Author's response to reviews

**Title:** Trends in TB Case Notification over Fifteen Years: The case Notification of 25 Districts of Arsi Zone of Oromia Regional State, Central Ethiopia

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**Author's response to reviews:** see over
To: Editor in Chief
BMC Public Health

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Subject: Revised manuscript submission

Attached herewith please find the revised manuscript entitled “Trends in TB Case Notification Over Fifteen Years: The case notification of 25 Districts of Arsi Zone of Oromia Regional State of Central Ethiopia, so that it can be considered for publication.

We would like to extend our thanks for all reviewers for their critical review and voluble input to modify the manuscript as requested. We have made a review of all parts of the manuscript including the title of the manuscript, the abstract, background, the methods, results, discussion and conclusion according to the given comments. We have also made language edition using native English speaker. Our point by point responses to each Reviewer are indicated as below:

Author's response to reviews

Title: Trends in TB Case Notification over Fifteen Years: The case notification of 25 Districts of Arsi Zone of Oromia Regional State of Central Ethiopia

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Version: 02
Reviewer #1 Gemeda Abebe

We thank the reviewer as he has made us to review critically and providing both general as well as specific comments that could improve the quality of our manuscript. Accordingly, we have tried to accommodate the comments.

Major Compulsory Revisions

Study settings

1. The authors indicated that “About 89% of the population lives in the rural areas and only 70% of them were residing within two hours walking distance from a public health facility”. Since there was dynamic expansion of health facilities in the country it is not clear to which time line does the above information referring to.

   The time line was 2011 and incorporated in the manuscript as follow: “About 89% of the population lives in rural areas while the remaining 11% resides in urban areas. In 2011 about 70% of zonal population lived within two-hour walking distance from a public health facility.”

2. Definition of terms: Different categories of TB were defined following the different guidelines a country adopts. During the DOTS era there were different WHO guidelines that were adopted by Ethiopia. For instance WHO guideline 2003 and 2007. There are some differences in the definitions taking into account different patient populations specifically HIV sero-positive cases. The definition that was provided by the authors is consistent with the WHO 2003 guideline but not to that of the 2007. However, Ethiopia started to implement the 2007 guideline since 2009. The authors need to re-phrase their definitions (smear positive, smear negative and extra pulmonary TB) according to the time line


   “Type of tuberculosis (TB) is defined based on the National Tuberculosis and Leprosy Control Program guideline (NTLCP) adopted from WHO (8)”

   Pulmonary TB smear-positive (PTB+) is defined as a patient with at least two initial sputum smear positive for acid-fast bacilli (AFB) by direct microscopy or a patient with only one sputum smear positive for AFB and with chest radiographic abnormalities consistent with active pulmonary TB followed by clinician decision.

   Pulmonary TB smear-negative (PTB-) is defined as a patient with at least three initial sputum smear negative for AFB by direct microscopy and with chest radiographic abnormalities consistent with active pulmonary TB and no clinical response to two weeks of broad spectrum antibiotic therapy followed by clinician decision.
Extra pulmonary tuberculosis (EPTB) is defined as tuberculosis involving organs other than the lungs, such as skin, abdomen, joints, bones, lymph nodes, pleura, genitourinary tract, and meninges. The diagnosis is based on fine needle aspiration (FNA) for histopathological examination or biochemical analysis of ascitic/pleural/cerebrospinal fluid followed by clinician decision to treat with a full course of anti-TB drugs.

However, a patient with three initial sputum smear negative for AFB at health centre and with no clinical response to two weeks of broad spectrum antibiotic therapy, and also suspected of EPTB at health centre were referred to hospital for further radiological and histopathological investigation before diagnosis as TB cases at health centre level.

3. **Measurements**: What were the assumptions for dichotomizing the TB notification rate as below and above 120 (why 120 was taken as cut-off value)?

The comment is very important and the assumption for taking 120/100,000 case notification as cut-off value described as follows. Empirically, there are different ways to determine cut-off point values for dichotomizing data. For example, if there is standard value of cut-off point, the standard value can be taken to dichotomize the data. However, if there is no standard cut-off value and the data is normally distributed an average (mean) is used as cut-off value to dichotomize the data into below and above the average. In this case our data is normally distributed and the fifteen years average of all forms of TB case notification of the zone was 120/100,000. Therefore, we took this as cut-off value in the dichotomization of all forms of TB case notification into below 120 and above 120 per 100,000 in the bivariate and multivariate binary logistic regression analyses for which we have incorporated justification in the analysis part of the manuscript.

4. **Discussion**: The authors discuss that the trend in TB case notification did not increase steadily during the later years in the study period. They indicated it may be the effect of passive case finding. How do the authors discuss their data in line with the current declining trend in TB cases in Ethiopia to which Arsi zone is not exceptional:

This comment is very important; although there are undiagnosed TB cases in the community, TB case notification through passive case finding did not steadily increased after certain marginal point. This was reported from southern part of Ethiopia and also observed in our present findings. However, our current (Dec 2004) survey result on the prevalence of PTB+ cases in Hitosa districts of Arsi zone was 168/100,000, Dabat District of Northwest Ethiopia 174/100,000 and 169/100,000 in Tigray region in 2013. Therefore, it is not convincing that the stagnation in trends of TB case notification during the later years in the study period may not be due to the declining trends in TB cases in the study area other than it might be due to the
inability of facility based passive case finding strategy to identify the existing TB cases in the community.

5. The authors indicated that “The case detection rate (CDR), as estimated by the proportion of smear positive expected TB incident cases notified, showed an increase from 6.4% in 1997 to 58.7% in 2011”. However, the definition that the authors used and the figures did not coincide. Arsi Zone is one of the zones known to have very low smear positive TB case detection rate which is less than the figure that the authors reported.

We accepted the comment and corrected the definition of case detection rate (CDR) as follow:

The case detection rate (CDR), estimated by the proportion of PTB+ cases notified from the total expected PTB+ incidence cases in the community. Then we calculated the PTB+ CDR by taking the total number of PTB+ cases notified in each year in the zone as nominator and the total expected PTB+ incidence cases of the zone for each year as denominator and multiplying it by 100. However, according to Oromia Regional Health Bureau annual reports, Arsi zone is one of the zones in the region known to have relatively high TB case detection rate (CDR) compared to other zones in the region with an average of 65% over the past 3 years.

6. Cover page: Indicate the cities where the institutions to which the authors are affiliated are located

The comment is accepted and correction was made as per the comment.

7. Abreact and Methods: About 41,956---- The authors need to re-write this section since the authors analyzed exactly 41,956 TB patients’ data.

The comment is accepted and “about” is replaced by” A total of 41,956”

8. Epic-info- Is that to say Epi-info?

We accepted the comment and “Epic-info” is changed to” Epi-info”

Background

9. The authors indicate that to the best of their knowledge no study has evaluated how the DOTS strategy was implemented across districts in the country. But their result doesn’t indicate the details of the implementation except that it was done in phased approach.

The comment is very important, however, we tried to indicate in details of trend in TB case notification over fifteen years of the study period under “Trends in DOTS Site Expansion and TB Case Notification” and also made comparison of DOTS performance among 24 districts of the zone under “Fifteen-year Average TB Case Notification by Districts” of the manuscript.
Reviewer # 2 Gebretsadik Berhe

We thank the reviewer as he has made us to review critically and providing both general as well as specific comments that could improve the quality of our manuscript. Accordingly, we have tried to accommodate the comments as follows;

Major Compulsory Revisions
Methods:

1. In the study design and data collection section- The authors stated that they have Used Facility-based retrospective study design. Does the word “retrospective” represent a specific epidemiological study design (there could be different retrospective study designs)? So is this study design “cross-sectional” or other?.

   F We accepted the comment and corrected as follow:

   ”This was facility-based retrospective longitudinal study design” in this case we reviewed the profile of all forms TB cases registered between September 1, 1997 and August 31, 2011 to analyze the trends in TB case notification and making compression in TB performance across districts in Arsi Zone, Ormia Regional State of Central Ethiopia.

2. Although the data was collected from apparently large number of people (41,965), it is good if the minimum sample size is calculated for the study.

   F The comment is good, however, the study was facility-based retrospective longitudinal study design that included all forms of TB cases registered between September 1, 1997 to August 31, 2011 and all health facilities with DOTS services during the study period in Arsi zone. Therefore, as all forms of TB cases and all facilities provided DOTS service during the study period were included in the study, we didn’t apply sampling method and procedure to calculate the sample size and to identify the study subjects.

3. What sampling procedure (eg. multistage, cluster etc.) was used in this study and how did you select your samples starting from the zone to the health facility.

   F As indicated under # 2 comments above there is no need to calculate the sample size and applying sampling procedure.

4. The period of data collection and who collected the data needs to be described.
“TB Unit Registers in all health facilities during the period were identified by the principal investigator and brought to the regional health bureau office between January and March 2013. Then, 10 trained data clerks collected TB patients’ information on sex, age, address, TB type, patient category, date treatment started, and HIV testing and their status from the TB Unit Registers and entered the data onto a computer programme (SPSS version 20) from April to June 2013.”

5. Measurements –paragraph 3, line 6 – TB case notification was dichotomized into below 120 and 120 or above per 100,000 population. It will be clear to readers if authors justify how they categorize in such a way. Did authors use any criteria (eg. Oromia Regional State or National TB case notification) or was it used arbitrarily.

F The comment is very important and the assumption for taking 120/100,000 case notification as cut-off value described as follow. Empirically, there are different ways to determine cut-off point values for dichotomizing data. For example, if there is standard value of cut-off point, the standard value can be taken to dichotomize the data. However, if there is no standard cut-off value and the data is normally distributed an average (mean) is used as cut-off value to dichotomize the data into below and above the average. In this case our data is normally distributed and the fifteen years average of all forms of TB case notification of the zone was 120/100,000. Therefore, we took this as cut-off value in the dichotomization of all forms of TB case notification into below 120 and above 120 per 100,000 in the bivariate and multivariate binary logistic regression analyses for which we have incorporated justification in the in analysis part of the manuscript.

Results:

1. Table 1. The sub categories for TB Classification add up to 41,919, it is less by 46 from 41,965 study populations. Was this due to missing data or unknown classification, the reason for this discrepancy need to be stated?

F We accepted the comment: The missing data in Table 1 was incorporated in the table accordingly

2. Table 3. The categories under the variables do not add up to 41,965, so it is essential to state the study population for each category (eg. N=750).

F We accepted the comment and corrected as per the comment. We indicated the total number for each category variables indicated under Table 3.

Minor Essential Revisions
1. Under the abstract section – background, line 4. The authors stated that “its impact as not been assessed”. However, as the word “impact” may imply changes in terms of mortality and/or morbidity, it is better if it is changed with other words like progress/status/performance etc.

F The comment is accepted and the word “impact” changed by the word “progress”

2. Background- Paragraph 4, line 6. Although it is described that the study was conducted in the Arsi Zone of Oromia regional state, it is also important that the word Central Ethiopia or Ethiopia is added to the last paragraph for more qualification.

F We accepted the comment and included “Central Ethiopia”

3. Reference No. 28 is missing in the text, but listed in the reference list

F The comment was accepted and reference No 28 was inserted.

4. Multilevel analysis is mentioned in the discussion section, but not in the statistical analysis. So if it is used, it should be also mentioned in the statistical analysis section.

F The comment is very important and we removed the “Multilevel analysis” from the analysis and discussion part of the manuscript was excluded as it also suggested by another reviewer to exclude.

5. Results:

F Better to delete the word “vast” from the first paragraph, line 4, since it qualifies for area rather than people.

F We accepted the comment and the word “Vast” were deleted.

F Paragraph 3, line 8 and paragraph 5 line 5, paragraph 8 line 5- See Fig.1, see Table 2 and see Table 3 are used. In other parts of the manuscript, see is not used either with Fig or Table. So to be consistent, use either see Table/Fig or Table/Fig throughout the manuscript.

F We accepted the comment and Table/Fig used throughout the manuscript as per the comment

6. Discussion:

Paragraph 5, line No 2, you have used “PTB+ tuberculosis”. Better to delete the word tuberculosis to avoid redundancy as the word PTB+ represents Smear positive pulmonary tuberculosis.

F We accepted the comment and the word tuberculosis was deleted

Reviewer # 3 Christopher Parry
We are grateful and extend our appreciation for the reviewer as she/he has made us to review our manuscript critically and also providing us both general as well as specific comments that could defiantly improve the quality of the manuscript. Accordingly, we have tried to accommodate the comments.

Major compulsory revisions:

1. Methods, Study design and data collection: TB case notifications were studied between 1997 and 2011. However, in the 1st paragraph of the Results the time period was September 1997 to June 2011. As we do not know if there is seasonal variation in the notification rates I think only complete years should be analyzed – that is 1998 to 2010.

   We thank the reviewer for pointed out very important point about the duration of the study period. It is true that there could be a seasonal variation in TB case notification due to different reasons such as seasonal variation in accessing health facilities as most of the roads in rainy season in the rural areas of the country were not accessible. There is also an economic inaccessibility to health facilitates for the rural farmers as the time extended from harvesting season due to depletion of their harvest. There could also be an epidemiological variation in TB transmission across different seasons. However, the duration of our study was full year for all fifteen years of study period ranged from Septembers 1 to August 31 throughout the study period” the word “June” in the result part of the manuscript was due to typological error and correction was made accordingly.

2. Methods, Study Design, and Measurements: Please detail how the case detection rate, the TB-HIV co-infection rate, DOTS sites and DOTS population coverage (in Fig 1 and Table 2) were calculated. In particular it is not clear how the TB-HIV infection parameter was determined.

   We accepted the comments and correction were made accordingly:

   The detailed of TB case detection rate was described under Measurements section “The PTB+ case detection rate (CDR) for each year (1997 to 2011) of the zone was computed as follows: first we calculated the total number of expected incidence of PTB+ cases for each mid-year population of the zone (104/100,000 for Oromia) based on the 2011 National TB Prevalence survey result where Arsi zone was one of the zones in the region (9). Then we calculated the PTB+ CDR by taking the total number of PTB+ cases notified in each year in the zone as nominator and the total expected PTB+ incidence cases of the zone for each year as denominitor and multiply the result by 100.

   \[ \text{PTB+ CDR for each year (1997 to 2011)} = \frac{\text{Total number of PTB+ cases notified in each year in the zone}}{\text{Total number of expected PTB+ cases in each year in the zone}} \times 100 \]

   Detailed information on TB-HIV co-infection rate calculation described under Measurements section of the manuscript as follow: “Since 2008, all TB patients have been offered provide initiated voluntary counselling and testing service for HIV. Hence,
TB-HIV co-infection rate for each district was computed by taking all TB patients tested for HIV and found to be HIV positive as nominator and all TB patients tested for HIV during the study period as denominator multiplied by 100.”

DOTS sites and DOTS population coverage described under the Study Settings section of the manuscript as follow:

“Moreover, a hospital or a health centre with DOTS service during the study period was considered as a DOTS site. Accordingly, DOTS population coverage of each district of the zone was computed by taking population living within two-hour walking distance or 10 km radius (estimated at 250,000 for hospital and 25,000 for health centre) of a hospital or a health centre as nominator, and the total number of mid-year population of each district as denominator multiplied by 100.”

3. Results, Fifteen year average TB notifications by districts, paragraph 3: I am concerned about the validity of this multivariate analysis. In particular I am not clear that HIV status can be included as (I assume) this is a sample of the patients notified and not comparable with the data for all notifications.

We accepted the comment and excluded HIV from the bivariate and multivariate binary logistic regression analyses. As commented above, all TB patients were not tested for HIV due to the fact that provider initiated voluntary counseling and testing was initiated after 11 years of the study period in 2008 where only TB patients in the last four years of the study period were tested for HIV. In these 4 years only 25% of all forms TB case (10,428/ 41,965) was tested for HIV. Hence, we accepted the exclusion of TB/HIV co-infection from multivariate analysis as it might lead to bias. However, as we checked model adequacy and co-linearity assumptions, we feel that there is no validity problem on the rest of variables included in multivariate analysis of the manuscript.

3. Results, Fifteen year average TB notifications by districts, paragraph 3: I think the care should be taken in using the terms “predictors” and “less likely” or “more likely”. The analysis is looking at associations between one variable and another and one variable is not necessarily predictive of another. For example, rural areas were associated with lower notification rates compared with urban areas. There may be a variety of reasons for that which might include truly lower rates of TB in rural areas or alternatively lower rates of access or attendance among patients with symptoms.

We accepted the comment and corrected as follow:

“The predictors, less likely or more likely in the paragraph 3 of the result section were replaced by another appropriate words” In binary logistic regression analyses, area of residence, age, type of TB and population ratio to DOTS sites of the districts were associated with low TB case notification. In the final model, rural residence (AOR, 0.23; 95% CI: 0.21 to 0.26) and districts with population ratio to DOTS sites with more than 25,000 population (AOR, 0.40; 95% CI: 0.35 to 0.46) were associated with low TB case notification. However, TB case notifications were
significantly more common among 15-24 years of age (AOR, 1.19; 95% CI: 1.03 to 1.38), PTB- (AOR, 1.46; 95% CI: 1.33 to 64) and EPTB (AOR, 1.49; 95% CI; 1.33 to 1.60) TB cases (Table 3 “

5. Results, Fifteen year average TB notifications by districts, paragraph 3: It is not possible from the data to say “TB patients in the age group 15-24 years were more likely to be notified than other age groups”. This would require knowledge of the true rates of TB in all age groups. An alternative could be “TB notifications were significantly more common in the 15-24 age group compared with the other age groups”.

F We accepted the comment and correction was made as indicated under comment # 5 above or as follow:” TB case notifications were significantly more common among 15-24 years of age (AOR, 1.19; 95% CI: 1.03 to 1.38), PTB- (AOR, 1.46; 95% CI: 1.33 to 64) and EPTB (AOR, 1.49; 95% CI; 1.33 to 1.60) TB cases (Table 3)”

7. Results, Fifteen year average TB notifications by districts, paragraph 3: Similarly it is not possible to say that “TB patients with HIV were more likely to be notified compared with their HIV negative counterparts”. This would require knowledge of all the patients with HIV and TB or no HIV and TB in the population. The data shows (for the sample tested) in areas with higher case notifications the proportion of HIV positive patients was higher.

F We accepted the comment and HIV excluded from the analysis as indicated under comment number 3 above.

8. Discussion, paragraph 5, line 1: I think better to use the 1998 and 2010 data as discussed previously.

F The comment is very important but the typological error corrected for which the study period ranged from Septembers 1 to August 31. Hence, the duration of the period was fully year throughout from 1997 to 2011.

8. Figure 1: I think it is misleading to include all the lines on the same graph as different parameters are being recorded. It would be clearer to have a series of graphs one above each other. For example a single graph for TB CN all forms and TB CN of PTB+ (/100,000 population); and separate graphs for CDR PTB+ (%), Dots sites (number) and DOTS population coverage (%). The explanation of the following parameters should be made clearer: CDR PTB+; DOTS site; DOTS population coverage. I assume x2 trends should not be X2 trends – these Values are in the text and perhaps do not need to be repeated here

F We accepted the comment and corrected as follow:
Fig. 1. Trends in all forms of TB, Pulmonary smear positive TB case notification, DOTS site expansion and DOTS population coverage, Arsi Zone of Oromia Regional State, Central Ethiopia, 1997-2011

N.B: Trends in TB case notification increased with DOTS sites expansion for all forms of TB $X^2$ trend = 75.2, $p < 0.001$, PTB+ $X^2$ trends = 27.74, $P < 0.001$ and CDR PTB+ $X^2$ trend = 26.794, $p < 0.001$. 
9. Table 2: The heading could be made clearer. For example Yearly average number of TB cases notified; yearly average TB case notifications/100,000 population; yearly average TB-HIV co-infection. For Seru the average number of all forms of TB is 52.2 – does not need a decimal point.

   F We accepted the comment and correct accordingly “Table 2: Yearly average of TB case notification /100,000 population and TB /HIV co-infection rate(%) ,25 districts of Arsi Zone Oromia region, Centeral Ethiopia(1997-2011)”
   F We have also removed decimal for Seru “52.2” and corrected as 52.

10. Table 3: I am not sure that HIV status can be included in this analysis. Please explain what is meant be Population to DOTS ratio

   F The comment is very important and we described how TB/HIV co-infection rate was analyzed and definition of Population to DOTS ratio is indicated under comment #2 above.

Minor essential revisions

1. Abstract, methods: “About 41,965 cases” – why is the number qualified with about? “A total of 41,965 cases” would be better.

   F We accepted the comment and the word “about” replaced by “A total”

2. Abstract, results, line 6-7: TB patients from rural areas were less likely to be notified ….. suggest inserting “compared with urban areas”.

   F We accepted the comment and “compared to urban areas’ inserted

3. Abstract, Conclusions, Line 3: Should be “Further research is therefore recommended” ….

   F The comment is well taken and “Further research is therefore Recommended” inserted

4. Background, paragraph 2, 9: Should be “Moreover, evidence from northern …”

   F We accepted the comment and correction was made.

5. Methods, Study Design, Measurements, line 6-8: Does the extrapolation of population size for each year assume a constant population growth rate over the time period?

   F Yes, we have taken the population growth rate of 1997 to project the population size between the years 1997 and 2007 and population growth rate of 2007 to project the population size between the years 2007 and 2011 with the assumption of constant population growth rate during these years.
6. Methods, Study Design, Measurements, line 10: Should be “The fifteen year average of the number of all forms of TB …”

F We accepted the comment and corrected accordingly as per the comment.

8. Results, General characteristics, line 5: Should be “…were pulmonary smear positive ….”

F Comment is well taken and the word “pulmonary” was inserted

9. Results, Trends in DOTS Site Expansion and TB Case notifications, paragraph 1, line 1: Here and throughout when the term “DOTS Site expansion” is used it would be more accurate to say the “number of DOTS sites”.

F We accepted the comment” the word “DOTS site expansion” replaced by number of DOTS sites

10. Results, Trends in DOTS Site Expansion and TB Case notifications, paragraph 1, line 1: Here and throughout – the term trend here is unnecessary. Simply say “TB case notifications were significantly associated with the number of DOTS sites in Arsi zone (Fig 1, X2trends =75.2, p<0.001)”

F Yes of course, but in this study there are two main messages: first, to analyze the trend in TB case notification over fifteen years and, second, to measures the performance of TB programme across districts of the zone. Therefore, we feel that the word trend in this study is an important word to be kept in the manuscript in order to indicate the progress of TB programme over time.

11. Results, Trends in DOTS Site Expansion and TB Case notifications, paragraph 1, line 5: What does the X2 tend refer to here?

F We accepted the comment and remove the X2 as it was due to typological error

12. Results, Trends in DOTS Site Expansion and TB Case notifications, paragraph 2, line 1: No need for the word trend here.

F Comment was accepted and the word “Trends in” removed.

13. Results, Trends in DOTS Site Expansion and TB Case notifications, paragraph 2, line 5: No need for second trend in this sentence – for example “ Similar to the trend in all forms of TB notifications, PTB+ cases in the first four years of DOTS ….”

F We accept the comment and the second ‘trends’ removed
14. Discussion, paragraph 5, line 6-9: I do not fully understand this sentence – could be expressed more clearly

We accepted the comment and rephrased as follow: “However, our study showed that under the current passive TB case findings, the trend in TB case notification was not persistently increased though out the study period. This might warrant the involvement of health extension workers in active TB case finding in Ethiopian context to achieve the MDG of 70% case detection rate”

15. Discussion, paragraph 6, line 4: Should the sentence read “Likewise, the CDR increased by more than six-fold in fifteen years in Vietnam”?

Yes, we corrected as per the comment

16. Discussion, paragraph 8, line 1: Should the sentence read “Although the CDR of this study demonstrated an upward trend …”?

We accepted the comment and corrected accordingly

16. Discussion, paragraph 9, line 1: Should the sentence read “…..the PTB+ case notification and CDR of the zone steadily increased ….”?

Comment was well accepted and deleted “The findings of this study showed that”

17. Discussion, paragraph 9, line 7: pervious should be previous.

Comment is well taken and misspelled corrected

18. Discussion, paragraph 11, line 1: Should the sentence be “In this study, we identified variations in TB case notifications ….”?

Yes, correction made accordingly

19. Discussion, paragraph 12, line 2: Should the sentence be “….population, with a fourteen fold variation between different districts….”?

Yes, corrected accordingly

20. Discussion, paragraph 13: Repeats what has already been outlined in paragraph 12. Paragraph 12, 13 and 14 should be combined into one paragraph.

We accepted the comment and we made the change accordingly

21. Discussion, paragraph 15, line 2: Should be “… associated with the levels of TB notification.”

Comment was taken and corrected accordingly.

22. Discussion, paragraph 15, line 5-8: These two sentences do not make sense to me

We accepted the comment and removed two sentences in the paragraph 15 (line 5-8).