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Epidemiology, diagnostics and factors associated with mortality during a cholera epidemic in Nigeria, October 2020–October 2021: a retrospective analysis of national surveillance data

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ABSTRACT

Objectives Nigeria reported an upsurge in cholera cases in October 2020, which then transitioned into a large, disseminated epidemic for most of 2021. This study aimed to describe the epidemiology, diagnostic performance of rapid diagnostic test (RDT) kits and the factors associated with mortality during the epidemic.

Design A retrospective analysis of national surveillance data.

Setting 33 of 37 states (including the Federal Capital Territory) in Nigeria.

Participants Persons who met cholera case definition (a person of any age with acute watery diarrhoea, with or without vomiting) between October 2020 and October 2021 within the Nigeria Centre for Disease Control surveillance data.

Outcome measures Attack rate (AR; per 100 000 persons), case fatality rate (CFR; %) and accuracy of RDT performance compared with culture using area under the receiver operating characteristic curve (AUROC). Additionally, individual factors associated with cholera deaths and hospitalisation were presented as adjusted OR with 95% CIs.

Results Overall, 93 598 cholera cases and 3298 deaths (CFR: 3.5%) were reported across 33 of 37 states in Nigeria within the study period. The proportions of cholera cases were higher in men aged 5–14 years and women aged 25–44 years. The overall AR was 46.5 per 100 000 persons. The North-West region recorded the highest AR with 102 per 100 000. Older age, male gender, residency in the North-Central region and severe dehydration

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The study provided early evidence on the epidemiology, performance of rapid diagnostic test kits and context-specific factors associated with cholera-related deaths amidst the COVID-19 pandemic in Nigeria.
⇒ The study used a national surveillance data set, thereby enhancing the generalisability of the findings to the cholera epidemic in Nigeria.
⇒ Unlike the traditional WHO cholera case definition, the study included children under-5 years, who accounted for about 10% of laboratory-confirmed cholera cases.
⇒ Most suspected cholera cases were not confirmed by laboratory culture or rapid diagnostic test kits, thus increasing the chances of misclassification bias.
⇒ The analysed data had variables (eg, hospitalisation and setting) with a substantial proportion of missing data and lacked useful dates (eg, discharge from a health facility, death and report of laboratory results) information.

significantly increased the odds of cholera deaths. The cholera RDT had excellent diagnostic accuracy (AUROC=0.91; 95% CI 0.87 to 0.96).
Conclusions Cholera remains a serious public health threat in Nigeria with a high mortality rate. Thus, we recommend making RDT kits more widely accessible for improved surveillance and prompt case management across the country.

INTRODUCTION

An estimated 2.8 million cholera cases and 91 000 deaths occur annually in cholera endemic countries.[1] In response to this burden, the Global Task Force on Cholera Control's (GTFCC) roadmap targets a 90% reduction in cholera deaths and cholera elimination in about half of the 47 cholera endemic countries by 2030. Although fewer cholera cases were reported to the WHO during the COVID-19 pandemic in 2020 compared with previous years, 27 countries still reported 323 320 cholera cases and 857 deaths (case fatality rate (CFR) of 0.3%).[2] In 2019, 16 African countries reported 55 087 cholera cases, with a CFR of 1.6%, lower than the 2.0% reported for the region in 2018.[3] While the CFR from the African region has decreased, the opposite has been observed in specific country hotspots, such as a 0.4% increase in Cameroon, 1.2% in Liberia, 2.2% in Benin and 3.5% in Nigeria.[4] Collectively, this suggests that meeting the GTFCC's 2030 targets will require the adaptation of existing control strategies, especially given the significant disruptive threat of the COVID-19 pandemic.

Amidst the COVID-19 pandemic, 10 African countries, including Nigeria-reported cholera cases.[5] In October 2020 and against a background of the COVID-19 pandemic and Lassa Fever outbreak, sporadic cholera cases were reported to the Nigeria Centre for Disease Control (NCDC) by some states in the south-south region of the country. Increased reports of cholera cases by these states and states in the northern region resulted in the implementation of the Incident Management System and subsequent national multisectoral cholera Emergency Operation Centre (EOC) activation on 11 June 2021, with the primary mandate to coordinate preparedness and response activities across the country, predominantly in cholera hotspot areas in the northern region of the country. The NCDC-led cholera EOC is made of the following pillars: water, sanitation and hygiene (WaSH); surveillance and epidemiology; laboratory testing; case management and infection prevention and control; risk communication and community engagement; vaccination and logistics; leadership and coordination and research.

Following on from assessment of the country's preparedness and capacity for response to a cholera epidemic, the EOC identified a deficiency in diagnostics and the resultant impact on surveillance (eg, underestimation of cholera cases), case management (eg, inadequate preparedness of healthcare facilities to handle a surge in patients with cholera) and coordination (eg, difficulty in prepositioning essential commodities for diagnosis and case management). The limited diagnostic capacity was attributed to inadequate laboratory commodities, partly due to limited shelf-life and the unpredictable nature of the cholera epidemic and limited technical capacity in many cholera endemic states to perform cultures for cholera.[6 7] The national EOC addressed this challenge by supplying Crystal VC Rapid Diagnostic Test (RDT) kits (Arkray Healthcare Gujarat, India) to augment diagnosis in cholera-reporting states and those areas classified as cholera hotspots. The choice of Crystal VC RDT over other products was due to its high diagnostic sensitivity[8] and affordability. The assessment/validation of the diagnostic performance of RDT kits against laboratory culture that would be crucial to justifying wider distribution across Nigeria was not done before the demands of an outbreak response. This is pertinent given the poor specificity (59.3%) recorded by an RDT kit in ruling out cholera cases compared with culture during the epidemic from August to September 2017 in Maiduguri, Borno State of Nigeria.[9] In addition, a novel change for cholera surveillance and case management was the assessment and recording of dehydration levels by health workers; this was absent during the previous cholera epidemics[10 11] despite its clinical significance for cholera case management.

The extent to which the COVID-19 pandemic impacted the cholera epidemic in Nigeria and other cholera endemic settings is not entirely understood. On the one hand, the pandemic is believed to have negatively affected healthcare-seeking behaviour and access, reduced laboratory capacity for cholera testing, decreased local and national resources for cholera epidemic investigation, overburdened healthcare systems' capacity to manage cholera patients and reduced the rate of oral cholera vaccination campaigns.[2] On the other hand, COVID-19 preventive measures, such as frequent handwashing and hygiene, are believed to have improved general hygiene in health facilities, while lockdown measures may have decreased cholera transmission.[2]

Furthermore, previous cholera epidemics in Nigeria have been described in the context of fragility mediated by either natural disaster (eg, flooding) and/or armed conflict (eg, Boko Haram insurgency in the North-East).[10–12] This is the first occurrence of a cholera epidemic alongside a pandemic for which there is an NCDC infrastructure for surveillance. In addition, epidemic investigations and analysis of diseases other than COVID-19 and an attempt to understand how the COVID-19 pandemic had impacted other diseases, such as cholera, is of paramount importance. Moreover, given the need to maximise the allocation of scarce resources with competing demands, understanding the factors associated with adverse clinical outcomes is necessary. Therefore, this study aimed to address the following objectives: (1) to describe the epidemiology of cholera in terms of demographics (age and sex), place and time; (2) to assess the performance of cholera diagnostics in terms of coverage, timeliness and accuracy and (3) to identify the sociodemographic and clinical factors associated with cholera-related deaths.

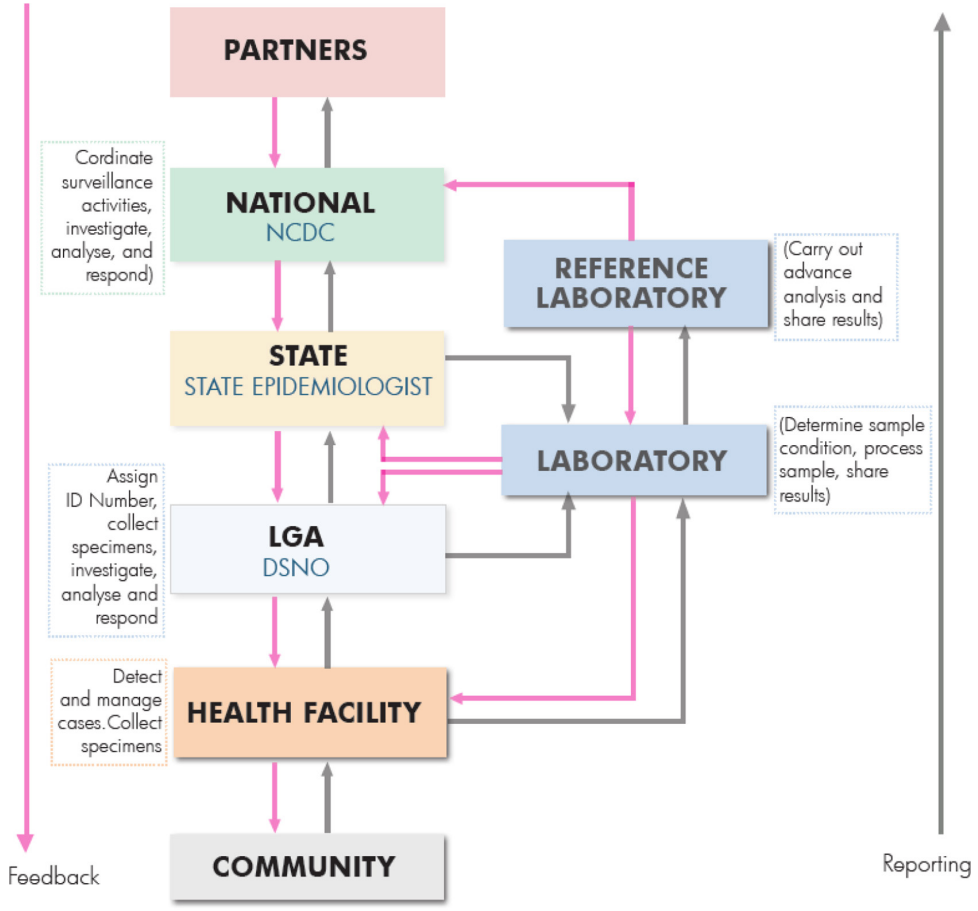


Figure 1 Flow of data within the surveillance system in Nigeria. Source: NCDC Surveillance and Epidemiology Department. Partner refers to the World Health Organization Country Office. DSNO, Disease Surveillance and Notification Officer; LGA, Local Government Area; NCDC, Nigeria Centre for Disease Control.

METHODS

Study design, period and settings

We retrospectively analysed surveillance data submitted by all the cholera-reporting states to the NCDC Surveillance and Epidemiology Department between 12 October 2020 and 25 October 2021. Nigeria comprises 36 states and the Federal Capital Territory (FCT) and is further stratified into 774 local government areas (LGAs) and six geopolitical zones.

Cholera surveillance

Each state and the FCT conduct mandatory surveillance of infectious diseases of public health importance using the Integrated Disease Surveillance and Response (IDSR) strategy.[13] The IDSR strategy is structured to capture surveillance data at all governance levels in Nigeria: LGA, state and federal (see online supplemental file 1) for additional detail on cholera surveillance in Nigeria). Figure 1 provides an overview of information flow as per the IDSR strategy in Nigeria. Additionally, NCDC uses an event-based surveillance (EBS) system to support the conventional surveillance system. The EBS system uses software called Tatafo (meaning 'gossip' in local parlance) for media monitoring of words that connote cholera from over 1250 local media sites and online dailies. These text-mined data are used to plot a time graph to display cholera trends on a daily, weekly and monthly basis as well as display the data graphically on maps.

Study population, cholera case definition and diagnosis

The study population comprised all the persons who met the NCDC definition for a suspected cholera case (herein referred to as cholera cases)[14] : a person aged ≥2 years with severe dehydration or death from acute watery diarrhoea; or during a cholera epidemic, any person with acute watery diarrhoea, with or without vomiting. A confirmed cholera case was defined as a suspected case in which *Vibrio cholerae* O1 or O139 was isolated in the stool by microbiological culture.[15] RDT kits (Crystal VC (Arkray Healthcare, Gujarat, India)) for *V. cholerae* O1 and O139 were used to test for cholera in direct stool samples from persons who met the suspected cholera case definition at health facilities or communities. RDTs were conducted in cholera-reporting states according to the manufacturer's guide. Laboratory culture of the specimen from cholera-reporting states was also performed on a handful of stool specimens to confirm *V. cholerae* according to a standard laboratory protocol.[16] The laboratory culture process involved the transportation of stool specimens using Cary-Blair transport media, linked to the patient's

Table 1 Description of study outcome variables and covariates

Variable	Definition
Attack rate (AR)	Defined as the ratio of cholera cases in a defined area (eg, state) to the estimated population of that area. AR for each reporting state was calculated based on the 2021 estimated population, based on a 3.2% projected growth rate from the 2006 national census results. AR was multiplied by 100 000 to aid the interpretation of small values and comparability of findings with those from other studies.
Case fatality rate (CFR)	Defined as the number of cholera cases who died divided by the total number of cholera cases (alive and dead). CFR was expressed in percentage (%).
Cholera death	Defined as the death of a cholera patient (as per the study case definition). The variable was treated as binary, coded death as '1' and survivor as '0'. A survivor is a cholera case who was not classified as dead by the state surveillance system. Where possible, deaths in the community were reported to the Disease Notification and Surveillance Officers (DSNOs) or health facility managers through community health volunteers or workers and religious leaders or community leaders.
Sensitivity	Measured the ability of an rapid diagnostic test (RDT) kit to correctly identify persons with cholera infection if they were diagnosed by culture. Using culture as a reference or gold standard test in the absence of PCR is a pragmatic approach to assessing an RDT kit's performance for cholera diagnosis.[40]
Specificity	Measured the ability of an RDT kit to correctly identify the persons who do not have cholera if they were diagnosed by culture.
Area under the receiver operating characteristic curve (AUROC)	AUROC measured the overall accuracy of how well an RDT kit predicts cholera by accounting for both sensitivity and specificity. The AUROC value of a screening test with good to excellent diagnostic capacity is closer to 1.00 (>0.70); thus, the AUROC value of 0.5 implies that the diagnostic performance of an RDT kit is no better than chance.
Positive predictive value (PPV)	PPV referred to the proportion of persons who tested positive for cholera, by an RDT kit that had cholera.
Negative predictive value (NPV)	NPV referred to the proportion of persons who tested negative for cholera, by an RDT kit that did not have cholera.

epidemiological data through a unique ID number, from reporting states to the NCDC National Reference Laboratory (NRL) in Abuja for laboratory culture confirmation.

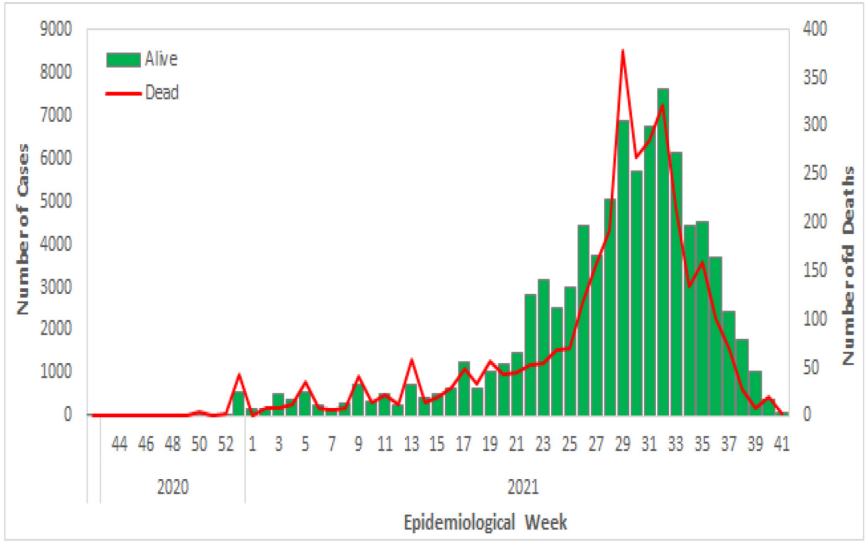
Study duration and data management

Overall, the present study covered weeks 42–53 of 2020 (ie, 12 October 2020 to 3 January 2021) and weeks 1–43 of 2021 (ie, 4 January to 25 October 2021). The definitions of key study variables are outlined in table 1 (see the definitions of demographic, clinical and laboratory time variables in online supplemental file 2). Missing data were handled using the missing-indicator approach, which involved assigning persons with a missing value a specific missing indicator code to ensure that they were not lost during analyses or in fitting models.

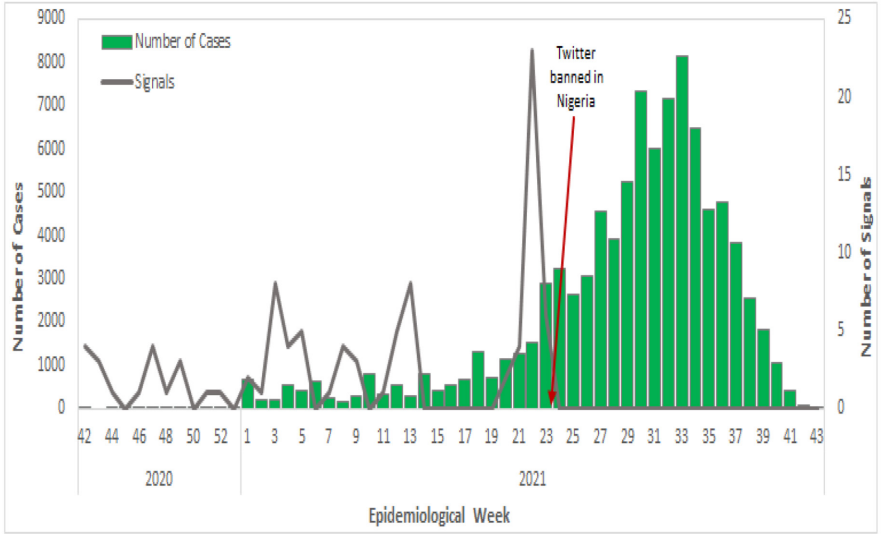
Statistical analyses

All statistical analyses were performed in Stata V.16 (Stata Corp. LP, College Station, Texas, USA). A p value of <0.05 was considered statistically significant. For the first study objective, we used a combination of epidemiological curves (plotted in MS Excel), maps (plotted in QGIS V.3.12.2) and descriptive statistics using frequencies and percentages (%) for binary/categorical variables and mean and SD for normally distributed continuous variables. To assess diagnostic coverage and timeliness, we also used descriptive statistics, including frequency and percentages and median and IQR for non-normally distributed continuous variables. Additionally, we used diagnostic measures of area under the receiver operating characteristic curve (AUROC), sensitivity, specificity, positive predictive value (PPV) and negative predictive value, to describe the diagnostic accuracy of RDT kits compared with a laboratory culture. Findings (excluding AUROC) on diagnostic accuracy were presented as percentages (%) with 95% CI.

To identify the factors associated with cholera death, univariable logistic regression analyses were performed in turn for each outcome variable, presenting the findings as unadjusted ORs and 95% CIs. The selection of covariates for modelling was based on previous research evidence[7 17–19] and availability in the analysed dataset. The unadjusted analyses were followed by multivariable analyses using a stepwise multiple logistic regression to assess the association between the outcome variable and each statistically significant covariate from the unadjusted analyses. Statistical significance was based on p values from the likelihood ratio test for categorical variables and Wald's test for binary variables. Findings from the adjusted model were presented as adjusted ORs (aORs) and 95% CIs. The **S**trengthening The Reporting of OBservational studies in Epidemiology checklist for cross-sectional study was used when writing the report.[17]



A Distribution of cholera cases and deaths by epidemiological week



B Distribution of cholera cases by epidemiological week using conventional surveillance system (green) and digital (Tatafo) event notification system (grey)

Figure 2 Distribution of cholera cases and deaths by epidemiological week and type of surveillance system. (A) Distribution of cholera cases and deaths by epidemiological week. (B) Distribution of cholera cases by epidemiological week using conventional surveillance system (green) and digital (Tatafo) event notification system (grey)

Patient and public involvement

Being an analysis of deidentified secondary dataset, it was not possible to involve patients or the public in the design, or conduct, or reporting or dissemination plans of this study.

RESULTS

A total of 93 598 cholera cases and 3298 deaths were reported by 33 of the 37 Nigerian States (including the FCT) between October 2020 and October 2021.

Description of cholera cases by demographics, time and place

The epidemic curve showing the distribution of cholera cases and deaths is shown in figure 2A. The magnitude of the cholera epidemic is generally high given the persistence of cholera cases and deaths across the reporting weeks of 2020 and 2021. The epidemic's mode of spread appears to be propagated, which possibly started at week 42 of 2020 and gained momentum by the end of 2020 (week 53). Still maintaining the increasing trajectory, the epidemic persistently increased from weeks 1 to 29 of 2021, while cholera deaths and cases reached peak levels at weeks 29 and 32 of 2021, respectively. The epidemic started declining from week 33 to the analysis point for this study.

The distribution patterns of cholera cases by conventional surveillance and EBS are presented in figure 2B. The notification of cholera cases by both surveillance

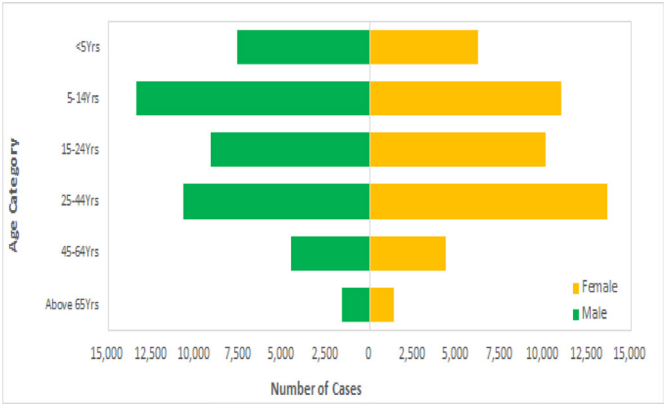


Figure 3 Distribution of cholera cases by age group and gender.

systems spanned between week 42 of 2020 and week 24 of 2021, reaching peak level at week 22 of 2021. However, the EBS notification system did not capture relevant signals between weeks 14 and 19 of 2021 but recorded a corresponding trend as the conventional surveillance system from weeks 20 to 24 of 2021. Cholera notification by the EBS ended abruptly at week 24 of 2021, attributed to the ban of Twitter by the Nigerian government, the major source of data for Tatafo.

Demographics

Men (n=46 722; 50.1%) and women (n=46 596; 49.9%) accounted for similar proportions of cholera cases during the study period (280 missing records on gender not presented). However, each gender had a marked variation in cholera cases by age group, with males aged 5–14 years and women aged 25–44 years accounting for the highest proportions of cases compared with the other age groups (figure 3).

Table 2 summarises the distribution of cholera cases (culture and RDT) by age group and gender. Of the 588 culture test results, 329 (56.0%) were positive for *V. cholerae*, of which the majority (72.4%; 240/329) were from specimens collected from persons aged 5 years or older. The proportions of confirmed *V. cholerae* infection in women and men were similar (41.0% vs 41.9%). Overall, 1,648 RDTs were performed during the study period, of which 1056 (64.1%) tested positive. Like culture, persons aged 5 years or older accounted for a higher proportion of positive RDTs (88.7%; 937/1,056), but men accounted for a higher proportion of positive RDTs than women (52.5% vs 47.4% of 1056).

Place

Bauchi, Kano, Jigawa and Zamfara States accounted for the highest absolute number of cholera cases and deaths during the study period, closely followed by their neighbouring states of Sokoto and Katsina (figure 4). Compared with states in the north, those in the south recorded fewer cholera cases and deaths during the study period.

Cholera ARs and CFRs by state, regional and national

Nationally, the AR across the 33 states was 46.5 per 100 000 persons (table 3). Regionally, the highest ARs were recorded in the North-West (102.1 per 100 000 persons), North-East (87.2 per 100 000 persons), and North-Central (21.4 per 100 000 persons). In the country's southern region, the ARs were as follows: South-South (4.4 per 100 000 persons), South-East (3.0 per 100 000 persons) and South-West (0.8 per 100 000 persons). The national CFR was 3.5%, higher than the CFR recorded in the North-East (2.1%) but lower than the values from the other regions. Regionally, the South-East and South-West recorded the highest and second-highest CFRs at 10.0% and 8.1%, respectively. Individually, Ogun (35.3%) and Ekiti (27.3%) States in the South-West, Kogi (24.5%) and Kwara (17.9%) States in the North-Central and Taraba State (18.5%) in the North-East recorded higher CFRs than the other states. The extent of cholera infection (ie, the number of LGAs affected) and the time spent on diagnosis by each reporting state are summarised in online supplemental file 3).

Table 2 Distribution of confirmed cholera cases by age group and sex

	Culture			RDT*		
	Negative	Positive	Total	Negative	Positive	Total
Variable	n=259 (%)	n=329 (%)	N=588 (%)	n=592 (%)	n=1056 (%)	N=1648 (%)
Age, year						
<5	27 (10.42)	29 (8.81)	56 (9.52)	62 (10.47)	115 (10.89)	177 (10.74)
≥5	162 (62.55)	240 (72.95)	402 (68.37)	524 (88.51)	937 (88.73)	1461 (88.65)
Missing	70 (27.03)	60 (18.24)	130 (22.11)	6 (1.01)	4 (0.38)	10 (0.61)
Sex						
Female	110 (42.47)	135 (41.03)	245 (41.67)	303 (51.18)	501 (47.44)	804 (48.79)
Male	99 (38.22)	138 (41.95)	237 (40.31)	289 (48.82)	554 (52.46)	843 (51.15)
Missing	50 (19.31)	56 (17.02)	106 (18.03)	0 (0.00)	1 (0.09)	1 (0.06)

*It was possible for stool specimen from a person to be tested by both RDT and culture, but with different test outcomes.
RDT, rapid diagnostic test.

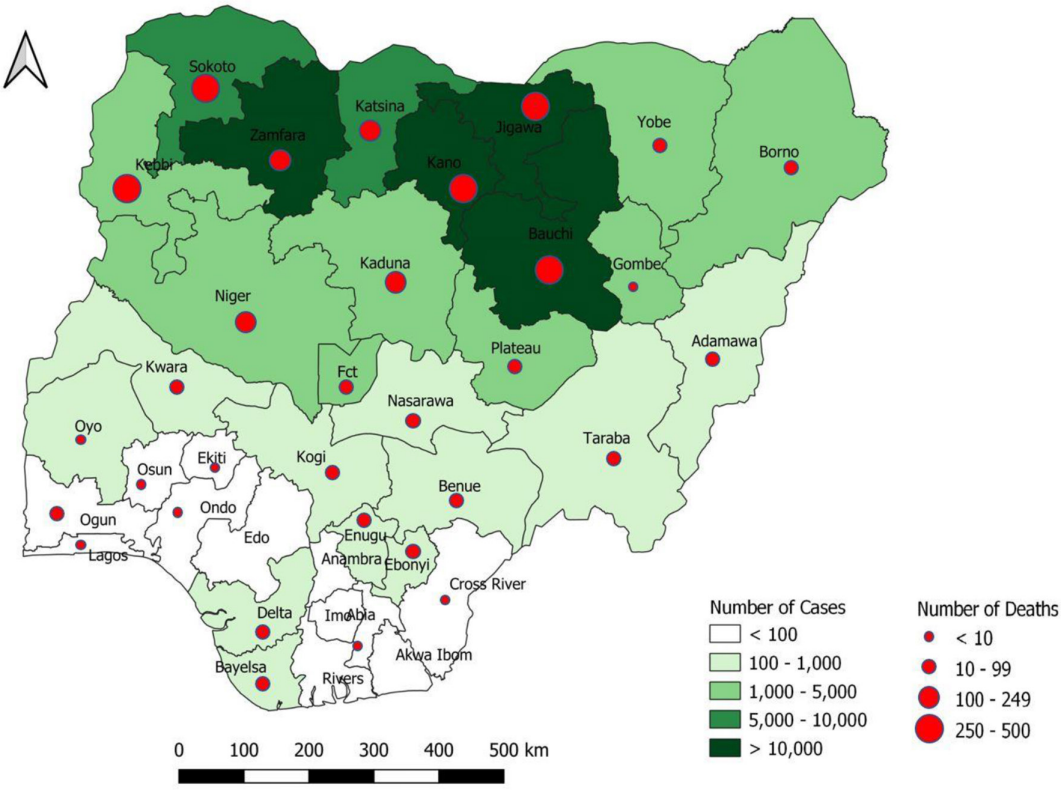


Figure 4 Spatial distribution of cholera cases and deaths on the map of Nigeria.

Cholera diagnostic coverage, timeliness and accuracy

Diagnostic coverage

The number of RDTs (1.8%; 1648/93 598) and laboratory cultures (0.6%; 588/93 598) performed during this study was low (table 4). However, over half of RDTs (64.1%; 1056/1648) and culture (55.9%; 329/588) performed were positive and confirmatory of V. cholerae, respectively. Specifically, Gombe State (15.8%; 167/1056) accounted for the highest proportion of positive RDTs in the North-East (and the entire country); Kaduna State (9.6%; 101/1056) in the North-West; Niger State (4.6%; 48/1056) in the North-Central; Oyo State (0.2%; 2/1056) in South-West and Enugu State (0.7%; 7/1056) in the South-East. Only Bayelsa State (0.3%; 3/1056) had recorded an RDT test in the South-South. Overall, unlike the northern region where only Sokoto State lacked results on RDTs, almost one-third (n=5/13) of southern states lacked RDTs during the study period. Like RDTs, most laboratory culture was conducted on stool specimens from states in the northern region, particularly those in the North-West and North-East. Katsina State (17.9%; 59/329) accounted for the highest proportion of confirmed cholera cases in the North-West (and the entire country); Adamawa State (17.6%; 58/329) in the North-East and Plateau State (9.1%; 30/329) in the North-Central. While scant laboratory results were available for southern states, 5.0% (15/329) of confirmed cholera cases had missing information on the specimen source (ie, state) during the study period.

Diagnostic timeliness

Table 5 describes the days for various time variables relative to laboratory diagnosis during the study period. In general, it took longer to collect and transport stool specimens from cholera-reporting states to NRL than to perform the laboratory culture after specimen arrival. On average, it took 7 days (IQR: 5–10 days) for stool specimens collected at illness onset to arrive at the NRL in Abuja.

Diagnostic accuracy

There were 345 diagnostic results available for both laboratory culture and RDTs, of which 61 and 263 were true positives and true negatives, respectively (see online supplemental file 4). Overall, the diagnostic accuracy of RDTs compared with culture was very high, with an AUROC value of 0.91 (95% CI 0.87 to 0.96), sensitivity of 95.6% and specificity of 87.1%table 6—. The PPV was equally very high at 96.7% (95% CI 93.8 to 98.5%).

Factors associated with cholera-related deaths

The average age of cholera patients who died was 26 years (table 7), and those aged 25–44 years (26.3%; 867/3298) and children aged 5–14 years (22.6%; 746/3298) accounted for the highest and second-highest proportions of cholera deaths. Men accounted for a higher proportion of cholera deaths (55.4%; 1828/3,98) than women (43.6%; 1439/3298). About half of cholera cases (49.8% of 93598) and deaths

Table 3 Cholera attack and case fatality rates by state, region and national, 12 October 2020–25 October 2021

State	2021 projected population*	Total cases, including deaths	AR (per 100,000)	Deaths†	CFR (%)
Nigeria (total)	201 171 425	93 598	46.53	3298	3.52
North-West					
Jigawa	6 677 055	10 763	161.19	470	4.37
Kaduna	9 451 506	2137	22.61	177	8.28
Kano	15 271 374	12 116	79.34	368	3.04
Katsina	9 024 648	8603	95.33	237	2.75
Kebbi	5 119 659	4568	89.22	296	6.48
Sokoto	5 759 804	8455	146.79	410	4.85
Zamfara	5 228 686	11 101	212.31	244	2.20
Total	56 532 732	57 743	102.14	2202	3.81
North-East					
Adamawa	4 864 404	754	15.50	32	4.24
Bauchi	7 721 928	19 453	251.92	323	1.66
Borno	6 854 582	1718	25.06	94	5.47
Gombe	3 775 545	1171	31.02	9	0.77
Taraba	3 501 527	119	3.40	22	18.49
Yobe	3 889 475	3468	89.16	84	2.42
Total	30 607 461	26 683	87.18	564	2.11
North-Central					
Benue	6 573 445	639	9.72	16	2.50
FCT	5 333 851	1286	24.11	77	5.99
Kogi	5 107 776	151	2.96	37	24.50
Kwara	3 694 079	195	5.28	35	17.95
Nasarawa	2 902 922	881	30.35	56	6.36
Niger	6 522 777	2820	43.23	174	6.17
Plateau	4 740 322	1481	31.24	21	1.42
Total	34 875 172	7453	21.37	416	5.58
South-West					
Ekiti	3 768 989	11	0.29	3	27.27
Lagos	14 457 412	78	0.54	5	6.41
Ogun	6 067 254	34	0.56	12	35.29
Ondo	5 361 003	11	0.21	1	9.09
Osun	5 491 238	16	0.29	2	12.50
Oyo	9 233 010	209	2.26	6	2.87
Total	44 378 906	359	0.81	29	8.08
South-East					
Abia	4 226 261	78	1.85	2	2.56
Ebonyi	3 288 945	175	5.32	23	13.14
Enugu	5 074 764	127	2.50	13	10.24
Total	12 589 970	380	3.02	38	10.00
South-South					
Bayelsa	2 615 391	278	10.63	16	5.76
Cross-River	4 435 811	64	1.44	1	1.56
Delta	6 573 684	592	9.01	32	5.41
Rivers	8 562 298	46	0.54	0	0.00
Total	22 187 784	980	4.42	49	5.00

*Projected growth rate of 3.2% for Nigeria in 2021 according to the National Population Commission (total projected population of Nigeria for 2021 is 225,083,708, but 201,171,425 is the value from all cholera-reporting states).
†92,639 total records with clinical outcome (89,341 alive and 3,298 dead).
AR, attack rate; CFR, case fatality rate; FCT, Federal Capital Territory.

Table 4 Coverage of laboratory culture and rapid diagnostic tests by state and region

State	Rapid diagnostic test*		Culture confirmation*	
	Proportion of tests, n (%)	Proportion of positive test†, n (%)	Proportion of tests, n (%)	Proportion of confirmed *V. cholerae*†, n (%)
Nigeria (total)	1648	1056	588	329
North-West				
Jigawa	37 (2.25)	24 (2.27)	40 (6.80)	21 (6.38)
Kaduna	190 (11.53)	101 (9.56)	–	–
Kano	21 (1.27)	20 (1.89)	20 (3.40)	15 (4.56)
Katsina	61 (3.70)	50 (4.73)	106 (18.03)	59 (17.93)
Kebbi	58 (3.52)	43 (4.07)	26 (4.42)	13 (3.95)
Sokoto	–	–	14 (2.38)	6 (1.82)
Zamfara	131 (7.95)	85 (8.05)	44 (7.48)	22 (6.69)
Total	498 (30.22)	323 (30.59)	250	136 (41.34)
North-East				
Adamawa	191 (11.59)	124 (11.74)	78 (13.27)	58 (17.63)
Bauchi	153 (9.28)	103 (9.75)	–	–
Borno	69 (4.19)	63 (5.97)	15 (2.55)	12 (3.65)
Gombe	216 (13.11)	167 (15.81)	62 (10.54)	27 (8.21)
Taraba	11 (0.67)	8 (0.76)	7 (1.19)	5 (1.52)
Yobe	111 (6.74)	86 (8.14)	10 (1.70)	9 (2.74)
Total	751 (45.57)	551 (52.18)	172	111 (33.74)
North-Central				
Benue	19 (1.15)	19 (1.80)	5 (0.85)	0 (0.00)
FCT	29 (1.76)	21 (1.99)	10 (1.70)	6 (1.82)
Kogi	9 (0.55)	7 (0.66)	–	–
Kwara	134 (8.13)	14 (1.33)	–	–
Nasarawa	17 (1.03)	17 (1.61)	15 (2.55)	11 (3.34)
Niger	78 (4.73)	48 (4.55)	66 (11.22)	15 (4.56)
Plateau	76 (4.61)	33 (3.13)	38 (6.46)	30 (9.12)
Total	362 (21.97)	159 (15.06)	134	62 (18.84)
South-West				
Ekiti	2 (0.12)	2 (0.19)	–	–
Lagos	–	–	–	–
Ogun	–	–	–	–
Ondo	4 (0.24)	1 (0.09)	–	–
Osun	2 (0.12)	1 (0.09)	–	–
Oyo	5 (0.30)	2 (0.19)	–	–
Total	13 (0.79)	6 (0.57)	–	–
South-East				
Abia	10 (0.61)	4 (0.38)	1 (0.17)	1 (0.30)
Ebonyi	3 (0.18)	3 (0.28)	–	–
Enugu	7 (0.42)	7 (0.66)	–	–
Total	20 (1.21)	14 (1.33)	1	1 (0.30)
South-South				
Bayelsa	4 (0.24)	3 (0.28)	10 (1.70)	4 (1.22)
Cross-River	–	–	1 (0.17)	0 (0.00)
Delta	–	–	5 (0.85)	0 (0.00)
Rivers	–	–	–	–
Total	4 (0.24)	3 (0.28)	16	4 (1.22)
Missing	NA	NA	1 (0.17)	15 (4.56)

*It was possible for stool specimen from a person to be tested by both RDT and culture, but with different test outcomes.
†Proportion of RDT positive=1056/1648; 64.1%; †Proportion of *V. cholerae* detected by culture=329/588; 56.0%.
NA, not applicable; RDT, rapid diagnostic test.

Table 5 Description of time variables relative to laboratory culture at NRL, Abuja

Time variable	Cholera cases	
	Total cases with data (N)	Median (IQR) number of days
Time from illness onset to specimen collection	134	1 (0–2)
Time from illness onset to sample arrival	193	7 (5–10)
Time from illness onset to sample testing	155	9 (7–10)
Time from sample collection to arrival	222	5 (4–6)
Time from sample arrival to testing	244	1 (1–2)

IQR, Interquartile range; NRL, NCDC National Reference Laboratory in Abuja.

(49.8% of 3298) were hospitalised, though a substantial proportion of persons had missing information on hospitalisation status.

All the variables explored in the univariable model as potentially associated with cholera death were statistically significant. However, apart from season, all the variables remained significantly associated with cholera death in the adjusted model. Compared with children under-5, the odds of cholera death decreased by 13% (aOR 0.87; 95% CI 0.76 to 0.99) in persons aged 15–24 years but increased by 60% (aOR 1.60; 95% CI 1.39 to 1.83) and two-fold (aOR 2.13; 95% CI 1.79 to 2.55) in persons aged 45–64 years and 65 years or over, respectively.

The odds of cholera death remained higher in men than in women (aOR 1.28; 95% CI 1.19 to 1.37). Compared with North-West residents, the odds of cholera deaths were significantly lower in North-East (aOR 0.48; 95% CI 0.43 to 0.54) and South-South (aOR 0.48; 95% CI 0.35 to 0.66) residents, but higher in North-Central (aOR 1.49; 95% CI 1.32 to 1.68) residents. The odds of death in persons who presented with severe dehydration at illness onset (aOR 4.04; 95% CI 2.36 to 9.82) was fourfold higher than in those without dehydration. Being hospitalised was associated with a 61% decrease (aOR 0.39; 95% CI 0.34 to 0.44) in the odds of cholera death relative to no hospitalisation.

DISCUSSION

Summary of key findings

The cholera epidemic in Nigeria between October 2020 and October 2021 is arguably the largest in the documented history of the country, with 93 598 cases and 3298 deaths across 33 of 37 states. Although similar proportions of cholera were recorded in men and women, men aged 5–14 years and women aged 25–44 years were most affected during the epidemic. The national AR and CFR were 46.53 per 100 000 persons and 3.52%, respectively; however, the North-West region recorded the highest AR at 102.14 cases per 100 000 while the South-East recorded the highest CFR at 10.00%. The coverage of RDT and laboratory culture was generally low, although higher in the northern than in the southern region. However, RDT accuracy compared with laboratory culture was excellent, with an AUROC of 0.91 (95% CI 0.87 to 0.96). Age 45 years or older, male gender, residency in the North-Central and severe dehydration were significantly associated with increased odds of deaths during the epidemic.

Interpretation of key findings

Cholera is reaffirmed as a significant marker of inequity that disproportionately affects the poorest populations.[20] Similar to findings of the 2018 Nigerian cholera epidemic,[8] the majority of cholera cases (84 426; 90.20% of 93 598) in the present epidemic occurred in the North-West and North-East, regions where over half of the populations belong to the poor and poorest wealth quintiles.[21] The latest (fourth quarter of 2019 and first quarter of 2020) WaSH survey in Nigeria indicated that access to potable water supply and sanitation services is abysmally poor in these same regions, with the North-East recording the lowest access at 2% in comparison to the South-West with the highest access at 31%.[21] Similarly, the preponderance of cholera cases in rural areas also mirrors the current state of WaSH services in Nigeria, with open defecation, a practice that is a significant driver of recurrent cholera transmission in Nigeria,[18] three times higher in rural areas than in urban areas.[21] While evidence from case-control studies identified poor WaSH conditions (eg,

Table 6 Predictive value of rapid diagnostic test kit as compared with culture (n=345)

Diagnostic test	AUROC value (95% CI)	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)
RDT	0.91 (0.87 to 0.96)	95.6 (92.5 to 97.7)	87.1 (77.0 to 93.9)	96.7 (93.8 to 98.5)	83.6 (73.0 to 91.2)

Calculation of predictive scores required complete observations for both culture and RDT (ie, 345).
AUROC, Area under the reciever operating characteristic curve; NPV, negative predictive value; PPV, positive predictive value ; RDT, rapid diagnostic test.

Table 7 Patients' characteristics in relation to cholera deaths

	Clinical outcome			Odds of cholera-related death			
		Dead	Total cases	Unadjusted OR		Adjusted OR	
Variable	Survivor (n=90 300 (%))	(n=3298 (%))	(n=93 598 (%))	(95% CI)	LRT p-value	(95% CI)	LRT p value
Age (SD), year*	22.01 (17.42)	26.22 (20.28)	22.15 (17.54)				
Age group, year							
<5	13 197 (14.61)	434 (13.16)	13 631 (14.56)	1	<0.0001	1	<0.0001
May-14	23 357 (25.87)	746 (22.62)	24 103 (25.75)	0.97 (0.86 to 1.10)		0.95 (0.84 to 1.07)	
15–24	18 458 (20.44)	532 (16.13)	18 990 (20.29)	0.88 (0.77 to 0.99)		0.87 (0.76 to 0.99)	
25–44	23 220 (25.71)	867 (26.29)	24 087 (25.73)	1.14 (1.01 to 1.28)		1.10 (0.97 to 1.24)	
45–64	8303 (9.19)	461 (13.98)	8764 (9.36)	1.69 (1.48 to 1.93)		1.60 (1.39 to1.83)	
≥65	2732 (3.03)	207 (6.28)	2939 (3.14)	2.30 (1.94 to 2.73)		2.13 (1.79 to 2.55)	
Missing	1033 (1.14)	51 (1.55)	1084 (1.16)†	1.50 (1.12 to 2.02)		1.12 (0.81 to 1.57)	
Sex							
Female	45 157 (50.01)	1439 (43.63)	46 596 (49.78)	1	<0.0001	1	<0.0001
Male	44 894 (49.72)	1828 (55.43)	46 722 (49.92)	1.28 (1.19 to 1.37)		1.28 (1.19 to 1.37)	
Missing	249 (0.28)	31 (0.94)	280 (0.30)‡	3.91 (2.68 to 5.70)		3.65 (2.38 to 5.61)	
Geopolitical zone of residence							
North-West	55 541 (61.51)	2202 (55.77)	57 743 (61.69)	1	<0.0001	1	<0.0001
North-East	26 119 (28.92)	564 (17.10)	26 683 (28.51)	0.54 (0.50 to 0.60)		0.48 (0.43 to 0.54)	
North-Central	7037 (7.79)	416 (12.61)	7453 (7.96)	1.49 (1.34 to 1.66)		1.49 (1.32 to 1.68)	
South-West	330 (0.37)	29 (0.88)	359 (0.38)	2.22 (1.51 to 3.25)		1.47 (0.98 to 2.20)	
South-East	342 (0.38)	38 (1.15)	380 (0.41)	2.80 (2.00 to 3.93)		1.36 (0.95 to 1.96)	
South-South	931 (1.03)	49 (1.49)	980 (1.05)‡	1.33 (0.99 to 1.77)		0.48 (0.35 to 0.66)	
Setting							
Rural	32 851 (36.38)	1485 (45.03)	34 336 (36.68)	1	<0.0001	1	<0.0001
Peri-urban	25 828 (28.60)	957 (29.02)	26 785 (28.62)	0.82 (0.75 to 0.89)		0.81 (0.74 to 0.89)	
Urban	31 621 (35.02)	856 (25.96)	32 477 (34.70)‡	0.60 (0.55 to 0.65)		0.72 (0.66 to 0.79)	
Season							
Rainy	85 098 (94.24)	3067 (93.00)	88 165 (94.20)	1	0.003§	1	0.358§
Dry	5202 (5.76)	231 (7.00)	5433 (5.80)†	1.23 (1.07 to 1.41)		0.93 (0.79 to 1.09)	
Dehydration at illness onset							

Continued

Table 7 Continued

Variable	Clinical outcome			Odds of cholera-related death			
	Survivor (n=90 300 (%))	Dead (n=3298 (%))	Total cases (n=93 598 (%))	Unadjusted OR (95% CI)	LRT p-value	Adjusted OR (95% CI)	LRT p value
No	67 447 (74.69)	2508 (76.05)	69 955 (74.74)	1	<0.0001	1	<0.0001
Low/mild	6019 (6.67)	72 (2.18)	6091 (6.51)	0.32 (0.25 to 0.41)		0.24 (0.18 to 0.30)	
Moderate	13 367 (14.80)	138 (4.18)	13 505 (14.43)	0.28 (0.23 to 0.33)		0.25 (0.21 to 0.30)	
Severe	3467 (3.84)	580 (17.59)	4047 (4.32)‡	4.50 (4.08 to 4.95)		4.04 (3.62 to 4.51)	
Time to health seeking, day							
Same day as illness onset	89 789 (99.43)	3270 (99.15)	93 059 (99.42)	1	0.0002	1	0.0008
1 day after illness onset	463 (0.51)	18 (0.55)	481 (0.51)	1.07 (0.67 to 1.71)		1.54 (0.95 to 2.51)	
Missing	48 (0.05)	10 (0.30)	58 (0.06)‡	5.72 (2.89 to 11.32)		4.81 (2.36 to 9.82)	
Hospitalisation							
No	4904 (5.43)	336 (10.19)	5240 (5.60)	1	<0.0001	1	<0.0001
Yes	44 982 (49.81)	1640 (49.73)	46 622 (49.81)	0.53 (0.47 to 0.60)		0.39 (0.34 to 0.44)	
Missing	40 414 (44.76)	1322 (40.08)	41 736 (44.59)‡	0.48 (0.42 to 0.54)		0.44 (0.39 to 0.51)	

*Based on 92 514 records.
†P value less than 0.05.
‡P value less than 0.001.
§Wald's p value.
LRT, likelihood ratio test; OR, Odds ratio; SD, Standard deviation.

inadequate hand hygiene, contaminated water sources and open defecation) as a significant risk factor for cholera transmission in Nigeria,[19 22–24] there is a distinct gap in knowledge regarding which WaSH interventions are most context-appropriate for cholera control.[25] Thus, we recommend a context-driven investigation to evaluate the array of WaSH interventions in Nigeria, with a particular focus on areas identified as cholera hotspots.

The number of cholera cases recorded within this study period could either be underestimated or overestimated, depending on the influence of the COVID-19 pandemic. Reassigning healthcare workers and resources decreases resources available for other disease surveillance, including cholera, especially in resource-limited settings like Nigeria.[26] Thus, it is possible that the present cholera epidemic started before the earliest reported cases, but detection and report of cholera cases were delayed amidst the surge in COVID-19 cases.[27] Increasing insecurity in cholera hotspots (eg, banditry in the North-West and insurgency in the North-East) in Nigeria may also have contributed to the underestimation of cases. Similarly, in Ethiopia, rising insecurity and the COVID-19 pandemic have hampered the response to the ongoing cholera epidemic, which has already caused around 15 000 cases and 250 deaths.[28] Conversely, the COVID-19 pandemic may have had an unintended positive effect on cholera surveillance in Nigeria. The emergence of COVID-19 resulted in an all-of-government approach to preparedness and response in Nigeria, which came with a massive investment of resources by local and foreign donors in the public health sector. Thus, states' cholera-reporting reluctance, often from fear of economic sanctions and losses,[29] may have decreased due to the expectation of similar support for cholera as for COVID-19 response.

When and where the present cholera epidemic began is unclear with the date of illness onset suggesting Bayelsa and Delta States (South-South) at week 42 and the date of presentation to health facility suggesting Zamfara State at week 42 of 2020. Given that the earliest cholera notifications occurred during the dry season in 2020, the epidemic's origin in the South-South (where a significant proportion of the communities live in riverine areas) seems more likely, especially with evidence from the region identifying the consumption of fish or water from estuarine water bodies as infection sources.[30] In contrast, most cholera epidemics originating from northern Nigeria tend to coincide and peak with periods of heavy rainfall and severe flooding.[31] Nonetheless, the potential origin of cholera epidemic from southern Nigeria implies that cholera interventions, including surveillance and case management, should go beyond the established hotspots in northern Nigeria.

Despite using a similar case definition, cholera cases (n=93 598) and deaths (n=3298) in the present study are much higher than the values reported in 2018 (43 996 cases and 836 deaths)[10] and 2010 (21 111 cases and 784 deaths) in Nigeria.[11] Additionally, more states and geopolitical regions reported cholera cases during the current epidemic than in previous epidemics: 33 states across all the six regions versus 20 states across four regions in 2018 and 18 states across two regions in 2010. While findings in the present study suggest a substantial increase in the magnitude and geographical spread of cholera in Nigeria, the current cholera AR (46.53/100 000 population) is far lower than that of 2018 at 127.43/100 000.[10] The differences in AR could be explained by the fewer number of cholera-affected states in 2018 and the country's increasing population density.

Only a fraction of stool specimens was tested for *V. cholerae* during the present epidemic, despite the importance of accurate laboratory results for effective cholera surveillance, management and prevention. While few laboratory culture tests are deemed sufficient to establish a cholera epidemic,[32] the proportion of tests done in the present epidemic could be reflective of limited capacity in Nigeria and overdependence on the NCDC reference laboratory. Although not a replacement for laboratory culture, RDTs with a sensitivity of at least 90% and a specificity of at least 85% are less prone to false positives and considered a suitable alternative.[33] Compared with laboratory culture, the sensitivity (95.1%) of the Crystal VC test during a cholera epidemic in Maiduguri, Borno State of Nigeria,[9] was similar to that recorded in the present study (95.6%), but substantially lower in terms of specificity (59.3% compared with the 87.1% in our study). A possible reason for the high diagnostic performance, including specificity, of Crystal VC RDT kit in the present epidemic is its predominant usage in the more severe and clinically obvious cholera cases.

Similar to 2010[34 35] and 2018[10] epidemics in Nigeria, the 329 *V. cholerae* isolates in the present epidemic were determined to be O1 Ogawa serotype, suggesting persistence in the serotypic properties of the bacteria in the country. However, the biotype of *V. cholerae* isolates in the current epidemic was not ascertained by the NCDC reference laboratory. From samples collected during the 2010 cholera epidemic in Nigeria, Oyedeji *et al*[34] identified the classical biotype while Dupke *et al*[35] the El Tor biotype, thus making it challenging to infer about the prevailing biotype in the present epidemic. Nonetheless, the El Tor biotype as identified by Dupke *et al*[35] may be more likely, given the identification of multidrug-resistant atypical El Tor strains from samples collected during the same epidemic by Marin *et al*.[36]

The CFR of 3.52% reported for the cholera epidemic is about two times as high as the 1.90% recorded in 2018[10] but lower than the 5.1% in 2010.[11] This could be explained by differences in the denominator population across the various epidemics. Notably, the CFR recorded in the present epidemic is far higher than the WHO-recommended threshold of 1%.[32] This potentially indicates weak health infrastructure and expertise (especially in the context of the COVID-19 pandemic); inadequacy of WaSH services in the health facility and community and weak surveillance systems to trigger a prompt response to the incidents of cholera cases. As noted earlier, the

potential impact of concurrent response to COVID-19 and cholera on the high CFR in the present study needs to be investigated further, especially given the pandemic's significant toll on Nigeria's health workforce and already fragile health system.[37] Regionally, the southern region recorded higher CFRs (5.00% in the South-South and 10.00% in the South-East) than other regions. This could be attributable, in part, to lower ascertainment of cases (denominator population) in the south compared with the north. The high cholera CFR in the South-West (8.08%), for example, could indicate a decrease in cholera surveillance (with emphasis on more severe cholera cases) amidst the high burden of COVID-19 in the region. This is a plausible explanation because Lagos State in the South-West is the epicentre of COVID-19 in Nigeria, given its high population density and busy local and international airports.[27] Compared with the North-West, the decreased risk of cholera-related death in the North-East (aOR 0.48; 95% CI 0.43 to 0.54) is remarkable, despite accounting for the second-highest number of cholera cases in the present epidemic. It appears that the North-East has become adapted to cholera case management and documentation of both milder patients and survivors. This is plausible, given the active presence and engagement of non-governmental organisations, such as Médecins Sans Frontières (MSF), in providing support for cholera case management in the region.

Being 45 years or older was associated with increased odds of cholera death in the present cholera epidemic. Dalhat *et al* postulated that increased risk of cholera death in the elderly might be attributable to neglect, reliance on relatives for care or high burden of comorbidities and malnutrition.[11] These findings would be helpful to frontline healthcare workers in triaging patients with cholera for care during a surge. This is particularly important given the protective effect of hospitalisation (aOR 0.39; 95% CI 0.34 to 0.44). Notably, women aged 25–44 years accounted for the highest cholera cases. This is typically the age when most Nigerian women are married and responsible for providing home care for the sick, including those infected with cholera, cleaning latrines, fetching and handling untreated water and preparing contaminated raw food.[7] While the postulated traditional role of women could enhance their acquisition of immunity to adverse clinical outcomes, such as death, following cholera infection, the reason for the higher odds of cholera death in men over women (aOR 1.28; 95% CI 1.19 to 1.37) remains unclear and warrants further exploration. Furthermore, the higher proportion of cholera cases in male children aged 5–14 years than in the other age groups is in accordance with international pattern.[38] However, while the finding underlines the increased vulnerability of this population to cholera, there remains a dearth of evidence to explain the reasons for these disparities.[38]

The decrease in the risk of cholera-related deaths in patients who presented with a low/mild level of dehydration as compared with those without dehydration could be explained by illness severity or misclassification of dehydration by healthcare workers. It seems that patients with a low/mild level of dehydration were not classified to be seriously at risk of experiencing adverse clinical outcomes, as evidenced by their decreased odds of being hospitalised in the present study (aOR 0.62; 95% CI 0.56 to 0.68). Alternatively, considering our pragmatic assumption in defining dehydration (see table 1), it is possible that the lower odds of death among patients with low/mild dehydration could be a case of wrong assessment. In contrast, patients with severe dehydration had higher odds of death (aOR 4.04; 95% CI 2.36 to 9.82) and hospitalisation (aOR 2.10; 95% CI 1.78 to 2.47) than those without dehydration, reaffirming the clinical significance of severe dehydration for prioritising cholera patients for care.

Study strengths and limitations

Our study provides the initial findings on the epidemiology of cholera in Nigeria in the context of the COVID-19 pandemic and uses data that is reasonably representative of the epidemic in Nigeria. The inclusion of children under-5 years is a strength of the study; children under-5 years—omitted from the WHO cholera case definition—accounted for almost 10% of the 329 laboratory-confirmed cholera cases in the present study. Our study has some limitations that are worth outlining. First, conventional surveillance was not uniform across all cholera-reporting states: most states used only the electronic system (transfer of data from LGA to the state epidemiologist and then to NCDC via email); only some states used a combination of email and real-time notification via SORMAS (Surveillance Outbreak Response Management and Analysis System). This surveillance approach could potentially bias the analysed data regarding surveillance timeliness and coverage if systematic differences existed across cholera-reporting states. It is also worth noting that the deliberate disconnection of the telecommunication system in some northern states (Zamfara and Katsina States in particular), as a security measure, to curb incessant attacks on communities by bandits might have affected the timeliness of the surveillance report. Second, most of the suspected cholera cases in the present study were not confirmed by laboratory culture or RDT, although the approach of testing a few specimens from suspected cases is in line with the WHO testing strategy.[32] However, the number of diagnostic tests (both RDT and laboratory culture) conducted during the cholera epidemic are believed to be suboptimal and could increase the likelihood for cholera cases and cholera-related deaths to have been misclassified for acute watery diarrhoea and associated deaths caused by pathogens other than *V. cholerae*. As well as the fact that watery diarrhoea could be caused by several other enteric pathogens, such as strains of *Escherichia coli*, the potential misclassification bias ensuing from our cholera case definition is crucial for children under-5 years, who are at higher risk of contracting rotavirus infection that is readily preventable

with an effective vaccine.[39] Third, we used CFR to estimate and compare the severity of cholera across states in Nigeria, an estimate that is often suboptimal when the disease is under-reported and dependent on the phase of an epidemic. This is likely for cholera in Nigeria where cholera-reporting states have different testing and public health response (including surveillance) capabilities, especially in northern Nigeria with high level of insecurity. Finally, the analysed data had some variables (eg, hospitalisation and setting with 44.6% and 34.7%, respectively) with a substantial proportion of missing data; and lacking some valuable variables, including occupation and dates of discharge from a health facility, death and report of laboratory results. Thus, SORMAS data quality improvement should be captured in the agenda of the national and state EOC as part of the planned after-action review after the ongoing epidemic.

CONCLUSION

Cholera remains a serious public health threat in Nigeria with a high mortality rate, including in areas previously considered non-hotspot; its burden could be influenced by other health events that can overwhelm existing public and clinical health systems. Thus, we recommend investing in the training of healthcare workers for improved case management and making RDT kits more widely accessible for better surveillance.

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