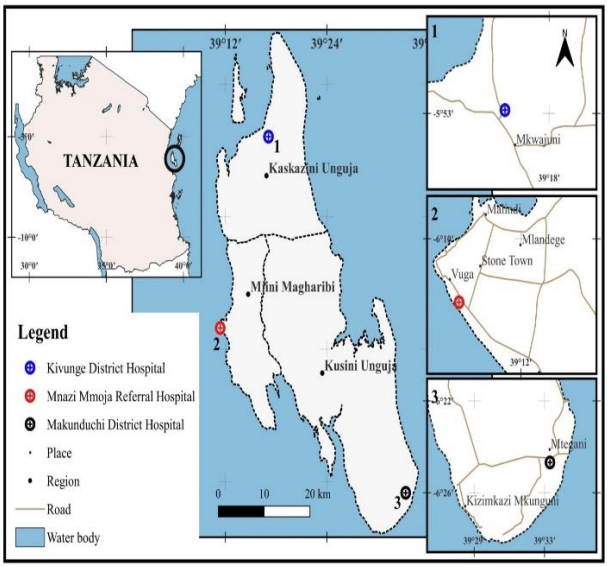

Figure 1. Map of Unguja Island indicating the study location of hospitals
Sources: QGIS Version 3.24 "Tisler" retrieved on August 22, 2022

Inclusion and exclusion criteria

The study involved patients of all ages with a fever who attended or were admitted to selected hospitals. The participants were orally informed that their blood could be tested for leptospirosis using an informed consent form as an agreement form. For all participants who could not give informed consent, such as those younger than 18 and those with learning disabilities, permission was granted by their family members on behalf of the participants. Participants who did not agree or family members who did not agree on behalf of participants to consent were excluded from the study. Participants were not interviewed to determine whether they had a history of symptoms related to leptospirosis because the symptoms of the disease are associated with other febrile illnesses, such as malaria.

Serum sample collection

Blood samples were collected from participants with fever who attended or were admitted to selected hospitals for various diseases. The participants were orally informed that their blood would be tested for leptospirosis after being used in a former hospital-recommended diagnostic test using an informed consent form. Participants' demographic information, such as sex, age, and occupation, was documented. The blood was collected by the hospital laboratory scientists and/or laboratory technicians using 2ml and/or 5ml sterile syringes and needles. The blood was immediately transferred into plain vacutainer tubes and allowed to clot for serum separation at room temperature for at least 30 minutes. Also, the un-separated blood was centrifuged for 10-15 min at 2000 rpm to acquire clear serum. The serum was transferred into labeled cryogenic tubes and/or Eppendorf tubes and stored frozen at -20°C in selected hospitals before transportation to the Institute of Pest

Management Research Laboratory at the Sokoine University of Agriculture Morogoro, Tanzania, for laboratory testing using the microscopic agglutination test (MAT) [6,8,14].

Laboratory procedures

Human Leptospira antibodies in the sera samples were tested against live Leptospira serovars antigens using the microscopic agglutination test (MAT) as a gold standard [23]. Five live reference Leptospira serovars frequently reported among humans in Tanzania were used, including L. Kirschner serogroup Ictero-haemorrhagiae serovars Sokoine, L. kirschneri serogroup Grippotyphosa serovar Grippotyphosa, L. interrogans serogroup Australis serovar Lora, L. interrogans serovars Hebdomadis, and L. interrogans serogroup Pomona serovar Pomona [8,14,24]. The Ellinghausen McCullough medium-Johnson and Harris (EMJH) was used to subculture a stock of pure selected live serovars and incubated at 30°C for at least 5 to 7 days with frequent screening to confirm the growth density, purity, and absence of bacterial contaminations using dark field microscope. A well-cultured live Leptospires serovar with a density of approximately 3x108 cells /ml on the MacFarland scale was used for MAT. A 50µl volume of phosphate-buffered saline (PBS) with a pH of 7.2 was filled in every one of the 96 wells of a microtiter plate except the wells of row 2 that were filled with 90µl of phosphate-buffered saline (PBS). A 10µl of sera samples were mixed with 90µl of phosphate-buffered saline (PBS) from row 2 in the microtiter plate to obtain initial dilutions of 1:10, 1:20, 1:40, and 1:80. Each dilution was thoroughly mixed and pipetting 50µl from the wells of row 2 to the following rows was done. Finally, 50µl remained after the last well was discarded. A 50µl volume of well-grown live leptospires antigen was added to all microtitration wells to obtain the last double dilutions of 1:20, 1:40, 1:80, and 1:160, then mixed carefully. The serum–antigen mixture in microtiter plates was incubated at 30oC for at least 2 hours, as recommended for screening. The serum–antigen mixtures were examined under a dark field microscope for observation by taking a drop of the mixture from wells, using a loop to attach it to a microscopic slide, and examining it under the microscope. All samples' titers that give 50% of the leptospira agglutination, leaving 50% of cells free compared with the negative control of a mixture of PBS with live culture serovars without serum, were counted as either positive or prior exposure to leptospira bacteria. Samples with MAT titers≥1:160 were counted as positive for the disease, and samples with MAT titers ranging from 1:20 to 1:80 were counted as exposed to Leptospira bacteria. In contrast, missing agglutination was counted as negative. All positive samples that reacted at a titer≥1:160 as a cut-off point were diluted again to final dilution to determine the end titration of significance. The agglutinating sera were re-tested at dilutions of 1:20, 1:40, 1:80, 1:160, 1:320, 1:640, 1:1,280, 1:2,560, 1:5,120, and 1:10,240. The end titer of significance was 1:2,560 [8,9,24,25].

Statistical analysis

The data were entered, cleaned, and coded in Microsoft Excel 2010, and the data were imported into Statistical Product for Service Solution (SPSS) version 26, 2019 (IBM SPSS Statistics). Descriptive analyses, including frequency, proportion, and mean, were performed. Logistic regression was performed to measure the association between the seroprevalence of leptospirosis and sex and age groups. Odds ratios and a confidence interval of 95% were calculated, and $p \leq 0.05$ was considered statistically significant.

Results

Socio-demographic characteristics of study participants

Of 402 participants, 144 (35.8%) were males, and 258 (64.2%) were females. The mean (SD) age of the study participants was 29.62 (±16.34) years, with a range of 0 days to 80 years. The age group 18-35 contributed the highest proportion (51.7%). Regarding occupation, a higher proportion of participants was unemployed (67.9%), as shown in Table 1.

Table 1: Socio-demographic characteristics of study participants (n=402)

Demographic characteristics	Categories	Number (%)
Sex	Males	144 (35.8)
	Females	258 (64.2)
Age group (years)	Less than 18	86 (21.4)
	18−35	208 (51.7)
	36−59	83 (20.6)
	≥ 60	25 (6.2)
Occupation category	Employed	129 (32.1)
	Unemployed	273 (67.9)

Seroprevalence of Leptospira antibodies in febrile patients in Unguja hospitals

Out of 402 tested sera samples, 31 (7.7%) (95% CI: 5.3-10.8), were positive for leptospirosis. Of the 31 positive, 13 (3.2%) were from Kivunge District Hospital, 10 (2.5%) from Mnazi Mmoja Hospital, and 8 (2.0%) from Makunduchi District Hospital. Regarding sex, leptospirosis rates in males were 11 (2.7%) and 20 (5.0%) in females. Study participants aged 18-35 years had a higher positive rate of disease with a seroprevalence of 2.7%, followed by participants under 18 years with a seroprevalence of 2.2%. The highest seroprevalence of leptospirosis based on occupation category was found among unemployed participants (5.5%), as shown in Table 2.

Table 2: Seroprevalence of leptospirosis in relation to socio-demographics information of the study participants (n=402)

Variables	**Total tested** (n=402)	**Leptospirosis positive** (%) MAT titer ≥1:160
Human participants	402	31 (7.7)
Sex category		
Males	144	11(2.7)
Females	258	20(5.0)
Age group (years)		
Less than 18	86	9 (2.2)
18−35	208	11 (2.7)
36−59	83	7 (1.7)
≥ 60	25	4 (1.0)
Occupation category		
Employed	129	9(2.2)
Unemployed	273	22(5.5)
Hospital category		
Kivunge District Hospital	134	13(3.2)
Mnazi Mmoja Referral Hospital	134	10(2.5)
Makunduchi District Hospital	134	8(2.0)

Number of study participants with past exposure to Leptospira bacteria

Out of 402 participants whose sera samples were tested for Leptospira antibodies, 65 (16.2%) participants were observed to have past exposure to Leptospira bacteria due to the MAT titer range from 1:20 to 1:80, of whom 26 (6.5%) were from Mnazi Mmoja Hospital, 21 (5.2%) were from Kivunge District Hospital, and 18 (4.5%) were from Makunduchi District Hospital. Based on the sex category, 39 (9.7%) were females and 26 (6.5%) were males. The age groups 18-35 years had greater exposure to Leptospira bacteria 30 (7.5%), followed by age groups less than 18 years 17 (4.2%), as shown in Table 3.

Table 3: Number of study participants with past exposure to Leptospira bacteria in relation to socio-demographic information of the study participants (n=402).

Variables	Total tested	MAT titre (1:20 to 1:80)
Human participants	402	65(16.2)
Sex category		
Males	144	26(6.5)
Females	258	39(9.7)
Age group (years)		
Less than 18	86	17(4.2)
18−35	208	30(7.5)
36−59	83	11(2.7)
≥ 60	25	7(1.7)
Occupation category		
Employed	129	20(5.0)
Unemployed	273	45(11.2)
Hospital category		
Mnazi Mmoja Referral Hospital	134	26(6.5)
Kivunge District Hospital	134	21(5.2)
Makunduchi District Hospital	134	18(4.5)

Comparison of seroprevalence of leptospirosis in different variables

The seroprevalence of disease among participants in different variables such as sex, age, and occupation groups were compared to determine whether certain groups were at greater risk of disease than others using logistic regression. The seroprevalence of leptospirosis in female participants was 1.016 times higher than in males, which was not statistically significant (AOR = 1.016, 95% CI: 0.47-2.185, p = 0.968). Concerning age groups, participants aged 18-35 were 2.093 times more likely to be infected with leptospirosis (AOR= 2.093, 95% CI: 0.835-5.250, p = 0.115) r, which was not statistically significant. Participants who were unemployed (AOR = 1.169, 95% CI: 0.522-2.615, p = 0.704) revealed a significantly higher likelihood of being infected with leptospirosis (Table 4).

Discussion

Human leptospirosis is little known in Unguja Island. The present study aimed to address the gap in human leptospirosis by examining the seroprevalence of leptospirosis among hospitalized febrile patients. The findings of this study revealed that the overall seroprevalence of human leptospirosis was 7.7%, which was in line with the previous studies in different parts of the world, including northern Tanzania, with a prevalence of 8.8% [16,26] and northeastern Malaysia, with a seroprevalence of 8.4% [27]. However, this study's seroprevalence was higher than the findings reported from Nepal (4.8%) [28], Mozambique (1.3%) [29], and Uganda 4.7% [30]. In contrast, the study prevalence was lower compared to a prevalence of 13% reported in Kilosa district, Tanzania [31], 14.7 % in Ecuador [32], 21% in Nepal [33], 11.2% in northern Peru [34], and 46.3% reported in Japan [35]. The difference in disease seroprevalence among febrile patients is probably due to different serovars and methodological and geographical differences [27].

Furthermore, the frequent use of the recommended antibiotics among non-malaria febrile patients could help clear the infection early. Therefore, previous exposure to recommended antibiotics among non-malaria febrile patients could probably lead to low seroprevalence of disease in the studies [25,30]. In terms of sex variables, the findings of this study showed that female participants have a higher seroprevalence of leptospirosis than males. This study's finding was comparable with the study of [33], which concluded that females have a higher prevalence of disease than males due to the high number of females attending hospitals for other treatments compared to males [33]. However, this finding was in contrast with previous studies conducted in different areas of the world that explain that males have a higher seroprevalence of leptospirosis than females because of greater involvement in economic activities that have high exposure to the Leptospira bacteria [4,36].

Regarding age groups, this study finding indicated that the participants in the middle age groups ranging from 18-35 years and 36-59 years were highly seropositive to leptospirosis and suggesting that they are the most risk groups. This result was equivalent to the studies of [33,37], which concluded the occurrence of higher seropositivity to leptospirosis among middle-aged 21 to 40 years due to their occupational and recreational exposure. In contrast, age groups above 60 years showed lower seropositivity to leptospirosis, probably due to less exposure to environmental contaminants or animals' reservoirs [38]. Furthermore, the prevalence of leptospirosis in this study is 7.7% higher than that of malaria, which is below 1% by 2013 in Zanzibar [19]; this gives the impression that the contribution of malaria among febrile patients is relatively small. Hence, proper diagnosis is essential before prescribing antimalarial drugs to non-malaria patients. Otherwise, mistreatment may lead to prolonged illness and death or drug resistance. In addition, the seroprevalence of disease in this study is higher than that reported by [18], which was below 1% in 2015. This difference in prevalence may be due to methodology differences, the number of sampling areas, and the range of time (years) from the former to the present study. This gives the concept that the prevalence of Leptospira infections in Unguja Island is increasing with time due to the changes in the human-socioeconomic activities of the study population.

In this study, serovar Sokoine was most prevalent (10.9%) compared to other serovars; this indicated that serovar Sokoine is the common serovar circulating among febrile patients in Unguja Island and widespread in different regions of Tanzania, including Kilosa district [31], Morogoro [39], Bahi District [14], Kagera [15] and Mwanza [40].

Table 4: Comparison of differences in seroprevalence between variables

Variables	Leptospirosis positive (%)	AOR	(95% Cl)	P-value
Sex category				
Males	11(2.7)		***	***
Females	20(5.0)	1.016	0.472−2.185	0.968
Age group (years)				
Less than 18***	9 (2.2)		***	***
18−35	11 (2.7)	2.093	0.835−5.250	0.115
36−59	7 (1.7)	1.269	0.450−3.581	0.653
≥ 60	4 (1.0)	0.614	0.172−2.191	0.452
Occupation category				
Employed	9(2.2)		***	***
Unemployed	22(5.5)	1.169	0.522−2.615	0.704

***Reference age group AOR= Adjusted odds ratio Cl=Confidence interval

On the other hand, the findings of this study showed the presence of some participants prior to exposure to Leptospira bacteria due to their antibodies reacting to MAT titers, which ranged from 1:20 to 1:80, below the cut-off point of significance. This result agreed with the study of [30], which concluded the presence numbers of participants' prior exposure to Leptospira infection. These conditions occur probably due to the routine practice of healthcare workers in primary and secondary levels of treatment to suggest the frequency of uses of recommended antibiotics among non-malarial febrile patients that may be un-diagnosed. Leptospira bacteria become highly susceptible to recommended antibiotics, and the history of Leptospira infections remains for a long time in humans due to the presence of the IgG antibody [30]. The present study had certain limitations. First, participants with fever who attended or were admitted to selected hospitals were enrolled in this study without being interviewed to determine whether they had a history of symptoms related to leptospirosis because the symptoms of the disease are associated with other febrile illnesses, such as malaria. Secondly, the estimation of seroprevalence of leptospirosis was limited due to the use of a single serum sample per participant. Thus, at least two serum samples were recommended to be collected from each participant.

Conclusion

In conclusion, this study revealed that leptospirosis is a public health threat among febrile patients in Unguja Island, with a seroprevalence of 7.7%. These results call for the inclusion of leptospirosis in the differential diagnosis of acute non-malaria febrile illnesses to reduce misdiagnosis and inappropriate uses of drugs, particularly in primary and secondary treatment. Finally, we recommend that public awareness of the causes and transmission of leptospirosis among healthcare workers and the general population is needed as an essential strategy for preventing and controlling the disease. Developing a rapid diagnostic test to diagnose leptospirosis disease among non-malaria patients in primary healthcare facilities is needed. This test is reliable, affordable, and simple to apply. The Ministry of Health in Zanzibar needs to initiate Integrated Disease Surveillance, which involves arboviral and zoonotic diseases of public health concern, such as leptospirosis. Further studies of human leptospirosis are needed, including the epidemiology and burden of the disease and coverage of Pemba Island...

Table 5: Circulating Leptospira serovars and its agglutination titers

L. Serovars	**Titers**							Total (%)
	1:20*	1:40*	1:80*	1:160	1:320	1:640	1:2,560	
L. *kirschneri* serovars Sokoine	0	12	19	7	5	0	1	44 (10.9)
L. *interrogans* serovar Lora	0	4	9	10	1	1	0	25 (6.2)
L. *kirschneri* serovar Grippotyphosa	0	5	11	4	0	0	0	20 (5.0)
L. *interrogans* serovar Pomona	0	2	5	3	0	0	0	10 (2.5)
L. *interrogans* serovars Hebdomadis	1	3	3	2	0	0	0	9 (2.2)
Total (%)	**1**	**26**	**47**	**26**	**6**	**1**	**1**	**108 (26.8)**

*The titers ranged from 1:20 to 1:80, indicating the participants were previously exposed to Leptospira bacteria, and titers≥1:160 indicate the positive for leptospirosis.

Abbreviation

ACE: African Centre of Excellence; BTD: Biosensor Technology Development; EMJH: Ellinghausen McCullough Medium-Johnson and Harris; IBM: International Business Machines; IRPM: Innovative Rodent Pest Management; MAT: Microscopic Agglutination Test; PBS: Phosphate Buffered Saline; WHO: World Health Organization; ZAHREC: Zanzibar Health Research Ethical Committee.

Declaration

Acknowledgment

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Availability of data and materials

Data will be available by emailing
ally.abdullah.ally@gmail.com

Authors' contributions

Ally Abdullah Ally (AAA) is the principal investigator (PI) who contributed to the conceptualization, data collection, analysis, and writing of the original draft of the manuscript. Athumani Msalale Lupindu (AML) and Robert Machang'u (RM) are the core supervisors, and Abdul Selemani Katakweba (AASK) is the main supervisor. AML, RM, and AASK contributed to the manuscript's supervision, review, editing, and re-writing. All authors have read and accepted the manuscript to the final version for submission.

Ethics approval and consent to participate

We conducted the research following the Declaration of Helsinki. The ethical clearance for conducting this study was granted by the Research Ethics Committee at Sokoine University of Agriculture (Ref No. SUA/ADM/R.1/8/767 on January 10, 2022). The permission to conduct research in Zanzibar was obtained from the Research Committee of the Office of the Second Vice President and the Office of the Chief Government Statistician (OCGS), Ref No. 61B6F85E745B7 on December 13, 2021). Research protocols were revised and approved by the Zanzibar Health Research Ethics Committee, Ref No ZAHREC/04/ST/NOV/2021/94, on November 30, 2021) under the Zanzibar Ministry of Health. Furthermore, the participants were orally informed that their blood could be tested for leptospirosis using an informed consent form as an agreement form.

Consent for publication

Not applicable

Competing interest

The authors declare that they have no competing interest.

Author details

[1]Department of Veterinary Medicine and Public Health, Sokoine University of Agriculture, P. O. Box 3015, Chuo Kikuu, Morogoro, Tanzania.
[2]ST Francis University College of Health and Allied Sciences, P.O. Box 175, Ifakara-Morogoro, Tanzania.
[3]African Centre of Excellence for Innovative Rodent Pest Management and Biosensor Technology Development (ACE II IRPM & BTD) at the Sokoine University of Agriculture, Morogoro, Tanzania.
[4]Institute of Pest Management, Sokoine University of Agriculture, P.O. Box 3110, Chuo Kikuu, Morogoro, Tanzania.

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