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Knowledge of Lassa Fever and Its Determinants among Traders in Izzi Community in South-East Nigeria

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Authors' contributions

This work was carried out in collaboration between all authors. Author EUN designed the study. Author AFU performed the statistical analysis. Authors EUN and UCM wrote the protocol. All authors wrote the first draft of the manuscript. Authors EUN, CA, AFU and NCE managed the analyses of the study. Authors CA, AFU, UCM, IE, LUO and ICA managed the literature searches. All authors read and approved the final manuscript.

Article Information

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Original Research Article

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ABSTRACT

Background: Lassa fever is a viral hemorrhagic fever found predominantly in West Africa with the potential to cause approximately 5,000 deaths per year. However, good knowledge of the disease may reduce the infection rate. The study assessed the knowledge of Lassa fever and its determinants among traders in Izzi community Ebonyi State, Nigeria.

Methods: A descriptive cross-sectional study was conducted among 248 traders selected by simple random sampling method. Data were collected from respondents who gave their informed consent using interviewer-administered semi-structured questionnaire and analyzed using Chi-square test (Fisher's exact test where appropriate) for categorical variables and binary logistic regression for predictors of the outcome variables. Statistical significance was set at p < 0.05**Results:** Most of the respondents (40%) were within the age group of 21 – 30 years. Majority of the

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traders were females (64.1%), married (64.1%) and predominantly Christians (97.2%). A large proportion of the respondents (43.1%) had secondary education level, and 10.1% had no formal education. Awareness of Lassa fever was high 197 (79.4%) among the traders. The commonest source of information was radio 152 (61.3%), and only 15% of the respondents heard about Lassa fever from health workers. Overall knowledge of Lassa fever was poor: 173 (70%) of the traders had poor knowledge, and only 53 (21.4%) had excellent knowledge. Majority of the traders 160 (64.5%) ate rat's meat. Factors found to be significantly associated with knowledge of Lassa fever include gender, educational status, and consumption of rat. Predictors of adequate knowledge include male gender and completing tertiary education.

Conclusion: The high level of awareness of Lassa fever in this study did not translate to adequate knowledge of the disease. The poor level of knowledge points towards a growing need to step up not just awareness of Lassa fever but also in-depth knowledge of the causes, mode of transmission and prevention of the disease through public education with special access to the female cohort.

Keywords: Lassa fever; knowledge; determinants; traders; Nigeria.

1. INTRODUCTION

Lassa fever is an acute viral hemorrhagic illness caused by Lassa virus, a member of the virus family "Arenaviridae." The disease is endemic in various West African countries including Sierra Leone, Guinea, Liberia, and Nigeria where Lassa fever virus infections rate per annum is estimated at 100,000 to 300,000 with approximately 5,000 deaths [1]. Outbreaks have been reported in Ghana, and serological evidence of human infection has been found in Ivory Coast. Senegal. and Mali. The virus has also been imported into countries where it is not endemic; for example, by returning travellers to Germany [2]. Outbreaks of the disease have been reported in various parts of Nigeria since it was first reported in 1969 with the worst outbreak recorded in 2012 where 623 cases including 70 deaths were reported from 19 out of 36 states, and case fatality rate put at 37.9% [3]. Lassa fever is commonly found in rural communities, where over 70% of the population resides [4].

The virus exhibits persistent, asymptomatic infection, with profuse urinary virus excretion in Mastomys natalensis, the ubiquitous and highly commensal rodent host. The virus is shed in their excreta (urine and feces), which can be aerosolized and inhaled by humans. The primary mode of spread is from rodent to man through contact with rodent excreta or urine in food or during hunting and processing of rats for consumption. The virus has the capacity for person-to-person spread, either within households during care for sick relatives or in health care settings [5] Percutaneous or permucosal exposure to blood and other infected body fluids can result in the secondary human spread, especially in health care settings [5].

Lassa fever presents at its early stage with symptoms and signs indistinguishable from those of other viral, bacterial or parasitic infections common in the tropics such as malaria, typhoid, and other viral hemorrhagic fever [6]. Untreated initial flu-like and gastrointestinal symptoms give way to bleeding, organ failure and neurological complications [7]. Laboratory testing is required for confirmation and the drug ribavirin is effective if administered early following infection [8].

The focus of this research into the level of knowledge of Lassa fever in a rural area has much implication for limiting mortality from Lassa fever, as a greater proportion of people live in the rural communities where poverty prevails, and standards of living are low. More so, the emergence of highly virulent and contagious Lassa virus in many more states and the increasing sporadic cases of Lassa fever outside the endemic regions within and outside the country as a result of huge inter-border traffic international travel necessitates and that should have comprehensive communities information about the virus and the disease it causes.

Good knowledge of Lassa virus means and modes of infection as well as adequate prevention measures may reduce the infection rate. The knowledge of Lassa virus was generally low among the populace in a descriptive cross-sectional study carried out among urban slum dwellers in South-western Nigeria. About 20.2% of the population had heard about Lassa fever out of which only 19.4%, 14.1%, 17.0% and 13.9% of respondents had good knowledge of occurrence, causes, disease transmission, and prevention of Lassa fever respectively [9]. The lack of existing adequate knowledge of Lassa fever among this population underscores the need for other studies to assess the level of knowledge among other sub-populations. Also, inadequate knowledge of Lassa fever among rural populace may reflect in their behavioral pattern to preventive measures. The study assessed the knowledge of Lassa fever and its determinants among traders in Izzi community Ebonyi State, Nigeria.

2. METHODOLOGY

This was a descriptive cross-sectional study carried out among traders in a rural market in Nwezenyi Igbeagu, Izzi Local Government Area of Ebonyi state. It is located at an elevation of 155 meters above sea level, and its population approximates to 250,459. Its coordinates are 6°34'60" N and 8°3'0" E. The climate is of the equatorial type with rainfall of about 1800 - 200 mm per annum. It has several other villages of which Nwezenyi is among. This market was used for this study because it is the only market in our rural practice center where our health Facility is located. It is majorly an agrarian society and farmers bring their produce to the market to sell them. The market trades every day and attracts men and women from different communities both far from and near Nwezenyi. Inclusion criteria used for recruiting respondents included having a permanent structure as a shop, a temporary structure but which occupies an easily locatable position and have given consent to participate in the study. An eligible person was excluded if he or she did not give consent to be part of the study. The formula for calculating sample size when the population is less than ten thousand was used to estimate our sample size as follows:

n=
$$\frac{z^2 pq}{d^2}^{10}$$

Where Z^2 is the standard normal deviate = $1.96 \approx 2$

p = 0.2 (20%) from another study [9] q = 1-p which is = 08 and

d = 0.05.

Substituting the above figures into the above formula will be equal to 256.

Then,

Nf =
$$\frac{n}{1+(n)/(N)}$$
 ------[10]

Where,

- n_f = the desired final sample size,
- n = the desired sample size when the population is more than 10000 which is equal to 256
- N = the estimate of the population size of the market which is equal to 2000.

When these were substituted into the formula, it was equal to 226, and an addition of 10% non-response rate brought the sample size to approximately 248.

Two hundred and forty-eight respondents were selected using simple random sampling technique after identifying each trader in the sampling frame. Where the respondent was not available in the shop, the next eligible trader represented on the random numbers was chosen. The data was collected by the researchers and with the help of other Doctors working in the health facility which served as The research assistants. researchers approached a selected shop and administered the questionnaire by themselves to the eligible trader. Data collection was made using a pretested, semi-structured, interviewer administered questionnaire which was developed by the researchers. There were sections which covered socio-demographic characteristics of respondents, awareness, and knowledge of Lassa fever transmission and the practice of rat hunting as a delicacy. The questionnaire was pretested among 20 rural market women in a neighboring community. A mini-analysis of the collected data was done to clarify and correct ambiguities. Also, the questionnaire was doubly translated from English to vernacular by an indigenous health worker. The vernacular version of the questionnaire was given to another health worker to translate again to the English language. The two English language versions of the questionnaire were compared and reconciled before embarking on the study. These were done to ensure consistency and validity of the document. Content validity was ascertained by applying the Cronbach's Alpha validity test, and the value was 0.8.

Knowledge of Lassa fever was assessed using 19 questions requiring a "yes or no" response. The questions covered knowledge of reservoir of Lassa fever virus, modes and sources of transmission, symptoms of Lassa fever, preventive measures and curability of the disease. The correct response was allocated 1 point while wrong one had no point. The scores were combined to form a composite score having a maximum score of 19 points and a minimum of zero. This composite score was converted to a percentage. Score \leq 50% was considered poor knowledge while those who scored 51% - 74% were rated as having good knowledge. Excellent knowledge described score ≥75% Responses to the questions. Data were analyzed using IBM SPSS version 21 statistics analysis software. The results of the study were presented in frequencies and proportion. Chi-square test was used for association between these proportions, and the p-value was set at <0.05. The outcome (dependent) variable was the graded knowledge of the respondents. The Fisher's exact test was read in some of the test results as appropriate. To determine the predictors of knowledge of Lassa fever, the outcome variable was dichotomized into good and poor knowledge using the score of 50% as the cut off (<50% was poor knowledge while ≥50% constituted good knowledge) and used in binary logistics regression model. Independent variables that had p-values ≤0.1 were fitted in the binary logistic regression model. The findings are shown below. Statistical significance (p-value) of the test of association and the predictors of the outcome variable (using Chi-square test and binary logistic regression) was set at p<0.05.

Ethical issues: To obtain consent from an eligible trader, we approached the trader, introduced ourselves and our objectives for

carrying out the study. The traders were also made to know that they were at will to decline from participating in the study without any consequences. When a trader agreed to participate, he or she was asked to sign or thumb-print on the informed consent form before the questionnaire was administered to the trader. Ethical approval for this study was obtained from the Research and Ethics Committee of Federal Teaching Hospital Abakaliki Ebonyi State, Nigeria.

3. RESULTS

A total of 248 questionnaires were distributed, and all were returned completed giving a response rate of 100%. This was possible being an interviewer administered process. The findings are shown below in Tables 1-5.

The average age of the market men and women was 29.6 ± 10.4 . The youngest age was 18 years while the oldest was aged 65. Traders aged 21 - 30 years were greatest in proportion 99 (40%), while those above 50 years of age were least 11 (4.4%). There were more female traders 159 (64.1%), and a similar proportion of the traders was married 159 (64.1%). One hundred and seven (43.1%) ended their education at secondary school. About 10% (25 respondents) had no formal education while less than 10% attained the tertiary level of education. The traders were predominantly Christians 241 (97.2%).

Variable		Frequency (N=248)	Percentage
Age groups (years)			
Mean = 29.6 ±10.4	< 21	59	23.8
Minimum = 18	21 -30	99	40.0
Maximum = 65	31 – 40	57	23.0
	41 – 50	22	8.9
	>50	11	4.4
Gender	Male	97	39.1
	Female	151	60.9
Marital status	Married	159	64.1
	Single	86	34.7
	Divorced	2	0.8
	Separated	1	0.4
Educational status	No formal education	25	10.1
	Primary	98	39.5
	Secondary	107	43.1
	Tertiary	18	7.3
Religion	Christian	241	97.2
5	Traditional	3	1.2
	Islam	2	0.8
	Sabatarian	2	0.8

Table 1. Socio-demographic characteristics of the traders

Variables	Frequency N = 248	Percentage
Aware of Lassa fever	• •	
Yes	197	79.4
No	51	20.6
Sources of information on Lassa fever (Mult	tiple responses)	
Radio	152	61.3
Health workers	38	15.3
Friends	29	11.7
Television	24	9.7
Family	16	6.5
Newspapers and magazines	13	5.2
Church	4	1.6
Market women	1	0.4
Lassa fever patient	1	0.4
Consumption of rat		
Yes	160	64.5
No	88	35.5
The frequency of rat consumption		
Often	12	4.8
Sometimes	47	19.0
Occasionally	25	10.1
Rarely	76	30.6
Not Applicable	88	35.5

Table 2. Awareness, knowledge, and rat consumption practices of the traders

Table 3. Correct responses to Lassa fever knowledge questions and grading of Lassa fever knowledge

Variable	Response (N = 248)	Percentage
Rat is the animal that transmits Lassa fever	185	74.6
Means of Lassa fever transmission		
Lassa can be transmitted by eating rat	167	67.3
Eating food contaminated with rat droppings	125	50.4
Contact with body fluid of infected persons	71	28.6
Improper handling of the corpse of an infected person	63	25.4
Symptoms of Lassa fever		
A headache	96	38.7
Fever	103	41.5
Weakness	77	31.0
Back pain	59	23.8
Diarrhea	59	23.8
A sore throat	53	21.4
Bleeding	80	32.3
Lassa fever is preventable	116	46.8
Lassa fever preventive measures		
Proper covering of food	116	46.8
Proper disposal of refuse	76	30.6
Regular hand washing	86	34.7
Clearing of bushes around houses	71	28.6
Avoid consumption of rat	129	52.0
Lassa fever is curable	157	63.3
Knowledge of Lassa fever		
Poor knowledge	173	69.8
Good knowledge	22	8.9
Excellent knowledge	53	21.4

Awareness of Lassa fever was high 197 (79.4%) among the traders. Their commonest source of information on Lassa fever was radio 152 (61.3%). About 15% of them had heard about Lassa fever from health workers. Less than 10% got the information from television and newspaper/magazine. As much as 160 (64.5%) were still consuming rat meat, and 4.8% did that often.

Table 3 shows that about three-quarter (74.5%) of the respondents knew that rats are the reservoir of Lassa fever and 167 (67.3%) knew that such transmission could occur by eating rat meat. Less than 30% of the traders knew that the virus could be contacted through contact with infected person 71 (28.6%) and the corpse of an infected person 63 (25.4%) respectively. Apart from fever, less than 40% of the respondents know other symptoms of Lassa fever. A sore throat was the symptom known to the least of the traders. One hundred and sixteen (46.8%) of them knew that it could be prevented. Avoidance

of the consumption of rat was the commonest preventive measure129 (52.0%) known to them while the least proportion 71 (28.6%) knew that clearing of bushes around the house could prevent Lassa fever. One hundred and fifty-seven (63.3%) knew that the infection is curable.

About 70% of the traders had poor general knowledge of Lassa fever while only 53 (21.4%) had excellent knowledge.

Table 4 shows that there was a significant statistical association between the trader's knowledge of Lassa fever and their gender as well as educational status (P < 0.05). The statistical association between Lassa fever knowledge and rat consumption of the traders was highly significant (p = 0.005). The association was not statistically significant for marital status and religion of the traders. There was no association between knowledge of Lassa fever and religion and marital status of the respondents (p > 0.05).

Knowledge N (%)			X ² (P - value)
Poor	Good	Excellent	
45 (76.3)	5 (8.5)	9 (15.3)	5.9 (0.62)*
70 (70.7)	8 (8.1)	21 (21,2)	
34 (59.6)	6 (10.5)	17 (29.8)	
15 (68.2)	3 (13.6)	4 (18.2)	
9 (81.8)		53 (18.2)	
59 (60.8)	9 (9.3)	29 (29.9)	7.3 (0.03)
114 (75.5)	13 (8.6)	24 (15.9)	
62 (72.1)	9 (10.5)	15 (17.4)	8.7 (0.07)*
110 (69.2)	12 (7.5)	37 (23.3)	
0 (0.0)	1 (100)	0 (0.0)	
	0 (0.0)		
()	()	()	
22 (88.0)	1 (4.0)	2 (8.0)	13.6 (0.03)*
	10 (10.2)		. ,
70 (65.4)	8 (7.5)	28 (27.1)	
8 (44 4)	3 (16.7)	7 (38.9)	
()	()	()	
166 (68.9)	22 (9.1)	53 (22.0)	2.2 (1.00)*
2 (100)	0 (0.0)	0 (0.0)	
2 (100)	0 (0.0)	0 (0.0)	
	. ,		
106 (66.7)	10 (6.3)	43 (27.0)	10.5 (0.005)
66 (75.0)	12 (13.6)	10 (11.4)	. ,
Fisher's exact tes	t (p-value)	. ,	
	Poor 45 (76.3) 70 (70.7) 34 (59.6) 15 (68.2) 9 (81.8) 59 (60.8) 114 (75.5) 62 (72.1) 110 (69.2) 0 (0.0) 1 (50.0) 22 (88.0) 73 (74.5) 70 (65.4) 8 (44 4) 166 (68.9) 2 (100) 2 (100) 2 (100) 106 (66.7) 66 (75.0)	PoorGood $45 (76.3)$ $5 (8.5)$ $70 (70.7)$ $8 (8.1)$ $34 (59.6)$ $6 (10.5)$ $15 (68.2)$ $3 (13.6)$ $9 (81.8)$ $0 (0.0)$ $59 (60.8)$ $9 (9.3)$ $114 (75.5)$ $13 (8.6)$ $62 (72.1)$ $9 (10.5)$ $110 (69.2)$ $12 (7.5)$ $0 (0.0)$ $1 (100)$ $1 (50.0)$ $0 (0.0)$ $22 (88.0)$ $1 (4.0)$ $73 (74.5)$ $10 (10.2)$ $70 (65.4)$ $8 (7.5)$ $8 (44 4)$ $3 (16.7)$ $166 (68.9)$ $22 (9.1)$ $2 (100)$ $0 (0.0)$ $2 (100)$ $0 (0.0)$ $2 (100)$ $0 (0.0)$ $106 (66.7)$ $10 (6.3)$	PoorGoodExcellent $45 (76.3)$ $5 (8.5)$ $9 (15.3)$ $70 (70.7)$ $8 (8.1)$ $21 (21,2)$ $34 (59.6)$ $6 (10.5)$ $17 (29.8)$ $15 (68.2)$ $3 (13.6)$ $4 (18.2)$ $9 (81.8)$ $0 (0.0)$ $53 (18.2)$ $59 (60.8)$ $9 (9.3)$ $29 (29.9)$ $114 (75.5)$ $13 (8.6)$ $24 (15.9)$ $62 (72.1)$ $9 (10.5)$ $15 (17.4)$ $110 (69.2)$ $12 (7.5)$ $37 (23.3)$ $0 (0.0)$ $1 (100)$ $0 (0.0)$ $1 (50.0)$ $0 (0.0)$ $1 (50.0)$ $22 (88.0)$ $1 (4.0)$ $2 (8.0)$ $73 (74.5)$ $10 (10.2)$ $15 (15.3)$ $70 (65.4)$ $8 (7.5)$ $28 (27.1)$ $8 (44.4)$ $3 (16.7)$ $7 (38.9)$ $166 (68.9)$ $22 (9.1)$ $53 (22.0)$ $2 (100)$ $0 (0.0)$ $0 (0.0)$ $2 (100)$ $0 (0.0)$ $0 (0.0)$ $106 (66.7)$ $10 (6.3)$ $43 (27.0)$ $66 (75.0)$ $12 (13.6)$ $10 (11.4)$

Table 4. Association between knowledge of Lassa fever and socio-demographic characteristics/rat consumption practices of the respondents

level of awareness in this study did not translate

to good knowledge of the disease. Knowledge of

the Lassa fever transmission process is key to

breaking the chain of infection. More than two-

third of the respondents had poor knowledge of

the etiology and mode of transmission of Lassa

Variable		Wald statistics (X ²)	p-value	AOR (CI)*
Gender	Gender – Male (Female)	4.1	0.04	1.9 (1.0 – 3.5)
Marital status	Married (Single)	0.7	0.40	0.35 (0.0 - 6.1)
	Separated (Single)	0.4	0.56	0.4(0.0-9.1)
	Divorced (Single)	0.0	1.00	0.2(0.0-0.0)
Educational	Tertiary (No formal education)	6.9	0.009	8.4 (1.7 – 40.7)
status	Secondary (No formal education)	3.3	0.07	3.4 (0.9 – 12.1)
	Primary (No formal education)	1.2	0.27	2.2 (0.6 - 8.4)

 Table 5. Predictors of adequate Lassa fever knowledge among the traders

*AOR = Adjusted Odds Ratio; CI = Confidence Interval

A binary regression model revealed that being a male and completing tertiary education were significant predictors of the dichotomized Lassa fever knowledge among the traders. Being a male is twice more likely to have adequate knowledge of Lassa fever relative to the female counterpart. A trader who completed tertiary education is eight times more likely to have adequate Lassa fever knowledge compared to those who did not get any formal education.

4. DISCUSSION

In this study, more than three-quarter of the traders had heard about Lassa fever. This was higher when compared with similar studies done in south-western part of the country that reported only about half of the respondents studied were aware of Lassa fever [11-13]. This difference may have been because Ebonyi State has been known as an endemic State for Lassa fever with peak periods at dry season [11,13]. Hence, sensitization by the government and other agencies through mass media may have been higher than other parts of the country. The observed role of the media suggests that the remains a veritable media means of disseminating information about health and health-related events although bias to perception may result [14]. It was also revealed in this study that the major source of information was the electronic media mainly radio, others were health workers and friends. The major source of information on Lassa fever identified in this study agreed with findings from other studies in Nigeria [11]. In a study among rural community dwellers in Ilorin and Ibadan majority of the respondents had heard of Lassa Fever through radio and television [12,15]. This finding supports the need for continuous campaigns and news items in the public media to sustain the dissemination of information on Lassa fever. The media remains a veritable means of disseminating information about health and health-related events. The high

fever. Only one-third had good/excellent knowledge. Looking at individual variables only about a guarter of the respondents knew about some non-specific symptoms such as fever. headache, diarrhea, sore-throat, backache, and bleeding. Although about three-guarter of the respondents in this study knew that rat was the reservoir for Lassa fever, not up to half of them knew Lassa fever could be prevented nor knew ways to prevent the disease. Poor knowledge of Lassa fever was also reported in similar studies conducted in the rural areas in Nigeria [11-13,15]. For instance, in the llorin study, 76% of the respondents had inadequate knowledge of the mode of transmission of the disease.[12] Also, in the study done in Ekpoma only 31% of the respondents had good knowledge of Lassa Fever transmission although they had a lower proportion of respondents who identified rat as being the reservoir of Lassa fever compared to this current study [13]. This difference could be due to the time gap between the studies (2010-2017). It is, however, worrisome that even though respondents in this study knew rats were the reservoir, they still lacked adequate knowledge on how the disease can be transmitted. The poor level of knowledge points towards a growing need to step up not just awareness of Lassa fever but also in-depth knowledge of the cause, mode of transmission and prevention of Lassa fever. This study also revealed risky practices like eating rats. More than half of the respondents in this study still consume rats, and a few of them ate rats often while only about one-third rarely eat them. This is a huge problem that needs immediate attention to educate the people in the rural areas as consumption of rats have been shown to be one of the risky behavior associated with the

occurrence and outbreak of Lassa fever disease [9,13-17]. Governments at the three tiers (Federal, State, and Local) must now make conscious effort aimed at increasing serious health enlightenment drives. This should be done in concert with village heads, churches, other non-governmental mosques, and organizations (NGOs). This will ensure that the entire people are actively enlightened against the eating of rats thus reducing contact with rats and subsequently preventing the spread of Lassa virus. As for the association between knowledge of Lassa fever disease and socio-demographic characteristics of respondents; there was a significant statistical association between the trader's knowledge of Lassa fever and their gender as well as educational status. More than a quarter of the respondents with excellent knowledge were males while more female respondents had poor knowledge of Lassa fever compared to the males. This is contrary to a similar study done among rural people in a south-western State in the country where good knowledge was recorded among females than males [13]. This difference may be because males in the south-eastern part of Nigeria are better educated than females mainly due to the male-child education preference by parents which has lingered for years [18]. Male traders are probably more likely to listen to radios than females and therefore, males get more information than their females counterpart. Also having a higher education was associated with good /excellent knowledge of Lassa fever. Respondents with secondary and tertiary education had good and excellent knowledge of Lassa fever respectively. These findings are in keeping with similar studies done in Nigeria [11-13]. There was also a statistically significant association between Lassa fever knowledge and rat consumption pattern among the traders. Majority of the respondents that reported eating rats had poor knowledge of Lassa fever. This calls for an urgent need to reenforce and increase knowledge level on the harmful effect of eating rats among the traders. Determinants of Lassa fever knowledge found in this study were; being a male and having a higher educational level. Having a higher education is in keeping with similar studies [11-13,19].

5. CONCLUSION

The study identified a high level of Lassa fever awareness among the traders. However, this appreciable level of awareness did not culminate in adequate knowledge about the disease. It was also evident from the study that the mass media constituted the most veritable means of Lassa fever information dissemination among these rural dwellers. It is necessary therefore to increase public education especially female education with special emphasis on in-depth education on the etiology, mode of transmission and prevention of Lassa fever and not just creation of awareness of the disease. Health education on Lassa fever should be carried out at ante-natal clinics, immunization clinics, market places, 'August' meetings (which is an annual meeting of women done in the south-eastern part of Nigeria) and everywhere female cohort can be found. This will help reduce the incidence and spread of the disease.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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