ORIGINAL ARTICLE

Characterization of Yellow Fever Suspected Cases and Confirmed Outbreaks in a Southwest State, Nigeria, 2021

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Abstract

Background: Yellow fever (YF) is an acute viral hemorrhagic fever caused by the yellow fever virus and transmitted by Aedes mosquito species. Despite the availability of a very effective vaccine, yellow fever virus (YFV) remains a public health threat across Africa. Enhanced disease surveillance, vector control, and high vaccination coverages are key to the prevention and control of YF. This paper aimed to describe yellow fever surveillance in Ondo state and the outbreak investigation activities conducted in the LGAs where outbreaks occurred in the year 2021.

Methods: This is a retrospective cross-sectional study. We conducted an epidemiological investigation of yellow fever suspected and confirmed cases in Ondo State in Nigeria in 2021, using the YF case-based surveillance data. We described outbreak investigation and response activities carried out in affected LGAs, where the outbreaks were confirmed.

Results: A total of 62 suspected YF cases were reported from January to December 2021, with no record of mortality. More than half (53%) of the cases were between the age of 15 to 29 years. About three-quarter of the reported cases (73%) had received the YF vaccine. The overall attack rate was 1.33 cases per 100,000 population. Only 3 out of the 62 reported cases were confirmed as yellow fever cases.

Conclusion: The resurgence of yellow fever in the state puts the state at high-risk for yellow fever transmission. To reduce the immediate risks to the health of the population, specific activities should be tailored towards increasing awareness on yellow fever transmission, prevention, and control. These include activities on risk communication and community engagement, active surveillance, vector control, strengthening of routine immunization, as well as continued implementation of preventive mass vaccination campaigns.

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Introduction

Yellow fever (YF) is an acute viral hemorrhagic fever caused by the yellow fever virus transmitted by Aedes mosquito species.[1] In Africa, the species of mosquitoes are the *Aedes africanus* in the forest areas and *Aedes aegypti* in urban areas.[2] The acute phase in humans occurs 3 to 6 days after infection. The symptoms vary

from mild illnesses such as flu-like symptoms to the severe illness of fever above 38^0C, jaundice, abdominal pain, vomiting, and bleeding.[3] Fifty percent of cases progress to the severe phase and die within two weeks due to toxic characterization of multiple organs failure and unexplainable bleeding.[3] There is no cure for yellow fever virus infection, so the treatment of cases is essentially supportive.[4] Yellow fever vaccination is the primary prevention for yellow fever incidence.[3] Yellow fever vaccine was first introduced into the national routine immunization schedule in Nigeria in the year 2004; however, since then, YF vaccination coverages have remained suboptimal. These low coverage levels are a consequence of accumulated susceptible, high-risk populations, which can ultimately trigger yellow fever disease outbreaks.[5, 6] In the national routine immunization schedule, the yellow fever vaccine is given to children under the age of 1 year, at 9 months.[7] There are documented gaps in population immunity against YF in Nigeria: the World Health Organization (WHO) and United Nations Children's Fund (UNICEF) estimated the national YF immunization coverage at 54% in 2020, significantly below the recommended 80% threshold necessary to prevent YF outbreaks.[8]

Yellow fever disease is confirmed by laboratory testing using ELISA for YF virus-specific IgM, isolating the virus from blood samples. This is the recommended standard method for the diagnosis of yellow fever.[9] Increased yellow fever transmission and high mosquito vector populations are linked to rapid urbanization, population migration, and climate change, especially in those who have never received yellow fever vaccination.[5] Nigeria, being the most populous country in Africa, is among the 47 countries in the world at risk of yellow fever infection (34 countries in Africa and 13 in Central and South America). Early case detection is essential for the prevention and control of YF and can be accomplished by enhanced disease surveillance, vector control, and high vaccination coverage rates.[10] According to WHO and Nigerian Centers for Disease Control (NCDC), a single suspected case of YF indicates a YF alert threshold. One presumptive positive case constitutes an outbreak alert which should prompt detailed investigation of the case, active case search, and institution of appropriate case management. The outbreak threshold for yellow fever is a single laboratory-confirmed case.[2, 11] As of the end of quarter three in 2021, a total of 1,518 suspected cases of YF were reported from 37 states in Nigeria, including the Federal Capital Territory (FCT) and from 458 LGAs. Nationally, 59 presumptive cases were detected; of them, 39 were confirmed in Institut Pasteur in Dakar (IPD).[12] This paper aims to describe yellow fever surveillance in Ondo state and also describes the outbreak investigation activities conducted in the LGAs where outbreaks occurred in the year 2021, from an epidemiological approach.

Methods

Description of the Area

The study area is Ondo State in the southwestern part of Nigeria. It has a land area of approximately 14,789km^2 and a projected population of 5.5 million persons, based on the 2006 national census population in Nigeria, at a growth rate of 3.0.[13] The state is divided into 18 LGAs and 203 political wards. During the study period, suspected yellow fever cases were reported from 16 out of the 18 LGAs (Figure 1). YF outbreaks occurred in only 2 LGAs- Ondo West, and Akoko Southwest. Ondo West LGA has its headquarters in the town of Ondo, with an area of 970km^2 and a projected population of 368,258. Akoko Southwest LGA, on the other hand, has its headquarters in the town of Oke-Oka. It has an area mass of 226km^2 and a projected population of 455,210. The population in these LGAs consists primarily of farmers, actively involved in agricultural production.[13] There are 48 and 34 government-owned health facilities in Ondo West and Akoko Southwest LGAs, as well as 5 and 15 privately operated facilities, respectively. These health facilities provide routine immunization services and other essential health services.

Study Design

This is a retrospective cross-sectional study. In this investigation, which was conducted from January to December 2021, data from yellow fever case-based surveillance was used. This study included all suspected and confirmed cases of YF reported to the department of disease surveillance and from all LGAs in the State.

Yellow Fever Surveillance

Yellow fever surveillance in Nigeria and in Ondo State is through both passive and active methods. Similar to surveillance for other priority diseases in Nigeria, yellow fever surveillance is conducted at both health facility and community levels. The surveillance network includes both public/government owned and private health facilities.[14] At community level, community informants (CIs) and community focal persons are involved in disease surveillance. These CIs include patent medicine vendors, traditional healers, traditional birth attendants, and village/community leaders amongst others. Ondo state has 622 reporting health facilities and 2,030 community informants across the 203 wards in the State.[14] The health facility surveillance focal persons receive reports regarding all suspected cases of yellow fever as well as other diseases discovered at the HF or in the community. In turn, they alert the LGA Disease Surveillance Notification Officers (DSNOs). Within 24 to 48 hours of disease notification, LGA DSNOs are to investigate these reported cases and collect

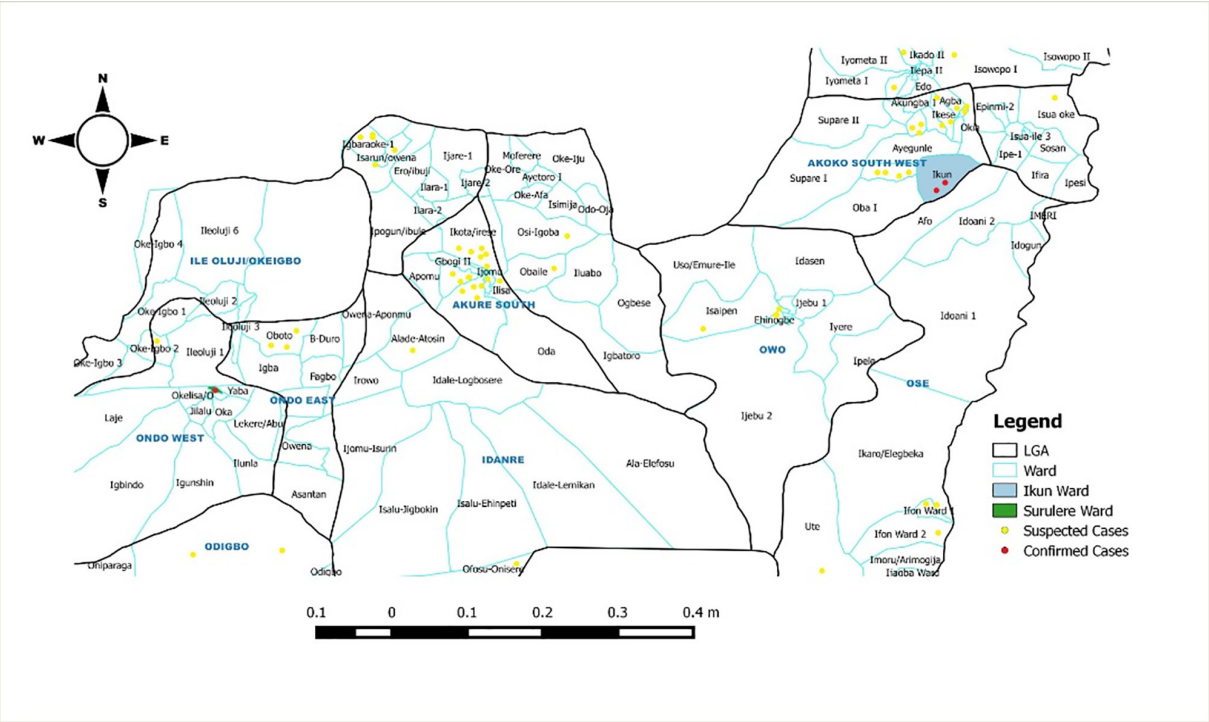

Figure 1: Map showing distribution of suspected and confirmed yellow fever cases in Ondo State, Nigeria, 2021. Map was drawn using QGIS 2.6.

appropriate blood samples for laboratory confirmation. Each case's characteristics and vaccination history are recorded on a paper-based form (IDSR 001A). For laboratory investigation, IDSR 001B is used to record information on the samples taken and the date of sample collection.

Operational Case Definitions
Suspected YF Case

Any person with acute onset of fever, with jaundice appearing within two weeks from the onset of the first symptoms.[11]

Community Case Definition

Any person with fever and yellow eyes or skin (sole of the feet, palms, nails, etc.).[11]

Probable Case

A case moves from suspected to probable when one of the following occurs: the presence of yellow fever IgM antibody in the absence of yellow fever immunization within 30 days before the onset of illness; positive post mortem liver histopathology; epidemiological linkage to a confirmed case or suspected cases during an outbreak.[11]

Confirmed Case

One of the following is observed in the absence of YF immunization within 30 days before the onset of illness: detection of YF-specific IgM; or detection of 4-fold increase between acute & convalescent serum samples in YF IgM or IgG antibody titres; or detection of YF-specific neutralizing antibodies.[11]

Outbreak Investigation Activities

The State received laboratory confirmation reports of two cases of yellow fever, one from Ondo West and one from Akoko Southwest LGAs, from the Central Public Health Laboratory (CPHL), Lagos, Nigeria, on September 22 and October 3, 2021,respectively. Within 24 hours after receiving lab confirmation, outbreak investigation began in accordance with national guidelines. The state epidemiologist, state disease surveillance and notification officers, field epidemiologists, laboratory scientists, public health physicians, and risk communication experts from the state ministry of health and primary health care development agency, including WHO state field office staff, made up the investigation team. Also included were members of the community and the LGA health team, which was led by the primary health care coordinator. An immediate plan was developed to control the outbreak, prioritizing surveillance, laboratory investigations, case management, social mobilization and health education, and the possibility of reactive vaccinations. Several activities were carried out which included advocacy visits to the traditional and community leaders, active case finding in health facilities situated within the affected communities, the settlements where the index cases resided, and contiguous settlements. Household YF vaccination coverage surveys and risk communication/community engagements alongside health workers and members

of the communities were conducted.

The NCDC line-listing template was used to collect all relevant data (age, sex, place of residence, date of onset of symptoms, immunization, migration history, etc.) from the health facilities where the cases were managed with clinical suspicion of yellow fever and to report new or missed cases found. To identify additional cases and ascertain the extent of the outbreak, the team proceeded into the community. This entailed house-to-house active case search for suspected yellow fever cases. A 100-household coverage survey was conducted in the settlements of confirmed cases and in contiguous settlements to determine yellow fever vaccination coverage with evidence of vaccination cards or by history. The community case definition for yellow fever, which is any person with fever and yellow eyes or skin, sole of the feet, palms, nails, etc., was used to detect additional cases within 30 days of the onset of symptoms. A household coverage survey was conducted concurrently with the active case search for additional cases to determine yellow fever vaccination coverage.

Laboratory Investigations

Prior to confirmation of the outbreak, blood samples of 2-5ml were collected from all suspected cases for YF-specific IgM determination at the CPHL and then for confirmation by plaque reduction neutralization test (PRNT) at the regional WHO laboratory in Dakar, Senegal.

Data Analysis

Microsoft Excel version 2021 was employed for the entry of all variables from the paper-based YF line-list and was used to obtain descriptive frequencies and proportions. Quantum Geographic Information system (GIS) was used to geographically map all the cases.

Results

Demographic Characteristics and Clinical History of All Cases

A total of 62 suspected YF cases were reported from January to December 2021. These cases were reported from 36 wards across 16 LGAs in the State. They included Akoko Northeast, Akoko Northwest, Akoko Southeast, Akoko Southwest, Akure North, Akure South, Idanre, Ifedore, Ileoluji/Okeigbo, Irele, Odigbo, Okitipupa, Ondo East, Ondo West, Ose, and Owo. Seventy-four percent of the cases reported were females. More than half (53%) of the cases were between the age of 15 to 29 years, and only 5% were 45 years old and above. About three-quarter of the reported cases (73%) had received the YF vaccine. Only 6% of the cases had no history of vaccination. Twenty one percent (13) of them reported they could not ascertain YF vaccination history (Table 1).

All the 62 (100%) cases reported met the case definition- presenting with fever and jaundice. A few cases also reported headache and fatigue, with no hemorrhagic illness. An equal proportionate distribution of cases was reported from health facilities (50%) and communities (50%). All 31 (100%) cases reported from the health facilities were out-patient cases (Table 1).

There was no record of mortality among the reported cases. Suspected cases were detected and reported all year round with peaks occurring during the rainy season, mostly in the month of July (Figure 2). The first reported case was in the 1st epidemiological week of 2021. In subsequent weeks, there was a gradual increase in cases. The cases peaked at epidemiological weeks 2, 26, 28, and 29. The number of reported cases began to decline from week 30 to the 50th epidemiological week of 2021 (Figure 3). The overall attack rate (case per 100,000 population) at

Table 1: Characteristics of the reported yellow fever cases in Ondo State, 2021

Characteristics	Frequency	Percent
Total reported cases	62	100
Deaths	0	0
Gender		
Male	16	26
Female	46	74
Age (years)		
<5	8	13
5 to 14	9	15
15 to 29	33	53
30 to 44	9	15
>45	3	5
Yellow fever vaccination history		
Zero dose	4	6
1 dose+	45	72
Unknown	13	21
Source of reported cases		
Health facility	31	50
Community	31	50

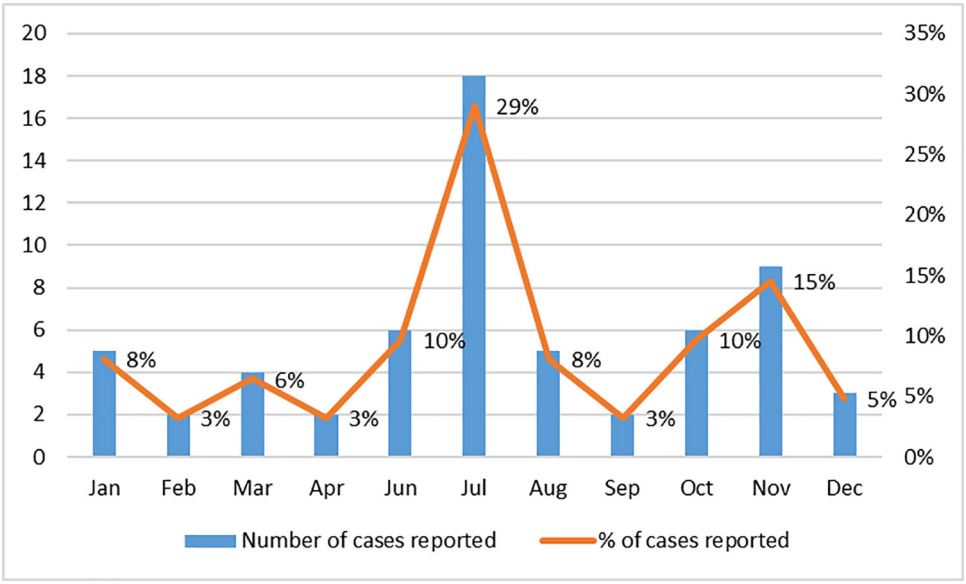

Figure 2: Suspected yellow fever cases reported by themonth of onset, Ondo State, Nigeria, 2021

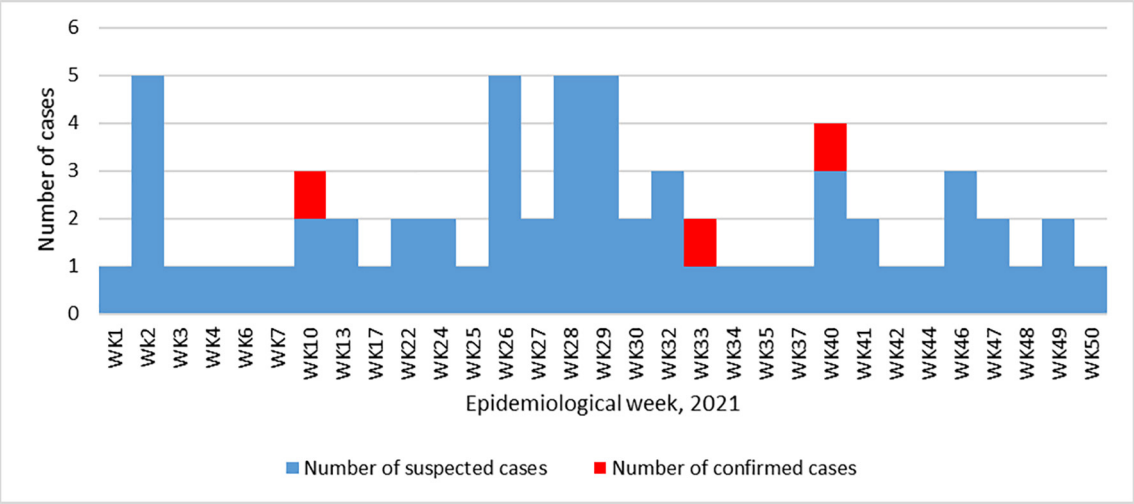

Figure 3: Epi curve of yellow fever cases by the week of onset, Ondo State, Nigeria, 2021

state level was 1.33/ 100,000 persons; however, this varied from 0.23/100,000 people in Ondo West LGA to 3.64/100,000 in Akoko Southwest LGA. The risk of disease transmission was highest in Akoko Southwest, Akure South, and Ondo East LGAs (Table 2).

Laboratory Findings

Blood samples were collected from all the 62 cases for testing. Only 3 cases from 2 LGAs (Ondo West-1 and Akoko Southwest-2) were confirmed positive for yellow fever: one by IgM testing from the national CPHL and two by PRNT at the regional laboratory in Dakar.

Yellow Fever Confirmed Index Case Investigations

On 11th of March 2021, a 30-year-old man (Mr. AS) suspected of yellow fever was reported from Surulere ward of Ondo West LGA. He presented with a history of fever and jaundice. Mr. AS had received YF vaccination during the last preventive yellow fever campaign held in the state in December 2020. This was confirmed through evidence of a vaccination card. He had no travel history two weeks and up to one month before the onset of symptoms. He sought treatment at home, from a relative who was a health worker.

In Akoko Southwest LGA, the index case, a 10-year-old female (Ms. AA) reported to a health facility with presenting complaints of fever and jaundice on the 20th August 2021, with a date of onset of symptoms on the 12th August 2021. She had no vaccination history and did not receive YF vaccination during the phased reactive mass YF campaign in 2019 for the northern senatorial district in the State. She sought treatment from a private clinic where the clinician reported to the LGA DSNO on suspicion of yellow fever. Ms. AA had no travel history outside her place of residence 30 days prior to the onset of symptoms. During a detailed case investigation, a

Table 2: Distribution of suspected yellow fever cases by Local Government Area in Ondo State, 2021

Local Government Area	Female	Male	Total	Population (2021)	Attack rate (cases/100,000)
Akoko Northeast	2	1	3	273,282	1.10
Akoko Northwest	2	1	3	333,081	0.90
Akoko Southeast	1	0	1	128,417	0.78
Akoko Southwest	10	3	13	357,532	3.64
Akure North	1	1	2	205,008	0.98
Akure South	12	3	15	550,291	2.73
Idanre	2	0	2	201,015	0.99
Ifedore	3	2	5	274,712	1.82
Ile Oluji/Okeigbo	1	0	1	269,326	0.37
Irele	0	1	1	226,164	0.44
Odigbo	1	1	2	358,879	0.56
Okitipupa	2	1	3	363,887	0.82
Ondo East	3	0	3	116,471	2.58
Ondo West	0	1	1	441,952	0.23
Ose	4	0	4	225,751	1.77
Owo	2	1	3	341,017	0.88
Total	46	16	62	4,666,785	1.33

Table 3: 100-household YF vaccination coverage survey in Ondo West and Akoko South- west Local Government Areas

Age group	Card only		History		Combine	
	#vacc.	%	#vacc.	%	#vacc.	%
Months	41	47.8%	45	52.3%	86	43.0%
>59 months	32	30.8%	82	78.8%	114	57.0%
Total	73	36.5%	127	63.5%	200	100%

contact, the mother of Ms. AA, was detected. She also did not have any history of YF vaccination (she reported to have traveled during the last reactive YF vaccination campaign).

During yellow fever vaccination coverage surveys conducted in LGAs where outbreaks were confirmed, 86 persons aged 9-59 months old and 114 persons >59 months old were sampled. Among the age group 9-59 months old sampled, 86 (100%) had received yellow fever vaccination; of them, 41 (47.8%) had evidence of vaccination card, while 45 (52.3%) were by history (Table 3). Similarly, among the age group >59 months old, 114 (100%) had received yellow fever vaccination; of them, only 32 (30.8%) had evidence of vaccination card, while 82 (78.8%) were by history. When we combined vaccination card and by history, 200 (100%) cases had received yellow fever vaccination. In total, only 73 (36.5%) had evidence of vaccination card, while 127 (63.5%) were by history (Table 3).

Discussion

This paper describes the characteristics of yellow fever (suspected and confirmed) cases reported and the outbreak of yellow fever in two LGAs in Ondo State, Nigeria in 2021. From January to December 2021, a total of 62 cases of acute febrile illness with Jaundice were reported. The incidence of suspected yellow fever occurred all year round with female preponderance. This finding is surprisingly converse to other studies. A study in Kano,[15] Nigeria, found the majority of YF suspected cases reported among males. Other studies in Brazil and Ethiopia reported similar findings of male preponderance among the reported cases.[16, 17] A study in Zambia[18] found no gender difference among the cases reported. Women may have been infected while engaged in outdoor activities during the day and dusk which are known as peak mosquito biting times.[19] Moreover, women also now engage in activities like farming, hunting, and rearing of animals which also predisposes them to vectors of the disease.

The most affected age groups were between the age of 15 to 29 years old. Persons within this age group are youths and are involved in agrarian activities which may predispose them to the disease.[19] Studies in Kano in Nigeria and in Southwest Ethiopia[15, 20] found that persons between the age group of 15 to 44 years were mostly affected. This is in the same line with our findings when our analysis was aggregated within this same age group. Vaccination against the yellow fever virus is the most effective public health intervention in preventing and controlling epidemics in areas that are endemic for YF.[21] Ondo State implemented a YF reactive mass campaign in the northern part of the state in 2019 and a preventive mass campaign in the southern part of the state in 2020. Yellow fever vaccination status among all reported suspected cases was approximately 72%. Even though this was for the majority of cases reported, this vaccination status is below the expected 80%.[8, 11] Administrative data from January to December 2021, on the District Health Information System 2 (DHIS2), put the state routine

immunization coverage for yellow fever at 74%.[22] This is below the recommended National target of 80%.[11] Akoko Southwest, Akure South, and Ifedore LGAs which had the highest number of cases had Admin YF coverages of 65%, 65%, and 84%, respectively. Ondo West LGA had only one case reported in the year 2021 and was confirmed YF positive. Its administrative YF vaccination coverage was 89%.

Of the 3 laboratory-confirmed yellow fever cases in the state, only 1 subject (from Ondo West LGA) had received the YF vaccine. This clearly depicts a gap in yellow fever vaccination. Suboptimal administrative coverage levels lead to the accumulation of highly susceptible individuals that could trigger outbreaks at any point in time.[8] Conversely, findings from the 100-household YF vaccination coverage survey revealed a good level of YF vaccination among both age groups (9-59 months and >59months) in the communities where the index case resided. However, only 36.5% had evidence of YF vaccination, i.e., the vaccination card. Although the remaining 63.5% of persons surveyed reported to have received YF vaccination either from the last mass vaccination campaign or through the health facility routine vaccination, there was no evidence of vaccination-only via word of mouth. This may corroborate the low administrative vaccination coverage and coverages for cases reported in the state.[22] The very low evidence of vaccination coverage using vaccination cards also highlights the problem of low vaccination card retention. It, thus, reveals a need for continuous sensitization of parents/caregivers and older adults on the importance of keeping vaccination cards. There may be a need for government to also look into interventions to maintain the cards after childhood vaccinations into adulthood and also during supplemental immunization activities.

Active case finding for additional suspected cases of YF was done concurrently during the household coverage surveys. Only one additional case was detected in Akoko Southwest, which was a contact of the index case, suggesting person-person infection. There was an equal proportion in the distribution of reported YF cases from the community and health facility. This further underscores the need to intensify the disease surveillance at community level, expanding the surveillance network for community surveillance focal persons, as well as intensifying health facility-based surveillance. Suspected cases of YF were reported all year round, but with some variations in months. The highest peaks were recorded during the wet season, from June to October 2021. This season is known to be characterized by high amounts of rainfall that facilitate the breeding of mosquitoes.[22, 23] The breeding of the Aedes mosquitoes is more favorable especially in rural areas which have vegetation. People residing in these areas are more predisposed to the mosquitoes bites.[24] This is consistent with the results of the studies conducted in Brazil[25] which found the majority of cases occurring during the wet season with mosquito vectors breeding abundantly during this season. Similarly, a study in Kenya documented the peak of yellow fever vector to be highest during the long raining seasons when compared to other periods.[26] Risk communication and community engagement (RCCE) activities on the risk factors, signs, and symptoms of yellow fever are necessary at the community level. Continuous health promotion on prevention and control measures which includes the elimination of breeding sites for the vector as well as to promote detection and notification of all suspected cases of YF to health facilities are necessary and should be strengthened.[11]

Statewide, the overall attack rate was 1.33 cases per 100,000 population. In the previous year, there was a marginal decrease in cases reported with only one laboratory confirmed case. Larger outbreaks have been documented from northern Uganda and Kenya, with attack rates of 13 and 27.4 cases per 100,000 population, respectively.[21, 27] There was no record of deaths during the outbreak in the State. The case fatality rate measures the quality of clinical care that is premised on timely and definitive diagnosis.[28] The zero deaths could also be possible due to the mild and self-limiting nature of the virus in the majority of infected persons.[29] Another reason may be the fact that ninety-five percent of the cases reported were of a younger age group who were more likely to be healthy. Conversely, there is still a possibility of cases to have severe forms of the disease which may lead to a bad prognosis or death eventually.[29, 30] Our study findings are consistent with those of the study carried out in Kano where no mortalities were recorded, with most of its cases being within the age of 5-44 years.[15]

All the YF cases reported presented with febrile illness and jaundice, with a few cases of headache and fatigue. This was in line with the case definition of suspected YF cases. This may be attributed to heightened awareness of health workers and community informants also known as community-based surveillance focal persons on case definitions following recent training on integrated disease surveillance and reporting. A study in Uganda,[27] however, reported very few (11.6%) YF cases with clinical manifestation of Jaundice. Another outbreak investigation in Sudan also observed that several patients with severe illness were IgM positive showing recent YF virus infection but surprisingly did not meet the case definition.[31] Investigation of the index confirmed cases in Ondo West and Akoko Southwest LGAs also revealed presentation of cases was consistent with febrile illness and jaundice. Both cases had no history of travel outside their communities thirty days prior to the onset of symptoms, neither

did they have a history of travel to forests. This may infer the likelihood of urban transmission and possibly due to the high sylvatic vector population in these communities.[19, 24] Several factors could increase the exposure of persons to sylvatic YF vectors: rainfalls which provide a conducive environment for the propagation of mosquitos in some areas, population migration, rapid urbanization, and increased travel.[24]

Poor community awareness on yellow fever was observed during the outbreak investigation; hence, sensitization was conducted on preventive practices towards yellow fever infection (such as sleeping under mosquito nets which were available in most households visited but not being used, getting rid of stagnant water, and keeping the surrounding environments clean to prevent the vector of the disease). Community members were also sensitized on reporting the suspected cases using community case definition and on the reporting channels. All health workers in all health facilities visited were sensitized on the importance of immediate reporting of suspected yellow fever cases and the need for a high index of suspicion for yellow fever.

A study limitation, based on the study design, is recall bias due to the retrospective nature of the investigation. This may have limited our ability to collect sufficient information correctly from the cases. There might have been underreporting of cases resulting from inaccessible settlements due to issues of insecurity, hard-to-reach areas, and bad terrain. Based on these, it is also likely to have setbacks to the performance of surveillance activities to determine the extent of the YF outbreak. Also, self-reporting of vaccination status, without evidence of vaccination cards, may have led to over-reporting of vaccination status, due to social desirability.

Conclusion

To reduce the immediate risks to the health of the affected population, particularly in relation to the yellow fever outbreaks, specific activities should be tailored to continuous awareness of yellow fever transmission, prevention, and control. Also, supporting communities to adopt safe behaviors through risk communication and community engagement activities. Conduct of active surveillance and referral of persons showing signs and symptoms of yellow fever to health facilities should be heightened. Vector control activities at household and community levels through volunteers and community-led campaigns to destroy the mosquito breeding sites as well as educating the communities on the use of mosquito repellants and fumigation exercises are needed. Also, very critical is boosting the yellow fever coverage through strengthening of routine immunization across all LGAs in the state, but with a focus on high-risk LGAs. The National Primary Health Care Development Agency (NPHCDA) should also continue the implementation of preventive mass vaccination campaigns in line with the Eliminate Yellow Fever Epidemics (EYE) strategy.

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Ethical Consideration

Ethical approval was not obtained as this study was conducted as part of an outbreak response activity.

Conflicts of interest*:* None declared.

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