Determinants of Presumptive Diagnosis of Yellow Fever in Nigeria, July 2017-December 2018

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Abstract

Background: Yellow fever (YF) epidemics have become more frequent in Nigeria since its re-emergence in 2017. Therefore, this study aimed at identifying the context-specific factors associated with the presumptive diagnosis of YF, with a view to strengthening the country's capacity for surveillance and outbreak response. **Materials and Methods:** A cross-sectional analysis of YF surveillance data spanning from July 2017 to December 2018. A presumptive diagnosis of YF was defined as YF virus-specific Immunoglobulin M (IgM) in a suspected case without a history of recent YF vaccination. Multivariable logistic regression analyses were performed to identify factors independently associated with a presumptive diagnosis of YF. Findings were presented using adjusted odds ratios (aOR) and 95% Confidence Intervals (CIs). **Results:** There were 2,057 suspected YF cases during the study period, of which 157 were presumptive positive, including 36 fatalities. Age groups 15-24 (aOR 3.46, 95% CI: 1.49-8.04), 25-34 (aOR 3.10, 95% CI: 1.27-7.53), and 35-44 (aOR 2.96, 95% CI: 1.06-8.25) years, south-south (aOR 4.03, 95% CI: 1.76-9.25), north-west (aOR 3.54, 95% CI: 1.56-8.02) and north-east (aOR 4.25, 95% CI: 1.40-12.84) residency, and presentation with general systemic symptoms (aOR 147.63, 95% CI: 71.21-306.06) significantly increased the odds of presumptive YF diagnosis. In contrast, delay in turnaround time by ≥8 days (aOR 0.28, 95% CI: 0.17-0.46) and presentation with gastrointestinal symptoms (aOR 0.05, 95% CI: 0.01-0.23) significantly decreased the odds of presumptive YF diagnosis. **Conclusion:** This study has identified context-specific factors associated with the presumptive diagnosis of YF in Nigeria, with the potential to strengthen in-country diagnostic capacity, clinical case management and surveillance system, and epidemic preparedness and response.

Keywords: Diagnosis; Nigeria; Outbreak; Presumptive positive; Surveillance; Yellow fever

Received: *10th March, 2023* ***Accepted:*** *1st May, 2023*

Introduction

Despite the availability of a vaccine, Yellow fever (YF) has remained a major public health problem, disproportionately affecting tropical areas of Africa and South America (1). The global burden of YF is estimated at 200,000 cases and 30,000 deaths per year, with more than 90% being accounted for by sub-Saharan African countries (1) . The World Health Organization (WHO) has estimated that 84,000–170,000 severe YF cases and 29,000–60,000 deaths occur annually in sub-Saharan Africa (2) . Moreover, a recent modelling of existing and high-risk infection zones of YF worldwide found Nigeria to be one of the three countries—the other two countries were the Democratic Republic of the Congo and South Sudan—accounting for the highest predicted average annual cases.

These high YF-burden countries were also estimated to record a lower vaccination coverage in 2016 than the recommended threshold to prevent disease outbreaks (3). It is, therefore, no surprise that Nigeria has had successive YF outbreaks since 2017, 21 years after the last confirmed case was recorded in the country (4) . According to Nwachukwu and colleagues, the report of a confirmed YF case in Kwara State by the Nigeria Centre for Disease Control (NCDC) in 2017 prompted the deployment of a Rapid Response Team (RRT) to investigate and initiate response activities (5) . The multi-agency RRT utilised a combination of door-to-door case finding and verbal autopsies to establish the disease transmission, resulting in the conclusion that the outbreak occurred in a non-immune human community, with the presence of the YF vector (5).

The recent surge in YF epidemics in Nigeria and other endemic countries has been linked, in part, to a breakdown in vaccination and vector control measures (1) , and unsafe land-use practices, including farming close to residential dwellings (4) . Also found to be significantly associated with increasing YF transmission in Nigeria is the poor attitude and reluctance of foreign travellers to preventive measures, such as vaccination against the disease, prior to visiting the country (6) . Importantly, recent YF epidemics in endemic countries, including Nigeria, underline a weak surveillance and laboratory capacity, with a deleterious impact on the prompt detection of YF clusters and implementation of control measures (7). Thus, the re-emergence of YF epidemics in Nigeria highlights the need to strengthen relevant components of the health systems and laboratory preparedness and proficiency in order to mitigate these challenges (8) . This is further reiterated in the WHO's initiative to Eliminate Yellow Fever Epidemics (EYE) which identifies surveillance and laboratory systems strengthening as a major prevention and control strategy in YF endemic countries (7); and an in-depth understanding of such context-specific factors posing either as barriers or facilitators to YF transmission will be fundamental to attaining the EYE strategic objectives—protecting at-risk populations, ensuring a ready supply of yellow fever vaccines, building resilience in urban centres, preventing international spread, and rapid containment of outbreaks (9). However, there appears to be a dearth of evidence on the in-country diagnosis of YF and its associated factors in order to inform the development and implementation of appropriate public health interventions. To this end, this study aimed to fill this important research gap by identifying the factors associated with YF diagnosis in the context of recent epidemics in Nigeria.

Materials and Methods

Study design and setting

This was a cross-sectional analysis of YF surveillance data reported across all the Nigerian states, including the Federal Capital Territory (FCT). Nigeria is divided into 36 States and the FCT, which are further sub-divided into 774 LGAs. Although the private health sectors are actively involved in the provision of health care services in Nigeria, the provision of health care and surveillance are primarily a concurrent responsibility of government-owned primary health facilities (under the Local government), secondary hospitals (under the State government) and tertiary hospitals (under the Federal government) (10) . The surveillance of YF and other infectious diseases of public health importance in Nigeria is under the Integrated Disease Surveillance and Response (IDSR) system (11).

Data source

De-identified data on YF was retrieved from the database of the Yellow Fever Technical working group (TWG) of the NCDC, which is a collation of data from the 36 states and FCT in Nigeria from July 2017 to December 2018, both months inclusive.

Yellow fever diagnosis

Serological diagnosis of YF by immunoglobulin M (IgM) is routinely used in Nigeria and formed the basis of diagnosis

in the current study; the assay was performed according to the WHO's interim guidance for yellow fever laboratory diagnosis in an outbreak setting in Africa (12) . Briefly, blood specimens collected from suspected YF cases by experienced phlebotomists in the study health facilities were transported to one of the four national YF diagnostic laboratories, with the choice of a laboratory dependent on the pre-arranged geographic distribution as per the six geopolitical zones in Nigeria. Tests were also carried out in three additional laboratories. To ensure the correct interpretation of diagnostic outcomes, relevant patient information, including age, sex, place of residence, date of symptom onset, YF vaccination status, among others was also recorded and sent alongside the collected specimens. Upon arrival of the specimen at a testing laboratory, YF diagnosis was conducted by enzyme-linked immunosorbent assay (ELISA) to test YFV IgM. As with any IgM test, a positive test was considered presumptive of a recent YF infection (13). For most of the period of the data under review, differential IgM tests were not conducted to rule out potential cross-reactivity between flaviviruses; however, all presumptive positive samples and inconclusive samples from all the testing laboratories were sent to the regional reference laboratory (i.e., Institut Pasteur (IP-Dakar) for confirmation by Plaque Reduction Neutralisation Test (PRNT).

Data management

To address missing data, thereby minimising the occurrence of selection bias, we used the 'missing-indicator' approach to ensure that cases with missing values were not lost during analyses (14) . Furthermore, to minimise false diagnostic outcomes, we restricted the analysed data to cases whose blood specimens were collected ≥3 days after symptom onset and to those who reported being vaccinated against YF ≥30 days (12) . See a flow chart showing the selection processes for the study participants in Figure 1.

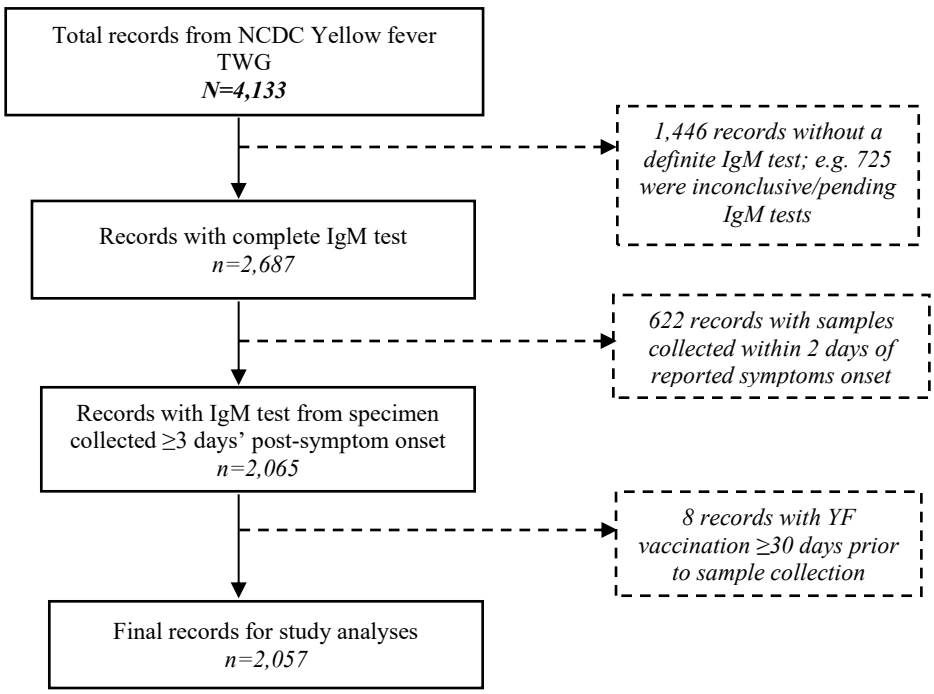

Figure 1. A flow chart of the data selection process and final study population

Definition and classification of key study variables

Outcome variable: A presumptive positive case (yes/no) was defined as a YFV-specific IgM antibody in a suspected case (i.e., any person with acute onset of fever, with jaundice appearing within 14 days of first symptom onset without a history of recent yellow fever vaccination).

Independent variables/covariates: Variables presumed to be potentially associated with YF diagnosis were identified based on biological plausibility and consultations with subject experts. Age group (in years) was based on self-reports by patients/caregivers; and the decision of whether to explore age as a continuous or categorical variable was based on the Likelihood Ratio Test (LRT) *p*-value, which was found to be statistically significant and indicative that age was better modelled as a categorical rather than as a continuous variable. For community setting, LGAs of each reporting state were initially classified either as rural or urban using the population division of the United Nations' definition: an urban area is a settlement with 20,000 or more inhabitants, of which 75% or more are engaged in work other than agriculture, while a rural area is a settlement with fewer than 20,000 inhabitants, of which the majority of the inhabitants are farmers. However, in recognition of the increasing population growth in Nigeria and rapid growth in urbanisation, the initial classifications were further verified by contacting either the Disease Surveillance and Notification Officers (DSNOs) or Epidemiologists of each reporting state. Where there were disparities between the initial classifications and those of the state contacts, the classifications of the latter were adopted as the final community setting, given their in-depth knowledge of each LGA/states. Total laboratory turnaround time (in days) was defined as the difference between the date result was reported by the testing laboratory in Nigeria and the date blood specimen was collected from a YF suspected case; it was classified as a binary variable (≤7 vs ≥8 days) in line with the NCDC's recommendation. The six geopolitical zones and their corresponding states were defined as follows: South-East (Abia, Anambra, Ebonyi, Enugu and Imo); South-South (Akwa-Ibom, Bayelsa, Cross-River, Rivers, Delta and Edo); and South-West (Ekiti, Lagos, Ogun, Ondo, Osun and Oyo); North-Central (Benue, Kogi, Kwara, Nasarawa, Niger, Plateau and Federal Capital Territory); North-West (Jigawa, Kaduna, Kano, Katsina, Kebbi, Sokoto and Zamfara); and North-East (Adamawa, Bauchi, Borno, Gombe, Taraba and Yobe).

Statistical analyses

We decided prior to analysis to drop variables with ≥40% missing data; hence, patient category (inpatient vs outpatient) with 74% missing data and case management location (primary healthcare centre, secondary hospital, tertiary hospital, private clinic, and community/home/chemist) with 94% missing data were excluded from the analysis. For descriptive analyses, binary and categorical variables with respect to YF presumptive diagnosis were described using frequencies and percentages (%). Then, univariable logistic regression was conducted such that the association between each covariate and YF diagnosis was investigated, in turn, and presented as unadjusted odds ratios (ORs) and 95% Confidence Intervals (95% CIs). This was followed by multivariable analyses using a stepwise multiple logistic regression (backward) approach, wherein the association between YF diagnosis and each statistically significant covariate from the univariable analysis was assessed. Here, all the covariates with significant *p*-values (*<0.05*) in the univariable model were included in the multivariable model and were then removed one at a time from the model according to statistical significance (the LRT was used for categorical variables, while Wald's test was used for binary variables), until all of the variables remaining in the model were statistically

significant. The findings were presented as adjusted ORs and 95% CIs. All analyses were conducted using Stata version 13 (StataCorp LP, College Station, TX, USA). This study was written according to the checklists outlined in the Strengthening the Reporting of Observational Studies in Epidemiology.

Ethics

The study protocol was reviewed and approved by the Federal Capital Territory (FCT, Nigeria) Health Research Ethics Committee (Approval Number: FHREC/2019/01/109/18-11-19). In addition, we adhered strictly to the NCDC principles on ethics and ethical considerations (e.g., anonymity, confidentiality, among others) in the conduct of research.

Results

Description of the baseline characteristics of the study population

Between July 2017 and December 2018, there were 2,057 YF suspected cases, of which 157 were presumptive positives by IgM (**Table 1**). The majority of presumptive positive cases (108/157; 68.8%) were recorded in males. The median age of the study population was 14 years (IQR: 6-27), but individuals aged 5-14 years (42/157; 26.8%) and 15-24 years (40/157; 25.5%) accounted for the highest proportions of positive cases. Geographically, residents of the south-south region of Nigeria accounted for the highest proportion (58/157; 36.9%) of positive cases, while residents of the north-east region accounted for the lowest proportion of positive cases with 3.8% (6/157). The majority (120/157; 76.4%) of the blood samples collected from patients for laboratory diagnosis were in adequate quantity; however, the total laboratory turnaround time was generally poor, with almost half (75/157; 47.8%) of presumptive positive cases recording a total turnaround time of 8 days or more. Most of the clinical variables were notably very few, with the exception of general systemic symptoms, which were recorded by half (78/157; 49.7%) of the cases diagnosed as being presumptive positive for YF. There were 36 deaths recorded in the study population during the outbreak period, of which YF presumptive positives accounted for 29 cases.

Factors associated with the presumptive diagnosis of yellow fever

With the exception of reporting year, time from symptom onset to sample collection, and some clinical variables, all the variables in the univariable model were significantly associated with YF diagnosis, although the significance of gastrointestinal symptoms was at borderline (p=0.050) (**Table 2**). Specifically, if a YF suspected case was a male the odds of presumptive diagnosis was almost twice as likely as compared to that of a female counterpart (OR 1.81, 95% CI: 1.28-2.57; $p<0.001$). As age group increased, the odds of a presumptive diagnosis of YF significantly ($p<0.0001$) increased, particularly among cases aged 15-24 years (OR 4.63, 95% CI: 2.21-9.68) and 45-54 years (OR 4.18, 95% CI: 1.43-12.17) when compared with those aged 1-4 years. Residents of urban areas were twice as likely to be diagnosed with presumptive YF as those residing in rural areas (OR 2.21, 95% CI: 1.59-3.08; $p<0.0001$), while residents of other geopolitical zones were significantly more likely to be diagnosed with YF as compared to south-east residents. Presentation with general systemic symptoms (OR 40.70, 95% CI: 26.46-62.59; $p<0.001$) and gastrointestinal symptoms (OR 3.68, 95% CI: 1.00-13.52; p=0.050) also appeared to be significantly associated with increased odds of YF presumptive diagnosis. In contrast, presumptive YF diagnosis during the rainy season (OR 0.62, 95% CI: 0.44-0.86; $p=0.004$) was significantly less likely in comparison to the dry season. A total laboratory turnaround time ≥8 days appeared to significantly ($p<0.0001$) decrease the odds of presumptive YF diagnosis by 64% as compared to ≤7 days (OR 0.36, 95% CI: 0.25-0.51).

Table 1. Distribution of factors associated with Yellow fever in Nigeria, 2017-2018 (N=2,057)

Factor	IgM negative (n=1,900)	IgM positive (n=157)	Total population (n=2,057)	LRT *p*-value
	n (%)	n (%)	n (%)	
Reporting year				
2017	643 (33.84)	55 (35.03)	698 (33.93)	0.762
2018	1,257 (66.16)	102 (64.97)	1,359 (66.07)	
Sex				
Female	857 (45.11)	49 (31.21)	906 (44.04)	0.001
Male	1,043 (54.89)	108 (68.79)	1,151 (55.96)	
Median age (IQR), year	14 (6-27)			
Age group, year				
1-4	357 (18.79)	9 (5.73)	366 (17.79)	<0.001
5-14	596 (31.37)	42 (26.75)	638 (31.02)	
15-24	343 (18.05)	40 (25.48)	383 (18.62)	
25-34	369 (14.16)	24 (15.29)	293 (14.24)	
35-44	151 (7.95)	14 (8.92)	165 (8.02)	
45-54	57 (3.00)	6 (3.82)	63 (3.06)	
55-64	41 (2.16)	4 (2.55)	45 (2.19)	
≥65	23 (1.21)	2 (1.27)	25 (1.22)	
Missing	63 (3.32)	16 (10.19)	79 (3.84)	
Season of start of symptom				
Dry	663 (34.89)	73 (46.50)	736 (35.78)	0.004
Rainy	1,237 (65.11)	84 (53.50)	1,321 (64.22)	
Community setting				
Rural	1159 (61.00)	65 (41.40)	1,224 (59.50)	<0.001
Urban	733 (38.58)	91 (57.96)	824 (40.06)	
Missing	8 (0.42)	1 (0.64)	9 (0.44)	
Geopolitical zone‡				
South-East	437 (23.00)	10 (6.37)	447 (21.73)	<0.001
South-South	253 (13.32)	58 (36.94)	311 (15.12)	
South-West	209 (11.00)	7 (4.46)	216 (10.50)	
North-Central	340 (17.89)	36 (22.93)	376 (18.28)	
North-West	574 (30.21)	40 (25.48)	614 (29.85)	
North-East	87 (4.58)	6 (3.82)	93 (4.52)	
Time from symptom onset to sample collection, days				
3-7	925 (48.68)	68 (43.31)	993 (48.27)	0.265
8-14	619 (32.58)	61 (38.85)	680 (33.06)	
≥15	356 (18.74)	28 (17.83)	384 (18.67)	
Condition of blood specimen on delivery at designated labs				
Adequate	1,737 (91.42)	120 (76.43)	1,857 (90.28)	<0.001
Inadequate	38 (2.00)	1 (0.64)	39 (1.90)	
Missing	125 (6.58)	36 (22.93)	161 (7.83)	
Turnaround time, day				
Within 7	298 (15.68)	62 (39.49)	360 (17.50)	<0.001
≥8	1,010 (53.16)	75 (47.77)	1,085 (52.75)	
Missing	592 (31.16)	20 (12.74)	612 (29.75)	
Self-reported YF vaccination status	986 (51.89)	88 (56.05)	1,074 (52.21)	0.005
Unvaccinated	182 (9.58)	25 (15.92)	207 (10.06)	
Vaccinated	732 (38.53)	44 (28.03)	776 (37.72)	
Missing				
General systemic symptoms*	1,855 (97.63)	79 (50.32)	1,934 (94.02)	<0.001

No	45 (2.37)	78 (49.68)	123 (5.98)	
Yes				
Chest or respiratory symptoms**				
No	1,898 (99.89)	157 (100.00)	2,055 (99.90)	0.684
Yes	2 (0.11)	0 (0.00)	2 (0.10)	
Bleeding symptoms***				
No	1,898 (99.89)	157 (100.00)	2,055 (99.90)	0.684
Yes	2 (0.11)	0 (0.00)	2 (0.10)	
Central nervous system symptoms****				
No	1899 (99.95)	157 (100.00)	2,056 (99.95)	0.774
Yes	1 (0.05)	0 (0.00)	1 (0.05)	
Gastrointestinal symptoms*****				
No	1,890 (99.47)	154 (98.09)	2,044 (99.37)	0.035
Yes	10 (0.53)	3 (1.91)	13 (0.63)	
Clinical outcome				
Alive	1,867 (98.26)	127 (80.89)	1,994 (96.94)	<0.001
Dead	7 (0.37)	29 (18.47)	36 (1.75)	
Missing	26 (1.37)	1 (0.64)	27 (1.31)	

‡: Geopolitical zones comprise the following States:
South-East: Abia, Anambra, Ebonyi, Enugu, and Imo
South-South: Akwa-Ibom, Bayelsa, Cross River, Rivers, Delta, and Edo
South-West: Ekiti, Lagos, Ogun, Ondo, Osun, and Oyo
North-Central: Benue, Kogi, Kwara, Nasarawa, Niger, Plateau, and Abuja (Federal Capital Territory)
North-West: Jigawa, Kaduna, Kano, Katsina, Kebbi, Sokoto, and Zamfara
North-East: Adamawa, Bauchi, Borno, Gombe, Taraba, and Yobe
*=Nausea, jaundice, anorexia, headache, weakness and fever
**=Cough and catarrh
***=Bleeding
****=Convulsion
*****=Abdominal pain, diarrhoea, and vomiting

Table 2. Results of univariable logistic regression analyses assessing the factors associated with Yellow fever

Factor	Unadjusted OR (95% CI)π	P-value (LR test)
Reporting year		
2017	1.00	0.762†
2018	0 .95 (0 .67-1.33)	
Sex		
Female	1.00	0.001†
Male	1.81 (1.28-2.57)	
Age group, year		
1-4	1.00	<0.0001
5-14	2.80 (1.34-5.81)	
15-24	4.63 (2.21-9.68)	
25-34	3.54 (1.62-7.74)	
35-44	3.68 (1.56-8.68)	
45-54	4.18 (1.43-12.17)	
55-64	3.87 (1.14-13.13)	
≥65	3.45 (0 .70-16.90)	
Missing	10.07 (4.27-23.80)	
Season		
Dry	1.00	0.004†
Rainy	0 .62 (0.44-0.86)	
Community setting		
Rural	1.00	<0.0001
Urban	2.21 (1.59-3.08)	
Missing	2.23 (0.27-18.09)	
Geopolitical zone		
South-East	1.00	<0.0001
South-South	10.02 (5.03-19.95)	
South-West	1.46 (0.55-3.90)	
North-Central	4.63 (2.26-9.46)	
North-West	3.05 (1.51-6.16)	
North-East	3.01 (1.07-8.51)	
Time from symptom onset to sample collection, day		
3-7	1.00	0.2723
8-14	1.34 (0.93-1.92)	
≥15	1.07 (0.68-1.69)	
Condition of blood specimen on delivery at labs		
Adequate	1.00	<0.0001
Inadequate	0.38 (0.05-2.80)	
Missing	4.17 (2.75-6.31)	
Test turnaround time, day		
Within 7	1.00	<0.0001
≥8	0.36 (0.25-0.51)	
Missing	0.16 (0.09-0.27)	
Self-reported YF vaccination status		
Unvaccinated	1.00	0.0065
Vaccinated	1.54 (0.96-2.47)	
Missing	0.67 (0.46-0.98)	
General systemic symptoms		
No	1.00	<0.001†
Yes	40.70 (26.46-62.60)	
Chest or respiratory symptoms		
No	*	*
Yes		

Bleeding symptoms	*	*
No		
Yes		
Central nervous system symptoms		
No	*	*
Yes		
Gastrointestinal symptoms		
No	1.00	0.050†
Yes	3.68 (1.00-13.52)	

OR: Odds ratio; CI: Confidence Interval; LR: Likelihood Ratio.
π: Values are unadjusted odds ratios (95% confidence intervals),
†: Wald's *P*-value
*Not possible to calculate odds ratios due to insufficient data.
Significant results are in bold fonts.

The fully adjusted multivariable model suggests that only age groups, geopolitical zone of residence, total laboratory turnaround time, presentation with general systemic symptoms and gastrointestinal symptoms were independently associated with YF presumptive diagnosis (**Table 3**). Compared with children aged 1-4 years, the odds of presumptive YF diagnosis in cases aged 15-24 years (adjusted OR 3.46, 95% CI: 1.49-8.04), 25-34 years (adjusted OR 3.10, 95% CI: 1.27-7.53), and 35-44 years (adjusted OR 2.96, 95% CI: 1.06-8.25) were about three-fold each. Compared with south-eastern residents, residents of south-south region (adjusted OR 4.03, 95% CI: 1.76-9.25), north-west region (adjusted OR 3.54, 95% CI: 1.56-8.02) and north-east region (adjusted OR 4.25, 95% CI: 1.40-12.84) were about four times more likely to be diagnosed with presumptive YF during the outbreak period. If a blood sample of a patient took a total turnaround time of 8 days or more for diagnosis, the odds of YF presumptive diagnosis appeared to decrease by 72% (adjusted OR 0.28, 95% CI: 0.17-0.46, $p<0.0001$). With regards to clinical symptoms, cases who presented with general systemic symptoms were 147.6 times more likely to be diagnosed with YF compared with their counterparts without any of these symptoms (adjusted OR 147.63, 95% CI: 71.21-306.06, $p<0.001$). Whereas, if cases presented with gastrointestinal symptoms, they were significantly less likely to be diagnosed with YF compared with their counterparts without any of these symptoms (adjusted OR 0.05, 95% CI: 0.01-0.23, $p<0.001$), though the direction of this association deviated from that recorded in the univariable model.

Table 3. Results of multivariable logistic regression analyses assessing the factors associated with the odds of Yellow fever

Factor	Adjusted OR (95% CI)¥	*P*-value (LR test)
Sex		
Female	1.00	0.076†
Male	1.49 (0.96-2.32)	
Age group, year		
1-4	1.00	0.0030
5-14	2.03 (0.88-4.70)	
15-24	**3.46 (1.49-8.04)**	
25-34	**3.10 (1.27-7.53)**	
35-44	**2.96 (1.06-8.25)**	
45-54	1.88 (0.48-7.33)	
55-64	1.48 (0.25-8.71)	
≥65	3.85 (0.67-22.06)	
Missing	11.69 (3.78- 36.18)	
Season		
Dry	1.00	0.618†
Rainy	0.89 (0.56-1.41)	
Community setting		
Rural	1.00	0.7685
Urban	1.13 (0.70-1.82)	
Missing	2.25 (0.16-30.76)	
Geopolitical zone		
South-East	1.00	0.0001
South-South	**4.03 (1.76-9.25)**	
South-West	0.96 (0.31-2.98)	
North-Central	1.63 (0.69-3.90)	
North-West	**3.54 (1.56-8.02)**	
North-East	**4.25 (1.40-12.84)**	
Condition of blood specimen on delivery at labs		
Adequate	1.00	0.4732
Inadequate	0.48 (0.06-3.94)	
Missing	1.51 (0.66-3.45)	
Test turnaround time, day		
Within 7	1.00	<0.0001
≥8	**0.28 (0.17-0.46)**	
Missing	0.03 (0.01-0.08)	
Self-reported YF vaccination status		
Unvaccinated	1.00	0.1051
Vaccinated	2.16 (1.08-4.35)	
Missing	1.26 (0.74-2.13)	
General systemic symptoms		
No	1.00	<0.001†
Yes	**147.63 (71.21-306.06)**	
Gastrointestinal symptoms		
No	1.00	<0.001†
Yes	**0.05 (0.01-0.23)**	

OR: Odds ratio; CI: Confidence Interval; LR: Likelihood Ratio.
¥: Values are adjusted odds ratios (95% confidence intervals) for all other variables.
†: Wald's *P*-value
Significant results are in bold fonts.

Discussion

Summary of key findings

For a country with limited diagnostic capacity for yellow fever, our findings are crucial in guiding public health planning and investments in Nigeria. The study found that the odds of a presumptive diagnosis of YF during the July 2017-December 2018 epidemics across Nigeria significantly increased with age groups (15-24, 25-34, and 35-44 years), residency in the south-south, north-west and north-east regions of the country, and presentation with general systemic symptoms; but significantly decreased with a delay in the total laboratory turnaround time by 8 days or more, and presentation with gastrointestinal symptoms.

Interpretation & clinical relevance of key findings

Although YF diagnosis in the current study was presumptive rather than confirmatory, the association between total laboratory turnaround time and its diagnosis during the 2017-2018 epidemics in Nigeria is not supportive of the WHO EYE strategic objective of a faster laboratory network and responses to outbreaks (2). Whilst the exact mechanism for how a delay in the total turnaround time could decrease the odds of YF diagnosis is unclear, the finding might be explained by a number of parameters. First, the use of sample batching in diagnostic laboratories and health facilities could explain the observed finding. Sample batching, often practised to balance efficiencies and minimise wastage of materials, can delay the transportation of blood specimens, thereby prolonging laboratory turnaround time. Additionally, this practice could compromise the integrity of the collected samples and possibly the diagnostic outcomes. Second, prevailing challenges affecting in-country diagnosis of YF, including shortage of accredited laboratories, a dearth of validated commercial assays for diagnosis, frequent interruptions and high cost of reagents and supplies, could contribute to delay in the total turnaround time. For instance, repeated reagent stock out has been demonstrated to be one of the significant reasons for late diagnostic turnaround time (15) . Thus, the current finding could be useful by serving as an evidential-basis for national public health institutions in Nigeria in making a compelling case for more funding and laboratory supplies, being one of the eligible countries for GAVI support for YF diagnosis (16) . Third, unlike Ebola virus disease and Lassa fever, which are considered fatal viral haemorrhagic diseases, the late turnaround time appears to be reflective of public health stakeholders' perception of YF as being a non-threatening disease, as evidenced by the retrospective use of its diagnostic outcomes for surveillance and case management purposes in many endemic settings (13). Overall, this finding underlines the need for in-country laboratories and policymakers to look beyond technical or analytical measures (e.g., diagnostic accuracy) in assessing the quality of diagnostic services and begin to consider other indicators, including diagnostic turnaround time (17) . In the context of epidemics, prompt diagnostic turnaround time is one of the most important parameters for health providers and public health professionals (18).

Geographically, residents of south-south, north-west and north-east regions each had about four-fold increase in the odds of YF diagnosis compared with their counterparts from the south-east region. With respect to the south-south region, a possible explanation for the increased odds of YF diagnosis could be attributable to recent improvements in the surveillance system given the prioritisation of endemic haemorrhagic viral diseases (e.g., Lassa fever) in the region by national public health institutions and partner agencies (19) . However, the fact that most of the national laboratories for YF diagnosis are located outside this region suggests that the observed finding could also be explained by other unknown factors. The increased odds of YF diagnosis in both the north-west and north-east regions of the country is

interesting and possibly be attributable to socio-cultural and security factors, rather than the strength of existing surveillance system. Although in the context of other diseases, evidence suggests that armed conflicts have had a devastating impact on vaccination coverage and impact in north-eastern Nigeria, thus predisposing vulnerable populations in this region at risk of contracting vaccine-preventable diseases (20) . It was therefore not surprising that residents of north-eastern Nigeria where armed conflicts are being perpetuated—predominantly in Borno, Adamawa and Yobe states—by Boko Haram insurgency group recorded increased odds of YF fever diagnosis in the current study. Moreover, although largely in the context of polio eradication, high prevalence of beliefs and misconceptions about vaccines in northern Nigeria have been extensively documented (21–23) . For instance, in assessing the reasons for oral poliovirus vaccine refusals in northern Nigeria, Michael and colleagues (21) found that a substantial number of residents believed that vaccination was either harmful, unsafe, or not necessary. These findings are however an indication of the need for active engagement of community stakeholders (e.g. community and religious leaders) in the formulation and implementation of public health interventions as part of the EYE strategy, especially in northern Nigeria where the odds of YF diagnosis appears high.

Despite the high proportion of insufficient data for many clinical variables (chest or respiratory symptoms, bleeding symptoms, and central nervous system symptoms), which resulted in our inability to assess their association with presumptive YF diagnosis, presentation with general systemic symptoms increased the odds of YF diagnosis as opposed to presentation with gastrointestinal symptoms which decreased the odds of YF diagnosis. These findings are typical of YF outbreaks in Nigeria, as evidenced by the dominance of general systemic symptoms over gastrointestinal symptoms among YF cases in Plateau State (24) and in Borno State (25) . Similar to many arboviruses, age is a significant determinant of susceptibility to YF infection, particularly in children and in the elderly with lowered levels of immunity (26) . However, our findings are a deviation from this trend in that young and mid-aged adult (aged 15-24, 25-34 and 35-44 years) were significantly at a higher risk of being diagnosed with presumptive YF compared with children aged 1-4 years. Susceptibility of these age groups to YF—and consequently increased odds of diagnosis—could be attributable to their tendencies to engage in outdoor activities such as farming and hunting as a means of livelihood rather than their immunological status (26) . Moreover, the increased odds of YF among these age groups could potentially serve as a clue to the YF transmission mechanism during the 2017-2018 epidemics, as the trend suggests a sylvatic and/or intermediate YF transmission. Such evidence will be useful for planning and preparing for epidemic response and risk communication by national public health institutions. Despite statistical significance (p=0.076), the 49% increase in the odds of YF diagnosis in males compared with females further supports our thinking, given the former tend to be more engaged in outdoor activities than the latter in traditional Nigerian settings.

Generalizability of findings

Our findings have the potential to be generalisable to YF transmission in epidemic contexts in Nigeria as the analysed data were collected from all the Nigerian states (including the FCT) and the laboratories under the IDSR system as well as during both the rainy and dry seasons; it is however possible that YF transmission in the current study might have been overestimated by the activation of the Emergency Operation Centre during the outbreak period, which is characterised by active case finding both within and beyond formal health facilities.

Strengths and limitations of the study

To the best of our knowledge, this is the first attempt at systematically identifying the factors associated with the presumptive diagnosis of YF in Nigeria, thus filling an important research gap and providing context-specific evidence for public health planning. We also made deliberate efforts to minimise the occurrence of diagnostic biases by excluding cases from whom blood samples were collected within three days of symptom onset (i.e., minimising occurrence of false negatives) and individuals who reported being vaccinated against YF within 30 days of sample collection (i.e. minimising occurrence of false positives). This study has some limitations that are worth discussing. First, differential diagnosis of YF by PRNT was not done to rule out possible cross-reactions from other flaviviruses (e.g., Zika virus and dengue fever) which have been found to be in circulation in Nigeria (27,28) . Serological cross-reactions between flaviviruses have been well described with sera from patients with YF yielding positive results in assays for other flaviviruses (29) , or sera from patients with other flaviviruses yielding positive results in YF serological assays (30,31) , implying that prior immunity from infection with any flavivirus other than YFV could have resulted in false positives and confounded the specificity of the diagnostic outcomes (32) recorded in this study. Second, a number of variables had a substantial proportion of missing data, even though the missing indicator approach was used to handle such missing data; thus, our findings are potentially susceptible to selection biases irrespective of the data missingness mechanism (33,34), and the need for caution when interpreting the findings is recommended. Nonetheless, our study has underlined the need for relevant public health institutions to adopt appropriate countermeasures to improve the quality and scope of YF surveillance data in Nigeria, while equally reflecting the challenges associated with the use of such datasets for research purposes in developing countries. For instance, the exclusion of patient category (inpatient vs outpatient) from analysis due to missing data meant that we missed the opportunity to assess the potential effect of illness severity on the diagnostic outcome and to evaluate the impact of active case search during response activities (more in outpatients than in inpatients) in the field.

Conclusively, this study has identified context-specific factors associated with the presumptive diagnosis of YF in Nigeria, with the potential to strengthen in-country diagnostics, clinical case management, epidemic preparedness and response, and surveillance system. Public health interventions targeting these factors are therefore recommended. This trend is exemplified by the adoption of a multi-sectoral approach wherein public health and security agencies form an active partnership that could be beneficial in the north-east region of Nigeria given the ongoing armed conflict.

References

1. Mutebi J-P, Barrett ADT. The epidemiology of yellow fever in Africa. Microbes Infect. 2002;4(14):1459–68.
2. World Health Organization. Yellow Fever. WHO Regional Office for Africa. 2019.
3. Shearer FM, Longbottom J, Browne AJ, Pigott DM, Brady OJ, Kraemer MUG, et al. Existing and potential infection risk zones of yellow fever worldwide: a modelling analysis. Lancet Glob Health. 2018;6(3): e270–8.
4. World Health Organization. Yellow fever – Nigeria. WHO. World Health Organization; 2019.
5. Nwachukwu WE, Yusuff H, Nwangwu U, Okon A, Ogunniyi A, Imuetinyan-Clement J, et al. The response to re-emergence of yellow fever in Nigeria, 2017. International Journal of Infectious Diseases. 2020; 92:189–96.

6. Jentes E, Han P, Gershman M, Rao S, LaRocque R, Staples J, et al. Travel characteristics and yellow fever vaccine usage among US Global TravEpiNet travelers visiting countries with risk of yellow fever virus transmission, 2009-2011. Am J Trop Med Hyg. 2013;88(5):954–61.
7. World Health Organization. A global strategy to Eliminate Yellow fever Epidemics 2017–2026. Geneva; 2018.
8. Domingo C, Charrel RN, Schmidt-Chanasit J, Zeller H, Reusken C. Yellow fever in the diagnostics laboratory. Emerg Microbes Infect. 2018;7(1):129.
9. Klitting R, Fischer C, Drexler J, Gould E, Roiz D, Paupy C, et al. What Does the Future Hold for Yellow Fever Virus?. Genes. 2018;9(9):425.
10. Federal Ministry of Health. National Health Facility Survey, 2016: Final Report. Abuja; 2017.
11. Isere EE, Fatiregun AA, Ajayi IO. An overview of disease surveillance and notification system in Nigeria and the roles of clinicians in disease outbreak prevention and control. Niger Med J. 2015;56(3):161–8.
12. World Health Organization. Yellow fever laboratory diagnostic testing in Africa: Interim guidance. Geneva; 2016.
13. Pan American Health Organization. Laboratory Diagnosis of Yellow Fever Virus infection. 2018.
14. Groenwold RHH, White IR, Donders ART, Carpenter JR, Altman DG, Moons KGM. Missing covariate data in clinical research: when and when not to use the missing-indicator method for analysis. CMAJ. 2012;184(11):1265–9.
15. Shiferaw MB, Yismaw G. Magnitude of delayed turnaround time of laboratory results in Amhara Public Health Institute, Bahir Dar, Ethiopia. BMC Health Serv Res. 2019;19(1):240.
16. The Vaccine Alliance (GAVI). Yellow Fever Diagnostics Support Guidelines. 2019.
17. Hawkins RC. Laboratory turnaround time. Clin Biochem Rev. 2007;28(4):179–94.
18. Watts NB. Reproducibility (precision) in alternate site testing. A clinician's perspective. Arch Pathol Lab Med. 1995;119(10):914–7.
19. Ilori EA, Furuse Y, Ipadeola OB, Dan-Nwafor CC, Abubakar A, Womi-Eteng OE, et al. Epidemiologic and Clinical Features of Lassa Fever Outbreak in Nigeria, January 1–May 6, 2018. Emerg Infect Dis. 2019;25(6):1066–74.
20. Sato R. Effect of armed conflict on vaccination: evidence from the Boko haram insurgency in northeastern Nigeria. Confl Health. 2019;13(1):49.
21. Michael CA, Ogbuanu IU, Storms AD, Ohuabunwo CJ, Corkum M, Ashenafi S, et al. An Assessment of the Reasons for Oral Poliovirus Vaccine Refusals in Northern Nigeria. Journal of Infectious Diseases. 2014;210(suppl 1):S125–30.
22. Umeh GC, Nomhwange TI, Shamang AF, Zakari F, Musa AI, Dogo PM, et al. Attitude and subjective wellbeing of non-compliant mothers to childhood oral polio vaccine supplemental immunization in Northern Nigeria. BMC Public Health. 2018;18(1):231.
23. Mohammed A, Sabitu K, Nguku P, Abanida E, Sheidu S, Dalhat M, et al. Characteristics of persons refusing oral polio vaccine during the immunization plus days - Sokoto, Nigeria 2011. Pan Afr Med J. 2014;18:10.
24. Jones EM, Wilson DC. Clinical features of yellow fever cases at Vom Christian Hospital during the 1969 epidemic on the Jos Plateau, Nigeria. Bull World Health Organ. 1972;46(5):653–7.
25. Ekenna O, Chikwem JO, Mohammed I, Durojaiye SO. Epidemic yellow fever in Borno State of Nigeria: characterisation of hospitalised patients. West Afr J Med. 2010;29(2):91–7.
26. Kolawole OM, Adelaiye G, Ogah JI. Emergence and Associated Risk Factors of Vector Borne West Nile Virus Infection in Ilorin, Nigeria. J Arthropod Borne Dis. 2018;12(4):341–50.

27. Mathé P, Egah DZ, Müller JA, Shehu NY, Obishakin ET, Shwe DD, et al. Low Zika virus seroprevalence among pregnant women in North Central Nigeria, 2016. Journal of Clinical Virology. 2018;105:35–40.
28. Herrera BB, Chang CA, Hamel DJ, Mboup S, Ndiaye D, Imade G, et al. Continued Transmission of Zika Virus in Humans in West Africa, 1992–2016. J Infect Dis. 2017;215(10):1546–50.
29. Waggoner JJ, Rojas A, Pinsky BA. Yellow Fever Virus: Diagnostics for a Persistent Arboviral Threat. J Clin Microbiol. 2018;56(10):e00827-18.
30. Allwinn R, Doerr HW, Emmerich P, Schmitz H, Preiser W. Cross-reactivity in flavivirus serology: new implications of an old finding? Med Microbiol Immunol. 2002;190(4):199–202.
31. Koraka P, Zeller H, Niedrig M, Osterhaus ADME, Groen J. Reactivity of serum samples from patients with a flavivirus infection measured by immunofluorescence assay and ELISA. Microbes Infect. 2002;4(12):1209–15.
32. Houghton-Triviño N, Montaña D, Castellanos J. Dengue-yellow fever sera cross-reactivity; challenges for diagnosis. Rev Salud Publica. 2008;10(2):299–307.
33. Donders ART, van der Heijden GJMG, Stijnen T, Moons KGM. Review: A gentle introduction to imputation of missing values. J Clin Epidemiol. 2006;59(10):1087–91.
34. Groenwold RHH, White IR, Donders ART, Carpenter JR, Altman DG, Moons KGM. Missing covariate data in clinical research: when and when not to use the missing-indicator method for analysis. CMAJ. 2012 7;184(11):1265–9.

How to Cite this article: Elimian, K. O., & Jafiya, A. (2023). Determinants of Presumptive Diagnosis of Yellow Fever in Nigeria, July 2017-December 2018. *Journal of Basic and Applied Medical Sciences*, 3(1), 50-64.