Author’s response to reviews

Title: Descriptive epidemiology of cholera outbreak in Nigeria, January-November, 2018: Implications for the Global Roadmap Strategy

Authors:
Kelly Osezele Elimian (kellyelimian@gmail.com)
Anwar Musah (a.musah@ucl.ac.uk)
Somto Mezue (mezue.somto@gmail.com)
Oyeronke Oyebanji (oyeronke.oyebanji@ncdc.gov.ng)
Sebastian Yennan (sebastian.yennan@ncdc.gov.ng)
Arisekola Jinadu (kola.jinadu@ncdc.gov.ng)
Nanpring Williams (nanpring.williams@ncdc.gov.ng)
Adesola Ogunleye (Adesola.ogunleye@ncdc.gov.ng)
Ibrahima Soce Fall (socef@who.int)
Michel Yao (yaom@who.int)
Womi-Eteng Eteng (womi.eteng@ncdc.gov.ng)
Patrick Abok (abokp@who.int)
Michael Popoola (micheal.popoola@ncdc.gov.ng)
Martin Chukwuji (chukwujim@who.int)
Linda Haj Omar (hajl@who.int)
Eme Ekeng (eme.ekeng@ncdc.gov.ng)
Thieno Balde (baldet@who.int)
Ibrahim Mamadu (mamadui@who.int)
Ayodele Adeyemo (adeyemo.ayodele@ehealthnigeria.org)
Geoffrey Namara (namarag@who.int)
General response
On behalf of the entire research team, I would like to thank the editorial team and the reviewers for the kind comments, suggestions, questions and, equally important, the opportunity to revise the manuscript for re-submission. In addressing the reviewers’ comments/suggestions, we specified in the revised manuscript the exact page numbers where changes have been made.

Responses to the report by Tawatchai Apidechkul (Reviewer 1)

a. General comment
1. Do health care settings along the study site are having similar capacity in diagnosis for a cholera? (how accuracy of data?)

Thank you for this important question, it would definitely aid the readers to better understand the study contexts as well as interpret the findings. The staff in each study health facility have the relevant training/skills to test for suspected cholera cases using the national case definition and a rapid diagnostic test; however, stool samples are usually transported in Carry-Blair containers to the Nigeria Centre for Disease Control (NCDC) National Reference Laboratory (NRL) in Abuja in order to ensure accurate confirmatory diagnosis, as well as to evaluate the tests being conducted in health facilities. At NRL, laboratory scientists with decades of experience perform confirmatory tests using culture and, in line with the Integrated Disease Surveillance and Response (IDSR) system, provide outcome of the tests to the epidemiological department at NCDC for further transmission to all reporting states and respective health facilities. In an attempt to address the reviewer’s query, we have provided additional texts in the Background section, line 115-120, page 5 (please also see track changes). Overall, we think the analysed data are accurate and reliable.

2. Cases were only those who were reported through a passive surveillance or any active surveillance data included into the analysis?

Thank you for this question. The NCDC uses the IDSR system for its surveillance activities but this has now been emphasised in the background section of the manuscript (please see changes in the Background section, line 119-120 on page 5). As such, cholera cases analysed in this study were recruited on the basis of an active surveillance.

3. Actually, in any descriptive work, all epidemiologist we look for what generated hypotheses from the data eventually. However, I did not see any further ideas on your work. This might be you have not had
what ultimate goal to do this descriptive epidemiology work? If you don't, it is not enough for publication because you cannot present the core or ultimate goal of your descriptive work, and not informative.

Thank you for this interesting comment, as it speaks to the essence or overarching aim of this research work. We used secondary data from the IDSR platform with the aim of assessing how well Nigeria, a country with a substantial burden of cholera, is performing in terms of achieving the Global Roadmap Strategy for cholera elimination by 2030 (as developed by the Global Task Force on Cholera Control (GTFCC) in conjunction with relevant stakeholders including Nigeria). We wanted to assess how the ‘current’ epidemiology of cholera (in terms of person, time, and place) could inform the country’s policies and practices towards achieving the aforementioned goal. Thus, the last paragraph in the background section, specifically line 110-116, underlines the rationale for this study as well as the predefined motive for writing and submitting the manuscript for publication.

As the reviewer rightly noted, surveillance activities globally are not undertaken with research in mind, but that does not hinder epidemiologists and researchers from cleaning, managing and analysing the datasets to address certain research questions. This principle is supported by some of our cited articles: Reference number 3 (lines 414-415), 12 (lines 433 -435), 13 (lines 436-439), and 20 (lines 458-460). Moreover, we discussed the findings mindful of the limitation associated with the use of surveillance data.

Madam/Sir, it may also interest you to note that from personal interactions with colleagues at GTFCC meetings in France, the publication of this study will be useful in informing global measures for Nigeria and countries with similar health profile, particularly those from sub-Sahara Africa.

b. In page no. 5, you used "a suspected cholera was defined as the detection of a cluster of persons aged 2 years or older with acute watery diarrhoea and severe dehydration or dying from acute watery diarrhoea from the same area within one week". This says that not everyone had been confirmed by a laboratory. There might or might not be a "cholera" in all cases. How do you address this point? It may be other causes of diarrhoea?

Many thanks for this important comment/observation; it’s in line with our study rationale as per assessing Nigeria’s preparedness towards achieving the global roadmap goals. As you rightly noted, we highlighted this gap in the cholera case definition and the potential impact it could have on the objective assessment of Nigeria’s progress towards cholera elimination, as well as the difficulty of comparing progress towards cholera elimination with other endemic countries using a different case definition. As part of the study limitation, beginning from line 400, changes have been made to the discussion texts in an attempt to address your comment. Please see the texts from line 400-412 in the discussion section of the manuscript.

It is also worth noting that colleagues from other endemic countries have raised similar question at the GTFCC meeting, and that the case management technical working group of GTFCC is currently working towards addressing this challenge. Thus our finding could further serve as a current evidence in this regard.

c. In page no.6, you start with; "First….". In this point, I as a reader is looking for second, and so on?

Thank you for this observation. The use of ‘First’ has now been deleted such that the sentence is now starting as follows: “Exploratory analysis …”

d. In results section, please split out as the traditional style of descriptive epidemiology "Place, Person, and Time". Then, it would be easy for readers and consisted with mentioned earlier.
Thank you for the recommendation, it is well appreciated. We have split the results into the following sections: Description of the study population, moving texts from lines 211-217 to lines 171-177; person and place; and time (using epidemiological wave). Indeed, the new arrangements make reading easier and consistent with traditional reporting of descriptive epidemiology as suggested by the reviewer.

e. Any difference of those characteristics among waves of outbreaks, it would be useful if you could run some basic statistic such as chi-square test? particularly in data table 4.

Thank you for the recommendations. As recommended by the reviewer, we have conducted another round of statistical analysis using chi-squared test, and included the p-values of association between the selected variables and epidemic waves (waves 1-4) for Table 4; with the exception of sex, all the variables were significantly associated with epidemic wave, which we have now highlighted using symbols (due to space): †=p-value <0.001; NS= not Significant (p-value=0.106). Furthermore, in consideration of the reviewer’s implicit recommendation, we have included an additional column for the total number of cases with a view to making the interpretation of results easier.

f. In discussion section, any limitation from the study?

Thank you for the question. Yes, lines 396 to 418 in the discussion section of the manuscript underlined two important limitations of the study. But based on your question, we have decided to use a subheading to buttress both the study strengths and limitation sections as shown in line 382, making the identification of key sections easier for readers.

Responses to the report by Asrat Genet Amnie, MD, MPH, EdD (Reviewer 2)

I commend the authors for their study of Cholera Epidemic in Nigeria. However, the manuscript needs a major review on multiple levels.

Many thanks for your commendation and the opportunity to address your comments/questions, which we believe will significantly enhance the overall quality of the study.

-The background needs to be expanded to provide historical, social, epidemiological, and environmental trends in the prevention and control of cholera and any advances (the use/effectiveness of vaccines) in the control and prevention of cholera in Nigeria or at the global level.

Thank you for the suggestion, its implementation will definitely enrich the background section of the manuscript, as well as put the findings and discussion in a better perspective. Based on the reviewer’s recommendation, additional texts and editing have been included to the background section of the manuscript:

Lines 78-88: a historical view of cholera outbreaks in Nigeria was presented, underlining the high case fatalities as needed.

Lines 95-101: An overview of the introduction of oral cholera vaccines in Nigeria was presented, and the paragraph ended with the need for a more robust preventive and control measures, of which findings from this study sought to provide the current evidential-basis for as outlined in the last paragraph of the background section (lines 129-136).

-Research Methods, sampling and Statistical Analysis: What is the purpose and the goal of the study? What parameters qualify this report as a well-designed study? What is/are the research question(s)?
We are grateful for your comments and passion to see that the manuscript shows fundamental components of a standard research. In the background section of the manuscript, specifically lines 129-136, we underlined the study purpose/goal, which is to provide the evidential-basis for public health planning and interventions aimed at actualising the global roadmap goals – reducing deaths from cholera by 90% by 2030. However, we are extremely grateful to the reviewer’s question as it informed the editing of the paragraph, including the additional texts. The specific research question was (although implicitly stated): What is the current epidemiology of cholera in Nigeria? We also made an attempt to explain the potential public health and clinical implications of the findings in the discussion section of the manuscript.

Regarding the parameters that qualify the manuscript as a well-designed study, we would like to justify the research work by making reference to the completed STROBE guidelines (please see Additional File 2 for details), which is an indicator for assessing the standard of an observational epidemiological study, such as ours. Additionally, we attempted to explain the findings in the context a background, methods, results, discussion and conclusion, especially making references to current global efforts towards cholera elimination in endemic countries.

What is presented as statistical analysis does not measure up to acceptable standards. For example, the use of a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram tool used in Systematic Reviews and Meta-Analysis studies has no place in retrospective studies such as used in this study (see page 5 of the manuscript). The final sample size after data cleaning should be used, the flow diagram does not add any value.

Thank you for the comment, it’s well valued by the research team. However, in line with the STROBE guidelines (please see item number 10 in the Additional File 2 containing the completed STROBE guide), we wanted to underline how the final sample size used for statistical analyses was arrived at including the reasons for excluding some observations. In line with global best practices, we believe the flow chart would be useful in guiding other researchers in replicating or verifying the study using the same dataset from the same source. Thanks to the reviewer’s point, we have included the study period in the Figure title in order to prevent any ambiguity as per study duration.

In contrast to the reviewer’s suggestion, however, we did not attempt to use the PRISMA guide in this study, rather we used a flow chart showing the selection process of data used in the current study. Furthermore, we think that the statistical analyses outlined in the current study are in harmony with the specific study objectives. Lastly, we think that using frequencies and percentages and that using attack rates and case fatality rates (including their definitions) by person, place and time is appropriate for a descriptive study as underlined in the study title and specific objective; and useful to the Nigerian public health sector in planning measures aimed at actualising the global roadmap strategic goal of cholera elimination.

The results need to describe any novel approaches used in the investigation of the epidemic; or provide evidence that expands our understanding on best experiences and best practices in the control and prevention of cholera epidemic in Nigeria. The results lack any inferential evidence generated as a result of the statistical analysis. This manuscript is more of a routine activity report of a cholera epidemic and control efforts in Nigeria rather than a scientific research.

Thank you for the comments and observation over the novelty of our adopted research analysis. Similar to the study by Camacho and associates published in the Lancet Global Health (reference number 27), we described the distribution of cholera cases in terms of time by epidemiological wave, which is more informative than the previous studies reported in Nigeria by Dalhat and colleagues (reference number 20). Additionally, to the best of our knowledge, spatial representation of cholera attack rates and case
fatality rates in Figure 3 is worth noting as none of the previous studies on cholera in Nigeria used this approach.

Because the specific objective of this study was neither to explore an association between variables nor test any predefined hypothesis, we did not see the need to adopt additional statistical approaches (e.g. multivariable logistic regression) to provide inferential evidence as suggested by the reviewer; however, we did make inferences in terms of the potential influence of armed conflict as perpetuated by Boko Haram insurgency activities in the north-east region of Nigeria, as well as the potential impact of recent surge in flooding in north central Nigeria on the observed cholera cases. Importantly, we noted in the discussion section of the need for the NCDC (the Nigeria public health agency) to extend its collaborative and partnership activities aimed at cholera prevention and control.

As per the manuscript being a routine report or a research piece, we strongly believe this to be a research work with a clear rationale, predefined objectives, clear methodology and findings, and appropriate interpretations of findings. We would also like to refer to the STROBE guidelines (Additional File 2) wherein the majority of essential items required in an observation study as ours were ticked.

The study does not expand our understanding of cholera epidemic and control; nor provide any new evidence that could be used in strategic public health interventions or influence public health policy or decision making.

Thank you for the comments and the emphasis on the need of the findings to expand knowledge of cholera and appropriate public health planning. Nonetheless, an extensive review of the literature by the research team suggests that there is dearth of evidence on the impact of armed conflict on cholera transmission, as evidenced by two studies in Yemen and Liberia (lines 320 in the discussion session). We think therefore that discussion of our findings as well as findings from another of our paper where conflict was significantly associated with increased odds of cholera death, are adding value to the scant evidence; and that current findings would be valuable in a future systematic review or a scoping review with a focus on the association between armed conflict and cholera transmission. Regarding policy and practice, the current findings, particularly the potential influence of armed conflict, flooding and religious festivals on cholera transmission, have begun to reshape how the Nigeria Centre for Disease Control (NCDC) and partners (e.g. WHO, UNICEF, MSF among others) design and implement public health activities such as surveillance and oral cholera vaccination campaigns. For example, the NCDC, the national public health agency with the mandate of disease prevention and control in Nigeria, has started reviewing its guidelines on collaboration with public health stakeholders, with one of the goals being active engagement with religious leaders and armed forces. While this may sound normal in other contexts, it is relatively new in Nigeria –a review of the findings in the current study by the NCDC research unit is instrumental in this revolution.

Rather than rely solely on the 2014 study by Dalhat et el published in the BMC Public Health with a focus on the epidemiological profile of the 2010 cholera outbreak in Nigeria and NCDC situation reports, we believe that findings from this study will be more relevant by providing current indicators for monitoring the national strategic plans towards cholera elimination by 2030. Moreover, should this manuscript be accepted, the findings will be strategic in the estimation of global cholera burden by researchers all over the world given the global reputation of articles published in BMC Public Health.

Final remarks for both reviewers
We are very pleased with and thankful for your comments, questions and suggestions –addressing them have indeed further enriched the scientific quality of the manuscript. Overall, we believe that this is an original piece of research and that there is sufficient justification that it would contribute substantially to the clinical literature in epidemiology, as well as public health policy and practice in Nigeria and
possibly similar endemic countries. The statistical approach leant very well to the study specific objectives, which was essential to arriving at the conclusions and understanding the prevailing drivers of cholera transmission in Nigeria.