PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Impact of political conflict on tuberculosis notifications in North East
	Nigeria, Adamawa State: a seven-year retrospective analysis
AUTHORS	Pembi, Emmanuel; John, Stephen; Dumre, Shyam; Usman,
	Ahmadu; Vuong, Nguyen; Ebied, Amr; Mizukami, Shusaku; Huy,
	Nguyen; Cuevas, LE; Hirayama, K

VERSION 1 - REVIEW

REVIEWER	James Mancuso
	USUHS, USA
REVIEW RETURNED	09-Dec-2019

GENERAL COMMENTS	Overall a nicely written paper which is very simple and clear. It would benefit further from: 1) use of rates rather than counts, 2) further stratification by sex and age when comparing the annual changes, and 3) more clear assessment of whether the changes are due to population changes (e.g. movement, enlistment into military type activities), or due to the lack of health care services available during this time, or both. The population at risk in each area and the health care facility status seems like it should be able to be estimated or at least explored further.
	Specific comments: The figures are not labeled in the proof, which makes it difficult to follow. Page 4, Introduction: it would be helpful to give an approximate date of when the state of emergency ended for those of us who are unaware. It seems like the services resumed. It also would be helpful to have a few more sentences about some of the locations if some were disrupted more than others, or at different times. Was there any population shifts over the time period? The methods section says 1.7 million displaced. Where to? Did they leave the area altogether or just move within it?
	Page 4 Materials and Methods, line 33: "Within Adamawa," Recommend rewording this sentence for clarity. "Within Adamawa, the LGAs of experienced the brunt" It seems like the information about the conflict should be in the introduction section. Why did you choose the "second most affected state" instead of the first one? These details could also be in the intro. Page 5 line 43: "chi-square for trend"it would be better to compare rates here instead of counts, or at least state that the population is assumed not to have changed significantly, and explain why you can't use rates or don't have population figures.

line 48-51: I'm not sure I agree with this interpretation. First it looks like we're using counts instead of rates, and it is not clear that the population is constant. Second, some of the small changes could be due to random variation. Even more problematic is that some LGAs increased over the interval; e.g. of the Moderate conflict areas, Hong and Maiha increased over the interval compared to what the authors call the 2010 baseline. Mobi North was about the same at the end of the period, and Gombi and mobi south decreased. There were additional possible decreases on Hong in 2014 and 2015 compared to 2013, but it is not clear why the counts increased there between 2010 and 2013. Was this population increases, disease transmission, better case finding (was GeneXpert introduced or some other intervention?). Madagali has the most compelling evidence of decrease in the high conflict area—there must be some information about why zero cases were reported in 2015—this should be explained. Was there no health care facility operational, no TB staff worker, etc? Michika showed increases between 2010 and 2013, then decrease in 2014 and 2015, then back up to levels higher than the 2010 baseline in 2016. Bottom line is that there appears to be a lot of heterogeneity between places and the description seems to not report it very accurately. It seems to me that this could be better explained by a deeper more nuanced explanation of the status of the population shifts, services available, and other access issues (was transportation too difficult to access services?).

Page 6: male female ratio—need rates to know whether the rate is going up in women, down in men, or both. My suspicion is that the rate in women is staying constant in some places and the rate among men is lower because of population movement due to migration or conscription into military service. Could you stratify rates by age among males to test this hypothesis? If the rates only went down in men of military service age that would be suggestive.

Page 6; trends by age group and period—trends over time would be more convincing as rates rather than counts, since the rates may not have changed due to population changes. Why did the counts of older adults and children increase? Better access to care, geneXpert, etc? Is this consistent across Nigeria? Rates across Africa were generally going down over this period so this is worth explaining.

Page 6: same section: The figure 4c is difficult to see the stratum specific trends. As above, it is not labeled either in the proof so difficult to figure out which figure I'm supposed to be looking at. Page 6, Discussion: I think this section should be expanded and made more precise. The statement that higher conflict was associated with lower TB notifications is too vague and simplistic. It would be more accurate to say that that there was heterogeneity and many factors during this complex humanitarian emergency which led to some locations having lower notification for a few years, while others did not. One location had a sustained decrease for reasons which were not explained, while the others appeared to rebound to pre-conflict rates (although counts were presented here). I would like to see a deeper exploration of the complexity behind these numbers. digging into why locations were different, such as changes in population due to migration, changes in health service delivery, changes in access due to transportation difficulties, or other reasons. Again, rates should be presented if possible, and further stratification at each location could provide insights as to the cause of these changes, e.g. if males age 15-64 have the main decrease and others remained constant, that would suggest lower rates due to

relocation for military service. The use of the word prevalence I believe to be incorrect. Notification typically refers to new cases, so the correct term should be incidence. The comparison to reference 18 discusses increased mortality—was that considered here? Mortality rate could also provide clues as to what the decrease was attributable to and would be helpful if available.
Conclusion page 7: Long-time span—not correct. 6 years is relatively brief and the decrease appears temporary.

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1 Reviewer Name: James Mancuso; Institution and Country, USUHS, USA

Comment: Please state any competing interests or state 'None declared':

Answer: The authors have no conflict of interest. And this statement has been given at the Declarations section in the main manuscript file.

Comment: Overall a nicely written paper which is very simple and clear. It would benefit further from: 1) use of rates rather than counts, 2) further stratification by sex and age when comparing the annual changes, and 3) more clear assessment of whether the changes are due to population changes (e.g. movement, enlistment into military type activities), or due to the lack of health care services available during this time, or both. The population at risk in each area and the health care facility status seems like it should be able to be estimated or at least explored further.

Answer: Thank you so much. We totally agree with preference to use rates. However, case counts instead of rates were used since population census were not available and population changes were not quantified. We are thus unable to use rates due to the difficulty in having accurate population figures. Nigeria's last population census took place in 2002 and since then only population estimates are available and utilized. However, they are likely to be inaccurate in areas of protracted conflict with cumulative displacement of population. The projected population estimates therefore were considered to be unlikely to provide a reliable denominator to build the true picture of the burden of TB. This has been explained /discussed in the discussion section as given below(page 6, line 45-page7 line 3)..... Generally, years and places of higher conflict were associated with lower TB notifications. All LGAs experiencing conflict reported lower numbers of cases from 2013 onwards and the decline was more severe in the most affected areas, with corresponding increase in case notifications in low conflict areas. The decline in case notifications coincided with the progressive capture of LGAs by Boko Haram, the displacement of population and disruption of health services.4-8,10-12 The lower numbers of cases notified in the places and times most likely reflected displacement of the populations to other locations that were considered safer, less access and disruption of TB services, decrease access due to transport, destruction of health facilities, and desertion of health staff. As a result of these major challenges, Madagali recorded no cases in 2015, which was attributed to the severity of the conflict in this LGA......

Regarding stratification by sex and age, we have a supplementary table in which this data has been analyzed as counts and not rate as explained above due to the lack of reliable census document and population displacement.

Specific comments:

Comment: The figures are not labeled in the proof, which makes it difficult to follow.

Answer: Thank you. The figure titles/legends has been incorporated and given as below:

Figure 1. A map of Nigeria showing the three North-eastern states affected by insurgency (A) and local government areas (LGAs) affected by insurgency in Adamawa State, Nigeria (B)

Figure 2. Number of TB case notifications by level of conflict (high, moderate and low) in Adamawa State, Nigeria

Figure 3. TB case notifications and gender ratio (male:female) by level of conflict (high, moderate and low) in Adamawa State, Nigeria

Figure 4. Number of TB case notification by age group and level of conflict in Adamawa State, Nigeria. Left, middle and right figures represent data from high, moderate and low conflict areas

Comment: Page 4, Introduction: it would be helpful to give an approximate date of when the state of emergency ended for those of us who are unaware. It seems like the services resumed. It also would be helpful to have a few more sentences about some of the locations if some were disrupted more than others, or at different times. Was there any population shifts over the time period? The methods section says 1.7 million displaced. Where to? Did they leave the area altogether or just move within it?

Answer: Thank You so much. The suggestions you have given have been meticulously adhered to as seen in the modified part of introduction(page 4, lines 14-36):

In Adamawa State, seven LGAs (Gombi, Hong, Maiha, Mubi North and South, Michika and Madagali) experienced the brunt of the violence, and these remained under the control of Boko Haram until their progressive recapture by the Nigerian Army (Hong, Gombi, Maiha and Mubi by December 2014, Michika by January 2015 and Madagali by March 2015).

Though the state of emergency was lifted in Feb 2014, the insurgents persisted until their dislodgment from Madagali from the aforementioned affected LGAs.

In order to guide health operational intervention/ implementation, all the LGAs in the Adamawa State were categorized into very high, moderate and low conflict by health policy makers and development partners in the State ministry. The categorization was based on proximity of the LGAs to Boko Haram Strongholds in Borno, the number of Internally Displaced Persons(IDP) camps, the estimated number of fatalities and damage to life and properties.15

Two LGAs (Madagali and Michika) in the very high conflict area are the closest to the Boko Haram stronghold in Borno State, followed by the 5 LGAs (Mubi North, Mubi South, Maiha, Hong and Gombi) in the moderate conflict area and then finally the 14 farthest LGAs (Song, Girei, Yola North, Yola

South, Fufore, Mayo-belwa, jada, Ganye, Tongo, Numan, Guyuk, Lamurde, Demsa, and Shelleng) are considered the low conflict area. Thus, the conflict initially progressed from the Northern to the Southern part of the state, which is farthest from the main Boko Haram camp.17.22.....

Comment: Page 4 Materials and Methods , line 33: "Within Adamawa,..." Recommend rewording this sentence for clarity. "Within Adamawa, the LGAs of ... experienced the brunt..." It seems like the information about the conflict should be in the introduction section.

Answer: Thank You Sir. This has been modified and also taken to introduction and reads as follows (page 4, lines 17-23)... Some of the displaced persons moved to relatively safer sites within the affected areas while others entirely left the affected areas as shown by the displacement tracking matrix produced by the UN International Organization for Migration.13-15

In Adamawa State, seven LGAs (Gombi, Hong, Maiha, Mubi North and South, Michika and Madagali) experienced the brunt of the violence, and these remained under the control of Boko Haram until their progressive recapture by the Nigerian Army (Hong, Gombi, Maiha and Mubi by December 2014, Michika by January 2015 and Madagali by March 2015).16-21

Comment: Why did you choose the "second most affected state" instead of the first one? These details could also be in the intro.

Answer: Choice of Adamawa for this study has been added to the methology part of the manuscript (page 5, lines 1-5) as follows.......it .was chosen for this study for its peculiarity of progressive recapture by the military and relative safety of travel at the time of data collection. Yobe in turn was no selected because it did not have a functional airport and insurgents abounded episodically on the highway and thus data was unreliable or not collected. Though an airport existed in Borno state, targeted bombings continue and some LGAS are still under the control of Boko Haram rendering impossible to access data......

Though other major parts in the methodology have been moved to introduction as the reviewer suggested, we however included this particular choice for Adamawa in the methodology to give a better flow and we hope the reviewer accepts this.

Comment: Page 5 line 43: "chi-square for trend" --it would be better to compare rates here instead of counts, or at least state that the population is assumed not to have changed significantly, and explain why you can't use rates or don't have population figures.

Answer: Case counts instead of rates were used as population census were not available and population changes were not quantified. We are thus unable to use rates due to the difficulty in having accurate population figures. Nigeria's last population census took place in 2002 and since then only population estimates are available and utilized. As highlighted earlier, the population estimates are likely to be inaccurate in areas of protracted conflict with cumulative displacement of population. The projected population estimates therefore were considered to be unlikely to provide a reliable denominator to build the true picture of the burden of TB. This has been explained /discussed in the discussion section as given below

Comment: line 48-51: I'm not sure I agree with this interpretation. First it looks like we're using counts instead of rates, and it is not clear that the population is constant. Second, some of the small changes could be due to random variation. Even more problematic is that some LGAs increased over the interval; e.g. of the Moderate conflict areas, Hong and Maiha increased over the interval compared to what the authors call the 2010 baseline. Mobi North was about the same at the end of the period, and Gombi and mobi south decreased. There were additional possible decreases on Hong in 2014 and 2015 compared to 2013, but it is not clear why the counts increased there between 2010 and 2013. Was this population increases, disease transmission, better case finding (was GeneXpert introduced or some other intervention?). Madagali has the most compelling evidence of decrease in the high conflict area—there must be some information about why zero cases were reported in 2015—this should be explained. Was there no health care facility operational, no TB staff worker, etc? Michika showed increases between 2010 and 2013, then decrease in 2014 and 2015, then back up to levels higher than the 2010 baseline in 2016. Bottom line is that there appears to be a lot of heterogeneity between places and the description seems to not report it very accurately. It seems to me that this could be better explained by a deeper more nuanced explanation of the status of the population shifts, services available, and other access issues (was transportation too difficult to access services?).

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In the discussion part of the manuscript, the reviewers concerns and suggestions were carefully addressed and adopted as shown in the discussion sections in page 6, line 45-page 7 line 22) as follows...... Generally, years and places of higher conflict were associated with lower TB notifications. All LGAs experiencing conflict reported lower numbers of cases from 2013 onwards and the decline was more severe in the most affected areas, with corresponding increases in case notifications in low conflict areas. The decline in case notification coincided with the progressive capture of LGAs by Boko Haram, the displacement of population and disruption of health services.4-8,10-122 The lower numbers of cases notified in the places and times most likely reflected displacement of the populations to other locations that were considered safer, less access and disruption of TB services, decrease access due to transport, destruction of health facilities, and desertion of health staff. As a result of these major challenges, Madagali recorded no cases in 2015, which was attributed to the severity of the conflict in this LGA. Madagali was the first LGA to be invaded and the last to be recaptured by the army. In 2015, all TB services in Madagali came to a standstill, all health staff and patients left the area and transport was unavailble. Other studies have shown similar low case notifications from areas of conflict in Sudan.246 In Adamawa State, areas of low conflict reported more case notifications than in previous years, while areas of very high conflict reported low number of cases. This is attributable to several factors, including population displacement from very high conflict to relatively safe areas, displaced persons in the host communities of low conflict areas accessing the TB services, displaced populations living in poor conditions and malnutrition, with overcrowding, which facilitates transmission and disease progression and the coincidental introduction of four GeneXpert machines, which have higher sensitivity than smear-microscopy, in the low conflict areas.

Most LGAs had increased notifications from 2012 to 2013. This period coincided with a TB Reachfunded project in all LGAs during which TB risk messages were broadcasted through jingles in the local radios, with the intention to increase case finding among nomadic pastoralists. At that time, health workers were re-trained on TB identification, diagnosis, treatment and follow-up and 402 community volunteers were engaged to boost awareness and reporting of cases. This intervention, coupled with the introduction of GeneXpert testing increased awareness on TB and provided additional resources, possibly resulting in improved health care seeking behavior, better case notification and reporting. Some LGAs also appeared to have a rebound of cases to pre-conflict notification levels (e.g. Michika) due to a massive return of displaced populations after the recapture of the areas by the military. In those situations, health services resumed with varying intensity across the areas and service availability was not evenly distributed across the LGAs.....

Comment: Page 6: male female ratio—need rates to know whether the rate is going up in women, down in men, or both. My suspicion is that the rate in women is staying constant in some places and the rate among men is lower because of population movement due to migration or conscription into military service. Could you stratify rates by age among males to test this hypothesis? If the rates only went down in men of military service age that would be suggestive.

Answer: Thank you so much. We totally agree with you on this. However, as we mentioned above, case counts instead of rates were used as population census were not available and population changes were not quantified. We are thus unable to use rates due to the difficulty in having accurate population figures. Nigeria's last population census took place in 2002 and since then only population estimates are utilized. However they are likely to be inaccurate n areas of protracted conflict with cumulative displacement of population. The projected population estimates therefore were considered to be unlikely to provide a reliable denominator to build the true picture of the burden of TB

For testing the suggested hypothesis, this is a very interesting aspect to be explored. However, due to the deficiency accurate census data as earlier mentioned, we are not able to explore this aspect.

Comment: Page 6; trends by age group and period—trends over time would be more convincing as rates rather than counts, since the rates may not have changed due to population changes. Why did the counts of older adults and children increase? Better access to care, geneXpert, etc? Is this consistent across Nigeria? Rates across Africa were generally going down over this period so this is worth explaining.

Answer: This has been addressed in (page 7, lines 30-43) as shown below:

A low number of children and elderly cases were also reported in all areas, which reflects the increased difficulty in reaching a diagnosis in those age groups and the lower accessibility of services for individuals with young and advanced age. These pre-established barriers seemed to worsen within conflict areas. The low proportion of cases diagnosed in elderly groups may reflect societal and economic barriers to access the services and a cohort effect where vulnerable individuals died at early age, with the selection of the fittest. Children in turn often have low bacilli numbers, are unable to produce sputum and are more difficult to diagnose at any time, requiring skills to obtain alternative clinical samples for diagnosis (e.g. gastric lavage). Added to this their dependence on parents separated by conflict and in poverty, it is not surprising the number of cases dwindled sharply during conflict years.33 34 Surprisingly, the trend analysis showed increasing numbers of cases in children and the elderly in pre-conflict and post-conflict periods. This may have been due to the TB Reach intervention described above during the pre-conflict period and then, the return of the population to their own areas. Other studies have attributed the increasing trends in under five notifications to a higher susceptibility to TB among displaced populations and better access to diagnostics and treatment services due to humanitarian organizations providing emergency services. 35

Comment: Page 6: same section: The figure 4c is difficult to see the stratum specific trends. As above, it is not labeled either in the proof so difficult to figure out which figure I'm supposed to be looking at.

Answer: The figure has been modified and appropriate legend has been added in the main manuscript file. (page 10, line 1-10)

Comment: Page 6, Discussion: I think this section should be expanded and made more precise. The statement that higher conflict was associated with lower TB notifications is too vague and simplistic. It would be more accurate to say that that there was heterogeneity and many factors during this complex humanitarian emergency which led to some locations having lower notification for a few years, while others did not. One location had a sustained decrease for reasons which were not explained, while the others appeared to rebound to pre-conflict rates (although counts were presented here). I would like to see a deeper exploration of the complexity behind these numbers, digging into why locations were different, such as changes in population due to migration, changes in health service delivery, changes in access due to transportation difficulties, or other reasons. Again, rates should be presented if possible, and further stratification at each location could provide insights as to the cause of these changes, e.g. if males age 15-64 have the main decrease and others remained constant, that would suggest lower rates due to relocation for military service. The use of the word prevalence I believe to be incorrect. Notification typically refers to new cases, so the correct term should be incidence. The comparison to reference 18 discusses increased mortality—was that considered here? Mortality rate could also provide clues as to what the decrease was attributable to and would be helpful if available.

Answer: These have been adhered to and reads as follows (page 6 line 42 to page 7, line 41-Y)...

.There was gross heterogeneity and many intricate factors during the complex humanitarian emergency that affected North East Nigeria. This heterogeneity led to some locations having lower TB notification for a few years, while others did not. Generally, years and places of higher conflict were associated with lower TB notifications. All LGAs experiencing conflict reported lower numbers of cases from 2013 onwards and the decline was more severe in the most affected areas, with corresponding increases in case notifications in low conflict areas. The decline in case notification coincided with the progressive capture of LGAs by Boko Haram, the displacement of population and disruption of health services.4-10.12 The lower numbers of cases notified in the places and times most likely reflected displacement of the populations to other locations that were considered safer, less access and disruption of TB services, decrease access due to transport, destruction of health facilities, and desertion of health staff. As a result of these major challenges, Madagali recorded no cases in 2015, which was attributed to the severity of the conflict in this LGA. Madagali was the first LGA to be invaded and the last to be recaptured by the army. In 2015, all TB services in Madagali came to a standstill, all health staff and patients left the area and transport was unavailable. Other studies have shown similar low case notifications from areas of conflict in Sudan.16 In Adamawa State, areas of low conflict reported more case notifications than in previous years, while areas of very high conflict reported low number of cases. This is attributable to several factors, including population displacement from very high conflict to relatively safe areas, displaced persons in the host communities of low conflict areas accessing the TB services, displaced populations living in poor conditions and malnutrition, with overcrowding, which facilitates transmission and disease progression and the coincidental introduction of four GeneXpert machines, which have higher sensitivity than smear-microscopy, in the low conflict areas.

Most LGAs had increased notifications from 2012 to 2013. This period coincided with a TB Reachfunded project in all LGAs during which TB risk messages were broadcasted through jingles in the local radios, with the intention to increase case finding among nomadic pastoralists. At that time, health workers were re-trained on TB identification, diagnosis, treatment and follow-up and 402 community volunteers were engaged to boost awareness and reporting of cases. This intervention, coupled with the introduction of geneXpert testing increased awareness on TB and provided additional resources, possibly resulting in improved health care seeking behavior, better case notification and reporting. Some LGAS also appeared to have a rebound of cases to pre-conflict notification levels (e.g Michika) due to a massive return of displaced populations after the recapture of the areas by the military. In those situations, health services resumed with varying intensity across the areas and service availability was not evenly distributed across the LGAs.

Overall, a higher number of males than females were notified. However, in areas of high and moderate conflict the sex ratio changed, with more female cases being notified. This was likely due to males avoiding contact with health services, as Boko Haram targeted males for killings and abductions. In contrast, in low conflict areas, the sex ratio increased, suggesting that males may have travelled to these relatively safe areas for health seeking.

The overall number of cases reported was lower among areas with moderate and severe conflict. Similar findings have been reported from other areas of conflict , as conflict interfere with identification and treatment TB patients.17 A low number of children and elderly cases were also reported in all areas, which reflects the increased difficulty in reaching a diagnosis in those age groups and the lower accessibility of services for individuals with young and advanced age. These pre-established barriers seemed to worsen within conflict areas. The low proportion of cases diagnosed in elderly groups may reflect societal and economic barriers to access the services and a cohort effect where vulnerable individuals died at early age, with the selection of the fittest. Children in turn often have low bacilli numbers, are unable to produce sputum and are more difficult to diagnose at any time, requiring skills to obtain alternative clinical samples for diagnosis (e.g. gastric lavage). Added to this their dependence on parents separated by conflict and in poverty, it is not surprising the number of cases dwindled sharply during conflict years.33 34 Surprisingly, the trend analysis showed increasing numbers of cases in children and the elderly in pre-conflict and post-conflict periods. This may have been due to the TB Reach intervention described above during the pre-conflict period and then, the return of the population to their own areas. Other studies have attributed the increasing

Comment: Conclusion page 7: Long-time span—not correct. 6 years is relatively brief and the decrease appears temporary.

Answer: Thank You so much for calling our attention on this. We have made the following changes in the conclusion and now reads as below (Page 6, line 5-8):

"Despite these limitations, we have shown that case notifications in LGAs in conflict areas decreased during the period of insurgency. However, notifications changes were not homogeneous and affected differently males and females and age groups. We believe this analysis is useful to plan TB services for areas in conflict and their neighboring areas receiving internally displaced populations."

Furthermore, we agreed not to use long-time-span, and now has been modified in our limitation and reads as below (page 3, line 33-42):

"Short time span of TB data was utilized to highlight challenges in TB services during conflict and stimulate research for resilient approaches."