Author’s response to reviews

Title: Epidemiology of Tuberculosis in a low-incidence Italian region with high immigration rates: differences between foreign-born and Italy-born TB cases

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Response to Reviewers

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The authors wish to thank the Reviewers for their helpful comments and suggestions. Below please find our response. We have coloured red sections in the manuscript where changes were made.

Reviewer: 1

Major comments:

1. “In the results section Authors wrote about a linear regression analysis but they didn’t report any methodological description of this regression in the Methods section. Furthermore, results of the regression are not well explained (for example: the confidence intervals are referred to a value that Authors don’t write in the text!”

   - This point has been clarified. A linear regression model with estimate of unstandardized coefficients (B) and their confidential intervals (95%CI) was used to investigate the annual trend for incident TB cases and TB incidence rates. In addition, a p value labelling the observed significance level for the t statistics (which tested the hypothesis that B was 0) was reported. We have added the description of this linear regression in the “methods” section. Moreover, we have better explained the results of the linear regression in the “results” section adding the value of B to which the confidence intervals were referred to.
2. “In the results section Authors reported that some incidence trends were not significant, but what did they mean? Did they refer to “statistically significant”? In this case, Authors should specify which statistical test they applied to evaluate trend variations.”

- This point has been addressed in our response to the previous bullet point. We meant that the increase (or decrease, depending which result is considered) of TB incidence over time was “statistically significant”: A linear regression model with estimate of unstandardized coefficients (B) and their confidential intervals (95%CI) was used to investigate the annual trend for incident TB cases and TB incidence rates. In addition, a p value labelling the observed significance level for the t statistics (which tested the hypothesis that B was 0) was reported. We have added the description of this linear regression in the “methods” section. In addition, we have better explained the results of the linear regression in the “results” section adding the value of B to which the confidence intervals were referred.

3. “In order to make comparison for continuous variables, Authors performed ANOVA test and Tukey post-hoc test, but they should explain the reason why they used these tests instead of t-test (for comparison between two groups: Italian born and foreign born cases). Moreover, results of these statistical procedures were not described in the manuscript.”

- Continuous variables’ (i.e. age at notification) comparison has been re-performed using the Student t-test for unpaired data. This point has been specified in the "data sources and statistical analysis” section and results were consequently modified.

Minor comments:
**Reviewer’s comments** | **Response**
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4) Please, the Authors should use the same definition for the acronym ISTAT. In fact in the reference no. 11 they wrote “National Institute of Statistics”, but in the manuscript they reported “National Statistics Office” in the methods and “Italian Institute of Statistics” in the description of the statistical analysis. | The term “Italian National Institute of Statistics”, which is the official translation provided in its website, has now been consistently used throughout the text.

5) In the methods section Authors should write “Italian Healthcare system” instead of “Italian Health system”. | “Italian Health system” has been changed to “Italian Healthcare system”.

6) Please, Authors should write “Tukey post-hoc test” instead of “Turkey post-hoc test”. | The paragraph which included this term was removed after having addressed “major comment n.3”.

7) In the results section, Authors should check the punctuation in the sentence describing the Geographical origins of the sample. | The sentence has been revised.

8) Tables are not clear and could be improved: for example, Authors should indicate what is the reference group. Moreover, Authors should add in the footnotes which statistical tests they applied. | Tables have been modified. For each comparison we have indicated which was the reference group and footnotes describing which statistical tests were used have been added.

Reviewer: 2

1. “*Roughly a third of the world's population has been infected with Mycobacterium tuberculosis. In 2009 we had an estimate of 2 million deaths from tuberculosis (Tb) and 9 million new infections. There is probably more Tb – a curable disease!* - today in the
world than at any other time in history. The rise in HIV infections and the neglect of Tb control programs have been implicated as causes for the resurgence of Tb. The estimated annual occurrence is highest in Africa (with 32 per 100,000). In the so called high-income countries, Tb is less common and is mainly said to be an urban disease. The emergence of resistant strains has also contributed to this new epidemic with, from 2000 to 2004, 20 percent of Tb cases being resistant to standard treatments with a growing problem of extensively drug-resistant Tb.”

- Most of the statements introduced by the reviewer in this paragraph were mentioned in the “background” section of the paper. World data on resistant strains was not included in this section for the sake of concision and because not relevant to support our data that didn’t comprise information on drug resistance. Still, references of the “background” section have now been updated to include the latest WHO data on Tuberculosis epidemiology published after the submission of the first draft of our manuscript.

2. “Tb merits close interest from a public health point of view. Whether it should be “a public health priority” (italics mine) as the authors claim (Background: §1) is perhaps dependent on the context.”

- Our intention was not to place TB in terms of public health priority among other public health issues but to underline how in Italy as in other high-income countries increasing immigration rates have contributed to the re-emerge of TB as public health threat. “A public health priority” has now been modified to “a matter of public health concern” with appropriate reference[a1].

3. Tb can be difficult to diagnose. Health care staff must be alerted as to the existence of this infectious disease, especially in a traditionally low-endemic area, which Emilia Romagna seems to have been at least up to the 2000s. It is thus of importance to know what risk-factors to look out for when evaluating individual patients but also to understand their roots in social-political determinants; the former to contain infection, the latter to inform preventive policies.
• The reviewer has raised an interesting issue: health care staff, especially in a traditionally low-endemic areas, is at higher risk of missing TB diagnosis because not alerted as to the existence of this infectious disease. We mentioned this point in the last paragraph of the “discussion” section. In addition, we highlighted (in the 6th paragraph of the “discussion” section and in the “conclusion” section) the importance to know TB risk factors both at an individual and a community level. We have now strengthened these concepts after reviewer’s comments.

4. The authors could be clearer here in formulating their aims and objectives. Is their intention to describe the occurrence of Tb in Emilia Romagna over a ten-year period on a population level? And/or the description of the clinical features of registered Tb cases, or just immigrant cases, during the same time period? The Background section ends with “The aim of the current study …” and it is not clear (especially when one reads the first paragraph under Methods) which is the studied population.

• This point has been clarified. Aim of our study was to present the epidemiology of TB in the Emilia-Romagna region over a ten-year period and to analyse in details the differences between foreign-born and Italy-born TB cases concerning personal data, clinical features and risk factors for TB infection and transmission. Subjects notified with TB over that period are the study population (which includes Italy-born and foreign-born subjects). The aims and objectives of the study have been better explained and concentrated in the last paragraph of the “background” section and not split between the “background” and the “methods” sections as was before.

5. “I think it important to be precise in how one defines and uses “foreign-born”, “legal”, “illegal immigrant” and other like concepts. Which leads over to the question of ethics.”

• We agree with the reviewer on the importance to be precise and objective when defining specific subgroups of the population in the migration framework. Therefore, we classified subjects by country of origin in “Italian-born” and
“foreign-born” subjects. In addition, foreigners were differentiated in “regularly registered” and “illegal” depending on possession of residence permit. Following the reviewer comment, we have now checked these two terms were consistently used through all the parts of the text and we have changed misleading definitions. We have also added a paragraph in the methods section (under “setting”) to explain how we defined specific subgroups.

6. “The paragraph on Ethics is not satisfactory at all. A register study does not absolve you from considerations of the consequences of what you are doing. A study like this can full well be used to stigmatize groups of people and even if this in no way was the intention by the authors, they should reflect on the moral of doing ‘risk group epidemiology’.”

- The paragraph has been modified. We have added that the protocol was reviewed not only by the Department of Public Health at the University of Parma but also by the Regional Health Authorities and that data were anonymous. Moreover, we are convinced that studying the differences between Italy-born and foreign-born subjects concerning the risk of TB infection and spread could help to contain TB infection, inform preventive policies and design effective TB control measures and it does not contribute to stigmatize groups of people. Our paper provides several references of important studies that focused on TB features among immigrant populations in low-TB-incidence countries without stigmatize groups of people.

7. “We know a lot about the natural course of an infection by M. tuberculosis and that Tb is a disease of poverty. We know that the occurrence of Tb varies with age. In high-endemic countries like Africa, Tb primarily affects adolescents and young adults. In countries where Tb has gone from high to low incidence, as in Scandinavia, Tb is mainly a disease of older people, or of the immune-compromised. The outcome of an infection with M. tuberculosis also varies with age. The initial infection is usually seen in small children. In nearly all cases the initial focus of infection is contained with no further spread of the infection. Ninety percent of those infected with Tb is said to mount an effective immune response and will never develop the disease. So called Secondary
tuberculosis (Adult Tb) is seen mostly in younger adults as a reactivation of a previous infection or as a re-infection. The infection is almost always acquired by inhalation of infected aerosol droplets generated by people with active pulmonary disease, cavitations, and coughing. So from a public health point of view the interesting issues would be to examine the risk factors for Tb transmission, i.e. pulmonary Tb.”

- This point has been addressed in our response to comments n.3 and n.4 and n.6

8. The registers in Emilia Romagna seem to contain a lot of variables. As a reader I would like to know how many and why some of them (or all?) were used. Which variables were discarded in the presentation and why? The idea that comes to mind is a figure of a ‘web of causation’ and an ensuing appropriate type of regression analysis.

- We have clarified on this point. The Regional TB surveillance system active in Emilia Romagna compiles TB notifications (TB disease in Italy is subject to mandatory reporting) of people diagnosed with TB in the region. It regularly records surveillance data, data on treatment outcome and from 2005 onwards, also data on drug resistances. From the database of the Regional TB surveillance system we extracted relevant information to describe characteristics of TB-affected population, to identify specific sub-groups at risk and to analyze temporal trend of disease in the region over the years. We have now added a paragraph in the “data sources and statistical analysis” section to explain what is the Regional TB surveillance system and which variables we extracted from it and why. Data on drug resistance were not included in our analysis because, although of interest for our aims, were found to be largely incomplete.

9. “In Data sources and statistical analysis the authors write “...were compared using ANOVA test and Turkey’s post-hoc test.” This is not precise enough and “Turkey” is wrong. ANOVA is not just one test, it stands for different analyses of variance, e.g. Student’s t-test for comparison of two groups. For which groups were Tukey’s post-hoc test used?”
• This point has been addressed in our response to Reviewer 1 (Major Comments, n.3). Continuous variables’ (i.e. age at notification) comparison has been re-performed using the Student t-test for unpaired data. This point has been specified in the "data sources and statistical analysis" section and results were consequently modified.

10. “The calculation of incidence is probably not made as a “rate”, but a ratio, since there is no indication that the authors have used a density approach.”

• The calculation of incidence is not considered as a ratio since the numerator (TB cases) is included in the denominator (total population for each year). Our calculation of incidence is an ‘incidence proportion’ in a year period. For its calculation, we considered number of TB cases for a given year on the total population for that given year expressed per 100 000 inhabitants which could be considered equal to incidence rate (new TB cases/100 000 population per year). Data on total population were taken, as detailed in the “data sources and statistical analysis”, from the demographic data of the Italian National Institute of Statistics and refers to the balances on resident population on 31st December of the previous year for each considered year. For the sake of precision, “incidence rate” has been replaced by “incidence” or “incidence proportion” all along the text.

11. The denominator is evidently a problem since people exist outside registers and tend perhaps to do more so, when they are afraid of being repatriated if they are diagnosed with Tb and/or HIV. Whether the figure of 20 percent for “illegal immigrant presence” is valid is difficult to judge, since the authors refer to an Italian source where the demographic balances for foreign population is not given in English. If the estimated “illegal population” is added to the denominator, then there should be consequences for the numerator too, according to the assumption above of fear for repatriation

• The reviewer has raised an interesting issue: estimation of TB incidence rates among foreign-born subjects is difficult. We agree that the denominator is evidently a problem as we stated while discussing the limits of our study in the “discussion” section. Denominator for the immigrant population which only
considers regularly resident immigrants leads to overestimation of TB incidence proportions. Moreover, illegal immigrants are not easily quantified and no official data are available in the Emilia-Romagna region. We used the estimate of 20% of illegal immigrant presence as previously inferred in the section on foreigners’ health status in the 2007 report of the report 2007 of the National Observatory of health in Italian Regions, a highly qualified Italian scientific institution. That has been the first publication that tried to quantify national TB incidence rates in the immigrant population. No modifications were made to the numerator neither in that model nor in ours. In fact, assuming that notification system is quite efficient in Italy and that heath assistance is guaranteed also to illegal immigrants in the Italian Healthcare system, we trusted the notification data to be a good estimate of TB occurrence in the region. In addition, In Emilia-Romagna as compared to other Italian regions, there is a quite efficient network of private, public and volunteer services offering healthcare assistance to “illegal” immigrants. Nevertheless, following the reviewer’s comments we have now given a more detailed description (in the “data sources and statistical analysis” section) of the content of the important publication we referred to as it is a non-English source. In addition, limitations of our work concerning this point have now been stated more clearly in the “discussion” section.

13. “Assistance with the article’s English language is needed”

- The paper had been revised by a native English speaker for English language editing. He has been acknowledged in the “acknowledgements” section

14. Conclusions:

The title does not accurately convey what has been done.
The research question posed by the authors is not well defined.
The methods chosen could be questioned and are not sufficiently well described.
Limitations of the work and problems with generalization could be stated more clearly.
The ethical problems need to be reflected upon.
All the points mentioned in the reviewer’s conclusion have been addressed and elaborated. With regard to the choice of the title, we partly agree that it does not accurately convey what has been done; on the other hand it gives information on the setting (a low-TB-incidence area of Italy) and on the major sub-group at risk for TB infection (foreign-born population) highlighting that its presence is increasing (high immigration rates). Taking into consideration reviewers’ comment, we have changed the title to: “Epidemiology of Tuberculosis in a low-incidence Italian region with high immigration rates: differences between foreign-born and Italy-born TB cases”