

## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Determinants of patient and health system delay among Italian and foreign-born pulmonary tuberculosis patients: a multicentre cross-sectional study
<b>AUTHORS</b>	Quattrocchi, Annalisa; Barchitta, Martina; Nobile, Carmelo; Prato, Rosa; Sotgiu, Giovanni; Casuccio, Alessandra; Vitale, Francesco; Agodi, Antonella

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Johann Cailhol Avicenne teaching hospital and University Paris Nord Seine-St-Denis, Infectious diseases unit, France
<b>REVIEW RETURNED</b>	09-Oct-2017

<b>GENERAL COMMENTS</b>	<p>This is an interesting and important topic about delay before pulmonary TB diagnosis in 4 provinces in Italy. However, there are a number of issues, including methodological, that need to be addressed before the paper could be considered for publication.</p> <p>The first issue is around inclusion criteria and definitions: are included TB cases smear positive or negative? did authors include illegal migrants? how did they exclude TB relapse? Etc. Authors cannot just write "definitions of delay are those adopted by USAID", in a paper on TB diagnosis delay. There are a number of "acceptable delay" definition in the literature, and authors need to explain why they chose the USAID definition and should detail the definition in the methods section.</p> <p>The second biggest issue is around statistics.</p> <ul style="list-style-type: none"> <li>• Could authors provide details on the sample calculation.</li> <li>• Authors should also describe the distribution of delays data and check whether it is better to use the mean of the median for comparison. Authors should consider using a common cut-off, such as 30 days for patients delay, or 15 days for health system delay, in order to compare their patients delay to an "acceptable" delay (even if there is no consensus, there are some hints in the literature).</li> <li>• Comparing the group with delay &lt; mean and the group with delay &gt; mean does not seem appropriate to the study. It would be more appropriate to see whether the whole group has a longer mean/median delay compared to what is known in other countries with similar contexts. And then authors should look at factors associated with delays &gt; 30 days (ideal delay for PD), and compare with median (mean ?) delays in neighboring countries.</li> </ul> <p>Minor issues Abstract Results and conclusions are not connected.</p> <p>Strengths and limitations The first bullet could be a strength but authors need to explain why.</p>
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	<p>The second bullet is not a strength nor a limitation of the study.</p> <p>What this study adds ? This section is a copy paste of the strengths and limitations section.</p> <p>Introduction Line 5 : authors should add a reference, especially for « poor response to therapies ». To me, it is a consequence of poor adherence, rather a consequence of diagnosis delay.</p> <p>Authors state, line 42, that « few studies explored social factors and epidemiology of diseases ». When I searched on pubmed « delay[All Fields] AND ("tuberculosis"[MeSH Terms] OR "tuberculosis"[All Fields]) AND ("diagnosis"[Subheading] OR "diagnosis"[All Fields] OR "diagnosis"[MeSH Terms]) AND social[All Fields] AND determinants[All Fields] », i found more than 900 articles. So they should probably reformulate their sentence and perhaps re-contextualise this in Italy.</p> <p>Methods The biggest issues are exposed in the first section of this review.</p> <p>Results Authors reported the degree of poverty and literacy, but this should be defined in the methods section first. Table 1 : what is included in the label « chronic diseases » ? Generally speaking, it is difficult to read the tables when included in the body of the manuscript.</p> <p>Discussion The study reports an association between longer PD and unintentional weight loss and chest pain. What are the authors' hypothesis ? Is this because patients relate the 2 symptoms to TB and are afraid of stigma ? What are the hypothesis in the literature on the association between longer PD and chest pain or weight loss ?</p> <p>There is no trial registration number nor data reporting quality checklist.</p>
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<b>REVIEWER</b>	Alicia Vedio Sheffield Teaching Hospitals NHS Foundation Trust, UK None declared
<b>REVIEW RETURNED</b>	16-Oct-2017

**GENERAL COMMENTS**

1. Is the research question or study objective clearly defined?



The research question is clearly defined as identifying barriers influencing patient delay and health system delay. However, these should not be considered to be ALL factors as suggested in the section strengths and limitations in page 3. A study addressing other stakeholders may be necessary to understand all factors.



2. Is the abstract accurate, balanced and complete?



The abstract is complete and balanced, the response rate (344 contacted) vs (253 analysed) it is not mentioned explicitly but assuming those are the figures, the response rate is very good. Can the authors verify no responses have been excluded?



3. Is the study design appropriate to answer the research question?



The study is carried out using a quantitative design in the form of a face-to-face survey. The research question aims to identify factors associated with delay in pulmonary TB diagnosis/treatment. The questionnaire is exhaustive and useful to identify factors from patient report of their experience. To explore further, for example motivations, opportunities and cultural issues could be done using a qualitative design.

		<p>Also studies based in health services may identify further factors not seen in this study. Overall the study is good.</p>
	<p>4. Are the methods described sufficiently to allow the study to be repeated?</p>	<p><input type="radio"/> The study is well described and sufficiently detailed to allow the study to be repeated.</p>
	<p>5. Are research ethics (e.g. participant consent, ethics approval) addressed appropriately?</p>	<p><input type="radio"/></p> <p><input type="radio"/> There were informed consent obtained by the authors from all participants, I am not sure of the procedures in Italy, the funder was the Ministry of Health and it appears to also have approved the study. Is there an Ethical approval registry or body?</p> <p><input type="radio"/></p>
	<p>6. Are the outcomes clearly defined?</p>	<p><input type="radio"/></p> <p><input type="radio"/> Not applicable</p> <p><input type="radio"/></p>

	<p>7. If statistics are used are they appropriate and described fully?</p>	<input type="radio"/> <input type="radio"/> I believe they are, but it would benefit from expert review <input type="radio"/>
	<p>8. Are the references up-to-date and appropriate?</p>	<input type="radio"/> <input type="radio"/> References seem to be up to date, although some do not seem to relate to the text (see discussion, line 27, reference 16) Please ensure all references are correct. <input type="radio"/>
	<p>9. Do the results address the research question or objective?</p>	<input type="radio"/> <input type="radio"/> The results do address the research question and provides useful evidence. <input type="radio"/>
	<p>10. Are they presented clearly?</p>	<input type="radio"/> <input type="radio"/> Results are presented in a manner that is <input type="radio"/>
	<p>11. Are the discussion and conclusions justified by the results</p>	<input type="radio"/> <input type="radio"/> Yes <input type="radio"/>

	<p>12. Are the study limitations discussed adequately?</p> <p><input type="radio"/></p> <p><input type="radio"/> Yes</p> <p><input type="radio"/></p>
	<p>13. Is the supplementary reporting complete (e.g. trial registration; funding details; CONSORT, STROBE or PRISMA checklist)?</p> <p><input type="radio"/></p> <p><input type="radio"/> No trial registration shown or strobe statement on supplementary material. Please see above for Ethical registration.</p> <p><input type="radio"/></p>
	<p>14. To the best of your knowledge is the paper free from concerns over publication ethics (e.g. plagiarism, redundant publication, undeclared conflicts of interest)?</p> <p><input type="radio"/></p> <p><input type="radio"/> Yes</p> <p><input type="radio"/></p>
	<p>15. Written English</p> <p><input type="radio"/></p> <p><input type="radio"/></p> <p><input type="radio"/> Yes.</p>

<b>REVIEWER</b>	Constantinos Siettos National Technical University of Athens, Greece None declared
<b>REVIEW RETURNED</b>	06-Dec-2017

<b>GENERAL COMMENTS</b>	<p>The authors present a study on the risk factors for patients and health system delays among Italian and foreign-born pulmonary TB in Italy. The study considers 4 regions of Italy, namely, Calabria, Apulia, Sardinia, and Sicily.</p> <p>For their analysis the authors considered main categories of factors such as socio-demographic, integration index, TB risk factors and knowledge/attitude about the infection and access to TB diagnosis and health seeking. Overall the study is interesting and contributes positively to the existing literature towards the better treatment and prevention of TB.</p>
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	<p>There are some minor and major points that I outline below which the authors should accommodate in a revised version of their manuscript.</p> <ol style="list-style-type: none"> <li>1. Grammatical and other minor points <ul style="list-style-type: none"> <li>-being permanent or temporary resident □ residency</li> <li>In “Strengths and limitations of this study”</li> <li>-all factors □ key factors</li> <li>-Please break the first sentence of the 2nd bullet in shorter sentences.</li> <li>-to identify all factors □ to identify key factors</li> <li>-with the task to facilitating □ to facilitate</li> <li>-study;[13] □ study [13];</li> </ul> </li> <li>2. The authors state that the quantitative variables were compared using Student’s t test or the Mann-Whitney U test. But they don’t say when they used the one or the other. Thus in the results the authors should also mention the test that they used for comparison between groups. For example, in the sentence “patients who refused the interview were older than patients who agreed (46.0 vs. 40.7 years, P &lt; 0.023)” the authors do not say about the choice of the statistical test. I guess that they used Students t-Test as the sample is big enough but they should explicitly mention it (as this is relevant to point 2 above)</li> <li>3. In the discussion the authors refer to the similarity with other countries but they don’t bring specific examples. For completeness they should also review the literature and compare their results with studies performed in other countries where available.</li> <li>4. The limitations of the study are not defined adequately. For example the authors discuss and analyse several factors. But they should justify their choice and also discuss about the possibility of including other factors in the analysis (e.g. environmental, the presence of other epidemics that would facilitate the emergence of TB). That’s why I suggested above substituting the term “all factors” with the term “key factors”. However a well structured discussion about the limitations of the study (citing also relevant studies in the field) is missing.</li> </ol>
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<b>REVIEWER</b>	Jamie Wagner University of Mississippi School of Pharmacy, USA
<b>REVIEW RETURNED</b>	07-Dec-2017

<b>GENERAL COMMENTS</b>	<p>The project idea is valuable to clinicians worldwide, however, the reporting of the methods and results makes it difficult to determine the full impact of this study. Some suggestions for improvement are listed below.</p> <p>Introduction:</p> <ol style="list-style-type: none"> <li>1. The sentence beginning with “In 2015 in Italy...” is out-of-place and can be removed.</li> <li>2. It is unclear which type of delay this study is focusing on: diagnostic delay or treatment delay. It would benefit the reader to have the authors clarify this within the “aim of the present study...” sentence.</li> </ol>
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	<p>Methods – Study Design:</p> <ol style="list-style-type: none"> <li>1. Please clarify what “in the framework of an Italian project” means.</li> <li>2. Please provide definitions for the following variables: permanent resident, temporary resident.</li> <li>3. Please list an appropriate study design (e.g., cross sectional).</li> </ol> <p>Methods – Data collection and definitions:</p> <ol style="list-style-type: none"> <li>1. Please clarify how the mediator facilitated communication and understanding (i.e., was this standardized from patient to patient)?</li> </ol> <p>Methods – Statistical analysis:</p> <ol style="list-style-type: none"> <li>1. If running a Shapiro-Wilk test for normality, should also be running the Levene test for homogeneity of variance. This will help clarify if you should use non-parametric (e.g., Mann-Whitney U and Fisher’s Exact and median [IQR]) tests and reporting. Based on the difference between the reported means and median delays, the data appear to be non-normally distributed with a heterogeneous variance.</li> <li>2. Unclear what the reason is for stating that the crude ORs were computed, as no comparison groups have been identified.</li> <li>3. Unclear why a correlation analysis was performed, as no outcomes or comparator groups were identified.</li> <li>4. Please provide a citation for using the median value as an appropriate cut-off point for dichotomizing quantitative variables. Otherwise, a more appropriate methodology would be to perform a classification and regression tree (CART) analysis to find the natural divide in the data.</li> <li>5. Please specify which delays were analyzed in the logistic regression model (e.g., patient, health system, total, all three).</li> <li>6. For the regression analysis, please specify the regression parameters (e.g., variables allowed into the model at any given point, breakpoint for removing variables for the model, if any variables were forced into the model, etc).</li> </ol> <p>Results:</p> <ol style="list-style-type: none"> <li>1. This section is very difficult to understand as no outcomes and comparator groups were identified in the methods. Once those are clarified, that should help to better frame this section.</li> <li>2. Be very cautious with collinear variables (e.g., stigma and good knowledge of TB), which will throw off your analyses and subsequently, your interpretation of the data.</li> </ol> <p>Discussion:</p> <ol style="list-style-type: none"> <li>1. Much of this section seems to be more speculation and using previous studies rather than drawing conclusions based on the data presented in the results section. Consider drawing conclusions based on your own data.</li> <li>2. Consider stating how limitations were accounted for or minimally and how those limitations could have impacted the study results. Additionally, pending choice of study design, would need to include limitations specific to that study design.</li> <li>3. Consider expanding on strengths of the study and how those strengths impacted the study results.</li> </ol> <p>Additional Suggestions/Comments:</p> <ol style="list-style-type: none"> <li>1. Information written in the abstract, “strengths and limitations of this study”, “what is already known on this subject”, and “what this study adds” is not addressed.</li> </ol>
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	<p>2. As per BMJ Open's requirement, please include IRB information (exempt, approved, etc) and information required in STROBE statement.</p> <p>3. Assessment of the tables is not addressed.</p>
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### VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Johann Cailhol

Institution and Country: Avicenne teaching hospital and University Paris Nord Seine-St-Denis, Infectious diseases unit, France

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

Please leave your comments for the authors below

This is an interesting and important topic about delay before pulmonary TB diagnosis in 4 provinces in Italy.

However, there are a number of issues, including methodological, that need to be addressed before the paper could be considered for publication.

The first issue is around inclusion criteria and definitions: are included TB cases smear positive or negative? did authors include illegal migrants? how did they exclude TB relapse? Etc.

In order to clarify inclusion criteria and definitions, the following sentence has been added to the text in the Methods section:

“Patients’ inclusion criteria were being diagnosed as a new smear positive of pulmonary TB case and living in one of the above-mentioned Italian regions. Negative smear, relapse, retreatment and extrapulmonary TB cases were excluded. Foreign-born patients were enrolled regardless of their legal status (e.g. refugees, asylum seeker, illegal migrants).”

Authors cannot just write "definitions of delay are those adopted by USAID", in a paper on TB diagnosis delay. There are a number of "acceptable delay" definition in the literature, and authors need to explain why they chose the USAID definition and should detail the definition in the methods section.

The definitions of each type of delay under study, together with the most relevant references, have been provided in detail, as follows:

“PD was defined as the time interval between the onset of symptoms and patient’s first contact with any type of health care service (including hospital and primary health care).<sup>16,17</sup> HSD was defined as the time interval between the first consultation with a health care provider and the initiation of treatment.<sup>16,17</sup> This can be subdivided into: diagnostic delay (DD) as the time interval between the presentation to a health care provider and the date of diagnosis and treatment delay (TD) as the time interval between TB diagnosis and initiation of anti-TB treatment. Thus, TOTD was defined as the time interval from the onset of symptoms until the treatment initiation.<sup>17,18</sup>”

16. World Health Organization. Diagnostic and treatment delay in tuberculosis. WHO; Geneva, 2006. <http://applications.emro.who.int/dsaf/dsa710.pdf> (accessed 26 Apr 2014).

17. USAID. Reducing Delays in TB Diagnosis: Data Collection Tools to evaluate the cause and frequency of TB delays. 2011.

[http://www.challengetb.org/publications/tools/ua/Data\\_Collection\\_Tool\\_TB\\_Patient\\_Delay.pdf](http://www.challengetb.org/publications/tools/ua/Data_Collection_Tool_TB_Patient_Delay.pdf) (accessed 26 Apr 2014)

18. Sreeramareddy CT, Qin ZZ, Satyanarayana S, et al. Delays in diagnosis and treatment of pulmonary tuberculosis in India: a systematic review. *Int J Tuberc Lung Dis* 2014;18(3):255-66. doi: 10.5588/ijtld.13.0585

The second biggest issue is around statistics.

Could authors provide details on the sample calculation.

A new paragraph in the methods section has been added providing details about sample size calculation as follows:

“Sample Size calculation and Sampling Procedure

A sample size of 261 was estimated by using single population proportion estimation formula with an assumption of 95% confidence interval, 6% margin of error, and 50.4% proportion of PD (> 30 days).<sup>14</sup>

Furthermore, considering 20% of nonresponse rate, the final sample size was 321. All patients meeting the inclusion criterion, attending the healthcare facility during the study period, were prospectively invited to participate in the study.”

14. Pezzotti P, Pozzato S, Ferroni E, et al. Delay in diagnosis of pulmonary tuberculosis: A survey in the Lazio region, Italy. *Epidemiol Biostat Public Health* 2015;12:1-10.

Authors should also describe the distribution of delays data and check whether it is better to use the mean of the median for comparison. Authors should consider using a common cut-off, such as 30 days for patients delay, or 15 days for health system delay, in order to compare their patients delay to an "acceptable" delay (even if there is no consensus, there are some hints in the literature).

We would like to thank the Reviewer for this important comment. The body of evidence about common cut-off for delay is still not exhaustive. Indeed, opinions on acceptable cut-off are discordant. Furthermore, an important issue to take into consideration is the study setting. Since the present study has been conducted in Italy, a Country with low TB prevalence, we decided to apply the cut-offs from previous Italian studies (Pezzotti et al., 2015; Gagliotti et al., 2006). Thus, we used a cut-off of 30 days for PD and the median value observed in the study population for HSD. Notably, in our study population the median PD value was also 30 days.

Thus, we amended the text of the manuscript, in the Methods section, as follows:

“Longer delays (outcome) were defined according to previous Italian studies. Particularly, long PD was defined as >30 days, while long HSD and TOTD were defined as > the median value observed in the study population, for HSD and TOTD, respectively.<sup>14,19</sup>”

We have added the following references:

14. Pezzotti P, Pozzato S, Ferroni E, et al. Delay in diagnosis of pulmonary tuberculosis: A survey in the Lazio region, Italy. *Epidemiol Biostat Public Health* 2015;12:1-10.

19. Gagliotti C, Resi D, Moro ML. Delay in the treatment of pulmonary TB in a changing demographic scenario. *Int J Tuberc Lung Dis* 2006;10(3):305-9.

Comparing the group with delay < mean and the group with delay > mean does not seem appropriate to the study. It would be more appropriate to see whether the whole group has a longer mean/median delay compared to what is known in other countries with similar contexts. And then authors should look at factors associated with delays > 30 days (ideal delay for PD), and compare with median (mean ?) delays in neighboring countries.

Accordingly, in the revised manuscript, comparisons of means delays have been deleted. Thus, all analyses investigating the factors associated with delay are now only performed using the established cut-offs. Furthermore, comparison with data from other countries is reported in the discussion section. Methods section:

“Longer delays (outcome) were defined according to previous Italian studies. Particularly, long PD was defined as >30 days, while long HSD and TOTD were defined as > the median value observed in the study population, for HSD and TOTD, respectively.<sup>14,19</sup>”

and

“The characteristics of patients with longer delays (all forms) were compared to those of patients without (comparators) and the crude odds ratios (ORs) and the corresponding 95% confidence intervals (95% CIs) were computed.”

#### Discussion section

“In our study, the median values for PD (30 days), HSD (11 days, of which 7 days for DD and 2 days for TD, respectively), and TOTD (45 days) are similar to those reported by other studies conducted in Italy and in other European countries with a low-TB incidence. Particularly, a recent Italian study reported median PD and HSD values of 31 and 15 days, respectively.<sup>14</sup> European studies reported median PDs of 14 days (France),<sup>26</sup> 28 days (Norway),<sup>27</sup> and 29 days (UK).<sup>20</sup> Considering HSD (and its two components), studies reported median values of 15 days (Croatia),<sup>28</sup> 25 days (for DD in France),<sup>26</sup> 30 days (UK),<sup>20</sup> and 33 days (Norway).<sup>27</sup> Median values for TOTD ranged between 62 days (UK),<sup>20</sup> and 63 days (Norway).<sup>27</sup>”

#### References

14. Pezzotti P, Pozzato S, Ferroni E, et al. Delay in diagnosis of pulmonary tuberculosis: A survey in the Lazio region, Italy. *Epidemiol Biostat Public Health* 2015;12:1-10.
19. Gagliotti C, Resi D, Moro ML. Delay in the treatment of pulmonary TB in a changing demographic scenario. *Int J Tuberc Lung Dis* 2006;10(3):305-9.
20. Saldana L, Abid M, McCarthy N, et al. Factors affecting delay in initiation of treatment of tuberculosis in the Thames Valley, UK. *Public Health* 2013;127(2):171-7. doi: 10.1016/j.puhe.2012.11.010
26. Tattevin P, Che D, Fraisse P, et al. Factors associated with patient and health care system delay in the diagnosis of tuberculosis in France. *Int J Tuberc Lung Dis* 2012;16(4):510-5. doi: 10.5588/ijtld.11.0420
27. Farah MG, Rygh JH, Steen TW, et al. Patient and health care system delays in the start of tuberculosis treatment in Norway. *BMC Infect Dis* 2006;6:33. doi: 10.1186/1471-2334-6-33
28. Jurcev-Savicevic A, Mulic R, Kozul K, et al. Health system delay in pulmonary tuberculosis treatment in a country with an intermediate burden of tuberculosis: a cross-sectional study. *BMC Public Health* 2013;13:250. doi: 10.1186/1471-2458-13-250

#### Minor issues

##### Abstract

Results and conclusions are not connected.

Please refer to the new version of the revised abstract

##### Strengths and limitations

The first bullet could be a strength but authors need to explain why.

The first bullet point has been modified as follows:

“This is the first multiregional cross-sectional study, in Italy, investigating the association of key factors with patient delay, health system delay and total delay in pulmonary tuberculosis patients.”

The second bullet is not a strength nor a limitation of the study.

This point has been eliminated

##### What this study adds?

This section is a copy paste of the strengths and limitations section.

According to the Journal guidelines, the section “What this study adds” has been eliminated.

#### Introduction

Line 5: authors should add a reference, especially for « poor response to therapies ». To me, it is a consequence of poor adherence, rather a consequence of diagnosis delay.

According to the Reviewer suggestion, the sentence has been amended and new references were added.

“Long delays lead to a more advanced disease that may result in poor response to therapies, undesirable clinical sequelae, and higher mortality risk.5 Delay also increases the risk of developing anti-TB drug resistance leading to treatment failure.6”

5. Gebreegziabher SB, Bjune GA, Yimer SA. Total Delay Is Associated with Unfavorable Treatment Outcome among Pulmonary Tuberculosis Patients in West Gojjam Zone, Northwest Ethiopia: A Prospective Cohort Study. PLoS One 2016;11(7):e0159579. doi: 10.1371/journal.pone.0159579

6. Mahato RK, Laohasiriwong W, Vaeteewootacharn K, et al. Major Delays in the Diagnosis and Management of Tuberculosis Patients in Nepal. J Clin Diagn Res 2015;9(10):LC05-9. doi: 10.7860/JCDR/2015/16307.6633

Authors state, line 42, that « few studies explored social factors and epidemiology of diseases ».

When I searched on pubmed « delay[All Fields] AND ("tuberculosis"[MeSH Terms] OR "tuberculosis"[All Fields]) AND ("diagnosis"[Subheading] OR "diagnosis"[All Fields] OR "diagnosis"[MeSH Terms]) AND social[All Fields] AND determinants[All Fields] », i found more than 900 articles. So they should probably reformulate their sentence and perhaps re-contextualise this in Italy.

According to the Reviewer suggestion, the sentence has been re-contextualised, as follows:

“However, especially in Italy and in other European countries, as well, few studies have focused on social determinants and TB delays”

#### Methods

The biggest issues are exposed in the first section of this review.

#### Results

Authors reported the degree of poverty and literacy, but this should be defined in the methods section first.

The following definitions have been provided:

“Poverty was defined in relation to housing circumstances as living in community centres, first aid centres or prisons. Education level was dichotomised into two categories (high and low), using a cut-off of 8 school years.”

Table 1: what is included in the label « chronic diseases » ?

In order to clarify, the following legend has been provided in table 1:

“† HIV/AIDS, diabetes, chronic obstructive pulmonary disease, disability, renal failure, cardiovascular disease”

Generally speaking, it is difficult to read the tables when included in the body of the manuscript.

Tables are now in a separate section at the end of the manuscript

#### Discussion

The study reports an association between longer PD and unintentional weight loss and chest pain. What are the authors' hypothesis ? Is this because patients relate the 2 symptoms to TB and are afraid of stigma ?

What are the hypothesis in the literature on the association between longer PD and chest pain or weight loss?

According to the Reviewer suggestion, the paragraph has been amended as follows:

“The reason that chest pain and weight loss were associated with PD is not clear. Although, these symptoms together with cough are considered key TB symptoms.

Other studies retrieved similar results. Chest pain was found positively associated with longer PD (> 90 days) in a Brazilian study,<sup>33</sup> and with TOTD (>60 days) in Ethiopia.<sup>29</sup> Similarly, weight loss was associated with longer PD, both in Brazil (>30 days)<sup>33</sup> and in Italy (>15 days),<sup>14</sup> with PD (>27 days) and TOTD (>50 days) in Uzbekistan,<sup>34</sup> and with HSD (>18 days) in another Brazilian study.<sup>35</sup> These results could be explained by the fact that patients considered these as transient symptoms from a general illness, hence, maybe, initiating self-treatment lasting until deterioration and manifestation of other specific symptoms. Furthermore, timely referral to healthcare facilities for disabling symptoms may be challenging for migrants due to financial constraints, poor health literacy, and stigma. In addition, a long delay, favours disease progression and therefore symptom appearance. Also, non-specific symptoms could lead to longer suspicion delays by the clinician.”

14. Pezzotti P, Pozzato S, Ferroni E, et al. Delay in diagnosis of pulmonary tuberculosis: A survey in the Lazio region, Italy. *Epidemiol Biostat Public Health* 2015;12:1-10.

29. Gebreegziabher SB, Bjune GA, Yimer SA. Patients' and health system's delays in the diagnosis and treatment of new pulmonary tuberculosis patients in West Gojjam Zone, Northwest Ethiopia: a cross-sectional study. *BMC Infect Dis* 2016;16(1):673. doi: 10.1186/s12879-016-1995-z

33. Maciel EL, Golub JE, Peres RL, et al. Delay in diagnosis of pulmonary tuberculosis at a primary health clinic in Vitoria, Brazil. *Int J Tuberc Lung Dis* 2010;14(11):1403-10.

34. Belkina TV, Khojiev DS, Tillyashaykhov MN, et al. Delay in the diagnosis and treatment of pulmonary tuberculosis in Uzbekistan: a cross-sectional study. *BMC Infect Dis* 2014;14:624. doi: 10.1186/s12879-014-0624-y

35. Deponti GN, Silva DR, Coelho AC, et al. Delayed diagnosis and associated factors among new pulmonary tuberculosis patients diagnosed at the emergency department of a tertiary care hospital in Porto Alegre, South Brazil: a prospective patient recruitment study. *BMC Infect Dis* 2013;13:538. doi: 10.1186/1471-2334-13-538

There is no trial registration number nor data reporting quality checklist.

This is an observational study and thus, no trial registration number was required.

Reviewer: 2

Reviewer Name: Alicia Vedio

Institution and Country: Sheffield Teaching Hospitals NHS Foundation Trust, UK

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

Please leave your comments for the authors below

This study is valuable and presents credible evidence. For my detailed review please see comments on all questions in attached document.

1. Is the research question or study objective clearly defined?

The research question is clearly defined as identifying barriers influencing patient delay and health system delay. However, these should not be considered to be ALL factors as suggested in the section strengths and limitations in page 3. A study addressing other stakeholders may be necessary to understand all factors.

According to the Reviewer suggestion, in order to better clarify, the term “all factors” was replaced with the term “key factors” throughout the text including the section “Strengths and limitations”.

Furthermore, the following sentence has been added in the Discussion section:

Discussion

“In the present study, several aspects have been investigating as key factors contributing to delay in TB patients. However, further studies addressing other components of delay<sup>7, 32, 38</sup> and other stakeholders may be necessary to understand all factors that are closely associated with delay.”

7. Storla DG, Yimer S, Bjune GA. A systematic review of delay in the diagnosis and treatment of tuberculosis. *BMC Public Health* 2008;8:15. doi: 10.1186/1471-2458-8-15

32. Li Y, Ehiri J, Tang S, et al. Factors associated with patient, and diagnostic delays in Chinese TB patients: a systematic review and meta-analysis. *BMC Med* 2013;11:156. doi: 10.1186/1741-7015-11-156

38. Getnet F, Demissie M, Assefa N, et al. Delay in diagnosis of pulmonary tuberculosis in low-and middle-income settings: systematic review and meta-analysis. *BMC Pulm Med* 2017;17(1):202. doi: 10.1186/s12890-017-0551-y

2. Is the abstract accurate, balanced and complete?

The abstract is complete and balanced, the response rate (344 contacted) vs (253 analysed) it is not mentioned explicitly but assuming those are the figures, the response rate is very good. Can the authors verify no responses have been excluded?

We have verified that no responses have been excluded and the abstract has been modified as follows:

“A total of 344 patients from 30 healthcare centres were invited to participate and 253 patients were included in the analysis (26.5% non-response rate).”

3. Is the study design appropriate to answer the research question?

The study is carried out using a quantitative design in the form of a face-to-face survey. The research question aims to identify factors associated with delay in pulmonary TB diagnosis/treatment. The questionnaire is exhaustive and useful to identify factors from patient report of their experience. To explore further, for example motivations, opportunities and cultural issues could be done using a qualitative design. Also studies based in health services may identify further factors not seen in this study. Overall the study is good.

The following sentence has been added in the Discussion section:

Discussion

“In the present study, several aspects have been investigating as key factors contributing to delay in TB patients. However, further studies addressing other components of delay<sup>7, 32, 38</sup> and other stakeholders may be necessary to understand all factors that are closely associated with delay.”

7. Storla DG, Yimer S, Bjune GA. A systematic review of delay in the diagnosis and treatment of tuberculosis. *BMC Public Health* 2008;8:15. doi: 10.1186/1471-2458-8-15

32. Li Y, Ehiri J, Tang S, et al. Factors associated with patient, and diagnostic delays in Chinese TB patients: a systematic review and meta-analysis. *BMC Med* 2013;11:156. doi: 10.1186/1741-7015-11-156

38. Getnet F, Demissie M, Assefa N, et al. Delay in diagnosis of pulmonary tuberculosis in low-and middle-income settings: systematic review and meta-analysis. *BMC Pulm Med* 2017;17(1):202. doi: 10.1186/s12890-017-0551-y

4. Are the methods described sufficiently to allow the study to be repeated?

The study is well described and sufficiently detailed to allow the study to be repeated.

5. Are research ethics (e.g. participant consent, ethics approval) addressed appropriately?

There were informed consent obtained by the authors from all participants, I am not sure of the procedures in Italy, the funder was the Ministry of Health and it appears to also have approved the study. Is there an Ethical approval registry or body?

The study was approved by the Ministry of Health, and due to observational nature of the study, and no sample collection, no further Ethical approval was required.

6. Are the outcomes clearly defined?

Not applicable

7. If statistics are used are they appropriate and described fully?

I believe they are, but it would benefit from expert review

8. Are the references up-to-date and appropriate?

References seem to be up to date, although some do not seem to relate to the text (see discussion, line 27, reference 16) Please ensure all references are correct.

Thanks for the suggestion. We have checked and all references are now corrected.

9. Do the results address the research question or objective?

The results do address the research question and provides useful evidence.

10. Are they presented clearly?

Results are presented in a manner that is

11. Are the discussion and conclusions justified by the results

Yes

12. Are the study limitations discussed adequately?

Yes

13. Is the supplementary reporting complete (e.g. trial registration; funding details; CONSORT, STROBE or PRISMA checklist)?

No trial registration shown or strobe statement on supplementary material. Please see above for Ethical registration.

The STROBE checklist is now attached to the revised manuscript

14. To the best of your knowledge is the paper free from concerns over publication ethics (e.g. plagiarism, redundant publication, undeclared conflicts of interest)?

Yes

15. Written English

Yes

Reviewer: 3

Reviewer Name: Constantinos Siettos  
Institution and Country: National Technical University of Athens, Greece  
Please state any competing interests or state 'None declared': None declared  
Please leave your comments for the authors below

The authors present a study on the risk factors for patients and health system delays among Italian and foreign-born pulmonary TB in Italy. The study considers 4 regions of Italy, namely, Calabria, Apulia, Sardinia, and Sicily. For their analysis the authors considered main categories of factors such as socio-demographic, integration index, TB risk factors and knowledge/attitude about the infection and access to TB diagnosis and health seeking. Overall the study is interesting and contributes positively to the existing literature towards the better treatment and prevention of TB. There are some minor and major points that I outline below which the authors should accommodate in a revised version of their manuscript.

1. Grammatical and other minor points  
-being permanent or temporary resident

The text describing Patient inclusion criteria has been amended as follows, thus the above statement has been eliminated:

“Patients’ inclusion criteria were being diagnosed as a new smear positive of pulmonary TB case and living in one of the above-mentioned Italian regions. Negative smear, relapse, retreatment and extrapulmonary TB cases were excluded. Foreign-born patients were enrolled regardless of their legal status (e.g. refugees, asylum seeker, illegal migrants).”

In “Strengths and limitations of this study”

-all factors key factors

Changes have been done accordingly:

“This is the first multiregional cross-sectional study, in Italy, investigating the association of key factors with patient delay, health system delay and total delay in pulmonary tuberculosis patients.”

-Please break the first sentence of the 2nd bullet in shorter sentences.  
The previous second bullet point has been eliminated

-to identify all factors □ to identify key factors

According to the Reviewer suggestion, the term “all” has been replaced with “key” factors

Introduction

“The aim of the present study was to identify the duration and the key factors related to PD, HSD and total delay (TOTD) in pulmonary TB patients, in four Italian Southern regions, with a focus on social determinants.”

-with the task to facilitating to facilitate

The sentence has been modified as follows:

“A standardised questionnaire available in Italian, English, and French was used, and, if possible, a cultural and linguistic mediator assisted the interview with the task to facilitate communication and understanding, both on linguistic and cultural level.”

-study:[13] □ study [13];

Reference style has been corrected

2. The authors state that the quantitative variables were compared using Student's t test or the Mann-Whitney U test. But they don't say when they used the one or the other. Thus in the results the authors should also mention the test that they used for comparison between groups. For example, in the sentence "patients who refused the interview were older than patients who agreed (46.0 vs. 40.7 years,  $P < 0.023$ )" the authors do not say about the choice of the statistical test. I guess that they used Student's t-Test as the sample is big enough but they should explicitly mention it (as this is relevant to point 2 above)

Thanks for the important suggestion. We previously used the Mann-Whitney U test when data were not normally distributed (based on results of the Shapiro-Wilk test). However, since our sample (and subgroups) analyses are big enough (>30 observations), when comparing means, we decided to use only t-test, which is a very robust test. Thus, the methods section has been modified as follows:  
Methods

"The two-tailed Chi-squared test was used for the statistical comparison of categorical variables, whereas quantitative variables were compared using Student's t test, as the sample was big enough. The Levene's test was performed to verify the homogeneity of variance across groups."

3. In the discussion the authors refer to the similarity with other countries but they don't bring specific examples. For completeness they should also review the literature and compare their results with studies performed in other countries where available.

According to the Reviewer suggestion, comparison with data from other countries is reported in the discussion section:

Discussion

"In our study, the median values for PD (30 days), HSD (11 days, of which 7 days for DD and 2 days for TD, respectively), and TOTD (45 days) are similar to those reported by other studies conducted in Italy and in other European countries with a low-TB incidence. Particularly, a recent Italian study reported median PD and HSD values of 31 and 15 days, respectively.<sup>14</sup> European studies reported median PDs of 14 days (France),<sup>26</sup> 28 days (Norway),<sup>27</sup> and 29 days (UK).<sup>20</sup> Considering HSD (and its two components), studies reported median values of 15 days (Croatia),<sup>28</sup> 25 days (for DD in France),<sup>26</sup> 30 days (UK),<sup>20</sup> and 33 days (Norway).<sup>27</sup> Median values for TOTD ranged between 62 days (UK),<sup>20</sup> and 63 days (Norway).<sup>27</sup>"

14. Pezzotti P, Pozzato S, Ferroni E, et al. Delay in diagnosis of pulmonary tuberculosis: A survey in the Lazio region, Italy. *Epidemiol Biostat Public Health* 2015;12:1-10.

19. Gagliotti C, Resi D, Moro ML. Delay in the treatment of pulmonary TB in a changing demographic scenario. *Int J Tuberc Lung Dis* 2006;10(3):305-9.

20. Saldana L, Abid M, McCarthy N, et al. Factors affecting delay in initiation of treatment of tuberculosis in the Thames Valley, UK. *Public Health* 2013;127(2):171-7. doi: 10.1016/j.puhe.2012.11.010

26. Tattevin P, Che D, Fraisse P, et al. Factors associated with patient and health care system delay in the diagnosis of tuberculosis in France. *Int J Tuberc Lung Dis* 2012;16(4):510-5. doi: 10.5588/ijtld.11.0420

27. Farah MG, Rygh JH, Steen TW, et al. Patient and health care system delays in the start of tuberculosis treatment in Norway. *BMC Infect Dis* 2006;6:33. doi: 10.1186/1471-2334-6-33

28. Jurcev-Savicevic A, Mulic R, Kozul K, et al. Health system delay in pulmonary tuberculosis treatment in a country with an intermediate burden of tuberculosis: a cross-sectional study. *BMC Public Health* 2013;13:250. doi: 10.1186/1471-2458-13-250

4. The limitations of the study are not defined adequately. For example the authors discuss and analyse several factors. But they should justify their choice and also discuss about the possibility of including other factors in the analysis (e.g. environmental, the presence of other epidemics that would facilitate the emergence of TB). That's why I suggested above substituting the term "all factors" with the term "key factors". However a well structured discussion about the limitations of the study (citing also relevant studies in the field) is missing.

According to the Reviewer suggestion, in order to better clarify, the term "all factors" was replaced with the term "key factors" throughout the text including the section "Strengths and limitations".

Furthermore, the following sentences have been added in the Discussion section:

#### Discussion

"Our study has some limitations, some of them specific to the cross-sectional study design. A selection bias should be considered. In fact, the mediator was not often available in hospitals, thus, foreign-born patients recently arrived in Italy, may have experienced difficulties during the interview, resulting in refusal or in missing data. Also, the low education level of the overall population may have contributed to an information bias. Furthermore, as the onset date of symptoms was self-reported, it may have been affected by recall bias. Another limitation is that data on HIV status and other risk factors (e.g. alcohol and drug use and detention status) were not available for the vast majority of patients.

In the present study, several aspects have been investigating as key factors contributing to delay in TB patients. However, further studies addressing other components of delay<sup>7, 32, 38</sup> and other stakeholders may be necessary to understand all factors that are closely associated with delay. Furthermore, in our regression model we did not take into account for the potential collinearity of explanatory variables, which could explain complex relationship involving several risk factors at the same time. A possible approach to combine the relevant variables into summary scores or indexes and assesses the relationship of these with the outcome of interest have to be explored.

This is the first multiregional cross-sectional study, conducted in Italy, which investigated the association of several factors with PD, HSD and TOTD delay in pulmonary TB patients. It provides new evidence which can be addressed through tailored actions, in order to reduce the burden of TB in Italy. Furthermore, the prospective collection of data in four Italian regions, using a multilingual standardised questionnaire and the adjustment for confounding factors with logistic regression analysis are among the strengths of the present study."

7. Storla DG, Yimer S, Bjune GA. A systematic review of delay in the diagnosis and treatment of tuberculosis. *BMC Public Health* 2008;8:15. doi: 10.1186/1471-2458-8-15

32. Li Y, Ehiri J, Tang S, et al. Factors associated with patient, and diagnostic delays in Chinese TB patients: a systematic review and meta-analysis. *BMC Med* 2013;11:156. doi: 10.1186/1741-7015-11-156

38. Getnet F, Demissie M, Assefa N, et al. Delay in diagnosis of pulmonary tuberculosis in low-and middle-income settings: systematic review and meta-analysis. *BMC Pulm Med* 2017;17(1):202. doi: 10.1186/s12890-017-0551-y

Reviewer: 4

Reviewer Name: Jamie Wagner

Institution and Country: University of Mississippi School of Pharmacy, USA

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

Please leave your comments for the authors below

The project idea is valuable to clinicians worldwide, however, the reporting of the methods and results makes it difficult to determine the full impact of this study. Some suggestions for improvement are listed below.

Introduction:

1. The sentence beginning with “In 2015 in Italy...” is out-of-place and can be removed.

According to the Reviewer suggestion, the sentence has been removed

2. It is unclear which type of delay this study is focusing on: diagnostic delay or treatment delay. It would benefit the reader to have the authors clarify this within the “aim of the present study...” sentence.

According to the reviewer’s recommendation the aim of the study has been modified as follows:

Introduction

“The aim of the present study was to identify the duration and the key factors related to PD, HSD and total delay (TOTD) in pulmonary TB patients, in four Italian Southern regions, with a focus on social determinants.”

Methods – Study Design:

1. Please clarify what “in the framework of an Italian project” means.

The above statement has been eliminated

2. Please provide definitions for the following variables: permanent resident, temporary resident. According to the reviewer’s recommendation, the text describing patient’s inclusion criteria has been amended as follows, thus the definitions above have been eliminated:  
“Patients’ inclusion criteria were being diagnosed as a new smear positive of pulmonary TB case and living in one of the above-mentioned Italian regions. Negative smear, relapse, retreatment and extrapulmonary TB cases were excluded. Foreign-born patients were enrolled regardless of their legal status (e.g. refugees, asylum seeker, illegal migrants).”

3. Please list an appropriate study design (e.g., cross sectional).

According to the Reviewer suggestion, the study design was defined as follows:

“The present cross-sectional study was conducted in four Italian regions (Calabria, Apulia, Sardinia, and Sicily) from October 2014 to July 2016, and was approved and financed by the Italian Ministry of Health.”

Methods – Data collection and definitions:

1. Please clarify how the mediator facilitated communication and understanding (i.e., was this standardized from patient to patient)?

The point has been clarified, adding a specific sentence in the Methods section, as follows:

“Operators with adequate background of the health topic, within the specific cultures/languages, supported and assisted patients and healthcare professionals during clinical examinations.”

Methods – Statistical analysis:

1. If running a Shapiro-Wilk test for normality, should also be running the Levene test for homogeneity of variance.

This will help clarify if you should use non-parametric (e.g., Mann-Whitney U and Fisher's Exact and median [IQR]) tests and reporting. Based on the difference between the reported means and median delays, the data appear to be non-normally distributed with a heterogeneous variance.

We would like to thank the Reviewer for this important comment. We previously used the Mann-Whitney U test when data were not normally distributed (based on results of the Shapiro-Wilk test). However, since our sample (and subgroups) analyses are big enough (>30 observations), when comparing means, we decided to use only t-test, which is a very robust test, even for not normally distributed data. Furthermore, we chose the P value according to the Levene's test result.

Thus, the methods section has been modified as follows:

Methods

"The two-tailed Chi-squared test was used for the statistical comparison of categorical variables, whereas quantitative variables were compared using Student's t test, as the sample was big enough. The Levene's test was performed to verify the homogeneity of variance across groups."

2. Unclear what the reason is for stating that the crude ORs were computed, as no comparison groups have been identified.

In order to better clarify outcomes and comparison groups we have amended the methods section as follows:

Methods:

"Longer delays (outcome) were defined according to previous Italian studies."  
and

"The characteristics of patients with longer delays (all forms) were compared to those of patients without (comparators) and the crude odds ratios (ORs) and the corresponding 95% confidence intervals (95% CIs) were computed."

3. Unclear why a correlation analysis was performed, as no outcomes or comparator groups were identified.

We took into account this suggestion and we have eliminated the correlation analyses both in methods and results sections.

4. Please provide a citation for using the median value as an appropriate cut-off point for dichotomizing quantitative variables. Otherwise, a more appropriate methodology would be to perform a classification and regression tree (CART) analysis to find the natural divide in the data.

We would like to thank the Reviewer for this important comment. The body of evidence about common cut-off for delay is still not exhaustive. Indeed, opinions on acceptable cut-off are discordant. Furthermore, an important issue to take into consideration is the study setting. Since the present study has been conducted in Italy, a Country with low TB prevalence, we decided to apply the cut-offs from previous Italian studies (Pezzotti et al., 2015; Gagliotti et al., 2006). Thus, we used a cut-off of 30 days for PD and the median value observed in the study population for HSD.

Notably, in our study population the median PD value was also 30 days.

Methods:

"Longer delays (outcome) were defined according to previous Italian studies. Particularly, long PD was defined as >30 days, while long HSD and TOTD were defined as > the median value observed in the study population, for HSD and TOTD, respectively. 14, 19"

14. Pezzotti P, Pozzato S, Ferroni E, et al. Delay in diagnosis of pulmonary tuberculosis: A survey in the Lazio region, Italy. *Epidemiol Biostat Public Health* 2015;12:1-10.
19. Gagliotti C, Resi D, Moro ML. Delay in the treatment of pulmonary TB in a changing demographic scenario. *Int J Tuberc Lung Dis* 2006;10(3):305-9.

5. Please specify which delays were analyzed in the logistic regression model (e.g., patient, health system, total, all three).

6. For the regression analysis, please specify the regression parameters (e.g., variables allowed into the model at any given point, breakpoint for removing variables for the model, if any variables were forced into the model, etc).

To better clarify points 5 and 6 raised from the reviewer, the paragraph has been amended as follows:

#### Methods

"The characteristics of patients with longer delays (all forms) were compared to those of patients without (comparators) and the crude odds ratios (ORs) and the corresponding 95% confidence intervals (95% CIs) were computed.

All variables with  $P < 0.1$  on univariate analysis were included in the multivariable logistic regression analysis, using a backward-stepwise selection procedure. The breakpoint for variable removal was set at 0.10. The adjusted ORs (aOR) with the respective 95% CIs were reported. A  $P$ -value  $< 0.05$  was considered statistically significant."

#### Results:

1. This section is very difficult to understand as no outcomes and comparator groups were identified in the methods. Once those are clarified, that should help to better frame this section.

Please refer to comment N.2 of the methods section and changes made in the Results section.

2. Be very cautious with collinear variables (e.g., stigma and good knowledge of TB), which will throw off your analyses and subsequently, your interpretation of the data.

We would like to thank the Reviewer for this important comment. We have cited this point as one of the methodological limits of our study

#### Discussion

"Furthermore, in our regression model we did not take into account for the potential collinearity of explanatory variables, which could explain complex relationship involving several risk factors at the same time. A possible approach to combine the relevant variables into summary scores or indexes and assesses the relationship of these with the outcome of interest have to explored."

#### Discussion:

1. Much of this section seems to be more speculation and using previous studies rather than drawing conclusions based on the data presented in the results section. Consider drawing conclusions based on your own data.

2. Consider stating how limitations were accounted for or minimally and how those limitations could have impacted the study results. Additionally, pending choice of study design, would need to include limitations specific to that study design.

3. Consider expanding on strengths of the study and how those strengths impacted the study results. According to the reviewer suggestion, the discussion section has been widely amended.

Please refer to the new version of the manuscript.

Additional Suggestions/Comments:

1. Information written in the abstract, “strengths and limitations of this study”, “what is already known on this subject”, and “what this study adds” is not addressed.

According to the Journal guidelines, sections: “what is already known on this subject” and “what this study adds” have been eliminated

2. As per BMJ Open’s requirement, please include IRB information (exempt, approved, etc) and information required in STROBE statement.

The STROBE checklist is now attached to the revised manuscript

2. Assessment of the tables is not addressed.

Tables are now in a separate section at the end of the manuscript

Having now prepared a completely revised version of the manuscript, according to the Reviewer’s comment and suggestion, we are pleased to submit the revised Article for publication on the BMJ Open.

We wish to thank you, the Reviewer and the Editorial Board for useful comments and suggestions which really helped us in ameliorating the quality of our manuscript, that we hope will be now suitable for being accepted for publication. Looking forward to hearing from you, we thank you very much again,

### VERSION 2 – REVIEW

<b>REVIEWER</b>	Johann Cailhol Universite Paris 13 Nord, Laboratoire Education et Pratiques de Santé None declared
<b>REVIEW RETURNED</b>	07-Feb-2018

<b>GENERAL COMMENTS</b>	<p>Authors should be congratulated for amending their paper in line with reviewers comments. All the remarks I raised were properly addressed. Other remarks emerged as I read again the paper, however.</p> <p><b>Introduction</b> I had a look at reference 6 (Mahato et al), but did not find any data regarding the risk of developing anti-TB drug resistance in case of delay. I don't understand the rationale for this statement.</p> <p><b>Methods</b> Extrapulmonary TB were excluded: did authors also exclude the case when pulmonary TB was associated with extra-pulmonary TB?</p> <p><b>Questionnaire content: iii)TB risk factors.</b> Socio-deographic data comprise already some risk factors; could authors find another label for this?</p> <p>In terms of statistical analysis, I wonder if authors could present the prevalence of delays longer than a certain cut-off, taken from the literature, or what authors think is acceptable.</p> <p><b>Results and Tables</b></p>
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	<p>In Table 1, if the median patient delay is 30 days, this means that amongst the 253 patients of your sample, 127 have a patient delay below 30 days, and 126 above it. Instead, in Table 1, 149 patients have a PD &gt;30 days (which is the median). So i must say i am very confused.</p> <p>Perhaps the cut-off could be the mean value, but you may have too much extreme delays, Also, the whole sample is 253 patients, but when I add alcohol abuse + no abuse I find 248, chronic diseases yes and no I find 251 and so on. When data are unknown, they should also be presented. This could have an impact on the statistical analysis.</p> <p>attitude towards Tb and stigma foreign born patients presented higher degree of stigma: is 53,9% the mean or the median?</p> <p>Access to TB centres I wonder whether the administrative burden to access hospitals or any care centre could be integrated in the discussion, especially for foreign-born patients, as well as the delay to get an appointment.</p> <p>Discussion Could authors precise which delay they refer to when discussing "TB delay"?</p> <p>Foreign born patients represent 50% of all cases of TB in Italy: which year was this? The section comparing different delays from this study with literature could be presented in a Table.</p> <p>The section on biases could be improved by incorporating the direction of biases (over or underestimation of OR), and whether biases affect homogeneously the whole sample or not. Since authors state that collinearity might exist between variables, perhaps they could analyze the extent of it. It could be interesting to include a discussion on why some patients see different providers. Along strategies authors propose, they could also include "alleviating stigma around TB".</p>
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<b>REVIEWER</b>	Dr AB Vedio Sheffield Teaching Hospitals NHS Foundation Trust and Academic Unit of Cardiovascular Disease, Infection and Immunity, University of Sheffield.,England, UK None declared
<b>REVIEW RETURNED</b>	09-Feb-2018

<b>GENERAL COMMENTS</b>	<p>I want to thank the authors for reviewing the manuscript, it is much improved and most comments have been responded to. I am happy to recommend the study for publication, although not before certain grammar mistakes are corrected. For example:</p> <p>Discussion, page 12 of 30, lines 17 to 21: "It is likely that patients who contact the health system lately could have more severe symptoms facilitating TB suspect and prompt diagnosis,14 thus the higher the PD, the lower the HSD, and vice versa." (replace lately</p>
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	with later and suspect with suspicion)
<b>REVIEWER</b>	Constantinos Siettos National Technical University of Athens None
<b>REVIEW RETURNED</b>	14-Feb-2018
<b>GENERAL COMMENTS</b>	The authors accomodate adequately my comments, hence I recomend its acceptance.
<b>REVIEWER</b>	Jamie Wagner University of Mississippi School of Pharmacy, U.S.A. none declared
<b>REVIEW RETURNED</b>	18-Jan-2018
<b>GENERAL COMMENTS</b>	Revisions were appropriately made and of sufficient quality for publication.

### VERSION 2 – AUTHOR RESPONSE

#### Reviewer: 4

Reviewer Name: Jamie Wagner

Institution and Country: University of Mississippi School of Pharmacy, U.S.A.

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

Please leave your comments for the authors below

Revisions were appropriately made and of sufficient quality for publication.

Response: We thank the reviewer for his approval for publication

#### Reviewer: 1

Reviewer Name: Johann Cailhol

Institution and Country: Universite Paris 13 Nord, Laboratoire Education et Pratiques de Santé

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

Please leave your comments for the authors below

Comment: Authors should be congratulated for amending their paper in line with reviewers comments.

All the remarks I raised were properly addressed.

Other remarks emerged as I read again the paper, however.

Introduction

1. I had a look at reference 6 (Mahato et al), but did not find any data regarding the risk of developing anti-TB drug resistance in case of delay. I don't understand the rationale for this statement.

Response: We thank the reviewer for flagging this. The sentence was not meant to be inserted in the revised version of the manuscript. Thus, in this version the sentence and the related reference have been deleted.

~~“Delay also increases the risk of developing anti-TB drug resistance leading to treatment failure.”<sup>6</sup>~~

~~6. Mahato RK, Laohasiriwong W, Vaeteewootacharn K, et al. Major Delays in the Diagnosis and Management of Tuberculosis Patients in Nepal. J Clin Diagn Res 2015;9(10):LC05-9. doi: 10.7860/JCDR/2015/16307.6633~~

Comment: Methods

2. Extrapulmonary TB were excluded: did authors also exclude the case when pulmonary TB was associated with extra-pulmonary TB?
- 3.

Response: In our study the information about the presence of extrapulmonary TB was not captured by the questionnaire.

Thus:

- if a patient had a clinical diagnosis of new extrapulmonary TB (without pulmonary TB), he/she was not included in the study.
- if a patient reported both forms (pulmonary and extrapulmonary TB) he/she was included in the study, but the information on the presence of the extrapulmonary form was not collected.

According to the reviewer’s suggestion, for the sake of completeness and to better clarify inclusion and exclusion criteria, in the manuscript, the sentence has been amended as follows:

“Patients’ inclusion criteria were being diagnosed as a new smear positive pulmonary TB case (with or without extrapulmonary TB) and living in one of the above-mentioned Italian regions. Foreign-born patients were enrolled regardless of their legal migrant status (e.g. refugees, asylum seeker, and illegal migrants). Negative smear, relapse, retreatment cases and those with only extrapulmonary TB cases were excluded.

Comment:

4. Questionnaire content: iii) TB risk factors. Socio-demographic data comprise already some risk factors; could authors find another label for this?

Response: According to the reviewer’s suggestion, we amended the sentence as follows:

“The questionnaire contained several domains: i) socio-demographic and lifestyle data; ii) integration index (II) in Italy (only for foreign-born patients), computed as described in a previous study;<sup>15</sup> iii) TB comorbidities ~~risk factors~~; iv) patient knowledge of TB-associated symptoms and attitudes towards TB.....”

Comment:

5. In terms of statistical analysis, I wonder if authors could present the prevalence of delays longer than a certain cut-off, taken from the literature, or what authors think is acceptable.
- 6.

Response: According to the reviewer’s suggestion we added the following sentences in the methods and discussion sections and a new table (Table S1) in the supplementary material

### **Methods – Statistical analysis**

“Prevalence estimates of longer delay, using cut-off values reported from other studies, were reported in Supplementary Table S1.”

## Discussion

“Table S1 shows the above mentioned median values and the prevalence of delay that would have been detected in our study, by using them.”

**Table S1. Median delays from literature and prevalence of delay in the present study**

Delay/ prevalence of delay	Pezzotti et al. 2015 (Italy) <sup>13</sup>	Saldana et al., 2013 (UK) <sup>19</sup>	Tattevin et al., 2012 (France) <sup>25</sup>	Farah et al., 2006 (Norway) <sup>26</sup>	Jurcev- Savicevic et al. 2013 (Croatia) <sup>27</sup>
Median PD (days)	31	29	14	28	
Prevalence of PD*	64.5	50.2	59.7	50.2	
Median HSD (days)	15	30	-	33	15
Prevalence of HSD*	40.9	29.3	-	25.3	40.9
Median TODD (days)	-	62	-	63	-
Prevalence of TODD*	-	42.3	-	40.9	-

\*Prevalence of delay that would have been retrieved in our study by applying median values of delays from other studies

Comment:

Results and Tables

In Table 1, if the median patient delay is 30 days, this means that amongst the 253 patients of your sample, 127 have a patient delay below 30 days, and 126 above it. Instead, in Table 1, 149 patients have a PD >30 days (which is the median). So i must say i am very confused.

Perhaps the cut-off could be the mean value, but you may have too much extreme delays,

Response: In order to clarify the reason for asymmetrical distribution of patients delay below/above the median value, please consider that for the analysis, all patients with delay equal to 30 days were included in the category “below or equal median value”, as also stated in the methods section.

In addition, in our sample:

1. the median value (average between 126th and 127th sorted observations) for patient delay was 30 days, and the interquartile range was 8-60 days.
2. 30 days was also the mode of the distribution of patient delay

The difference between the median value and the IQR value, suggests that patient delay largely skewed to the right.

For completeness, the mean value for patient delay in our study was 29 days.

Comment: Also, the whole sample is 253 patients, but when I add alcohol abuse + no abuse I find 248, chronic diseases yes and no I find 251 and so on. When data are unknown, they should also be presented. This could have an impact on the statistical analysis.

Response: As stated in the methods section, completion rate for the questions included in the analyses was at least 80%. However, when missing values were present we used only the valid percentage (denominator consisting of valid data only).

For completeness, we added the following sentence in the methods section:

“The response rate and descriptive statistics were used to characterise the sample using frequencies, means, medians and interquartile ranges (IQRs). Valid percentage was reported when missing data were excluded.”

In addition, we added the number of valid observations for each variable, in brackets in the following tables:

Table 1 (manuscript)

Table S1 (supplementary material)

Table S2 (supplementary material)

Comment:

attitude towards Tb and stigma

foreign born patients presented higher degree of stigma: is 53,9% the mean or the median?

Response: The above-mentioned percentage refers to the proportion of foreign-born patients who reported TB related stigma higher than the median value.

The sentence has been modified as follows:

“Overall, 53.9% of foreign-born patients reported TB related stigma above the median value, compared with 41.4% of Italian born (P= 0.049). ~~Compared with Italians, foreign-born patients reported higher degree of stigma (53.9% vs. 41.4%, P= 0.049).~~”

Access to TB centres

I wonder whether the administrative burden to access hospitals or any care centre could be integrated in the discussion, especially for foreign-born patients, as well as the delay to get an appointment.

Response: According to reviewer’s suggestion we added the following paragraph in the discussion section:

“Especially for foreign-born patients, language barriers, poor knowledge of symptoms, fear of immigration authorities and long wait for appointment have been associated with delay in seeking care<sup>35 36</sup> raising concerns about the equity of access to care among TB patient. Thus, understanding immigrants’ views of TB and the obstacles that they face when accessing the health system taking into consideration the social, economic and legislative context of the new country where they live has an important role and should be considered in TB control programmes.”

35. Asch S, Leake B, Anderson R, et al. Why do symptomatic patients delay obtaining care for tuberculosis? *Am J Respir Crit Care Med* 1998;157(4 Pt 1):1244-8. doi: 10.1164/ajrccm.157.4.9709071

36. Abarca Tomas B, Pell C, Bueno Cavanillas A, et al. Tuberculosis in migrant populations. A systematic review of the qualitative literature. PLoS One 2013;8(12):e82440. doi: 10.1371/journal.pone.0082440

## Discussion

Could authors precise which delay they refer to when discussing "TB delay"?

Response: According to reviewer's suggestion we clarified the type of delay in the discussion section. Please find below the sentences that have been amended.

"Although there is no general consensus on what may constitute an acceptable interval between onset of symptoms and initiation of TB treatment,<sup>20</sup> it has been suggested that overall TB delay could be used as a key indicator of programme performance."

"However, it is worth noting that some studies evaluated both forms of TB (pulmonary and extra-pulmonary), and tools for data collection and definitions of delays were widely heterogeneous among studies, thus comparisons should be made with caution"

"Our results are consistent with findings of the WHO Eastern Mediterranean Region study, where stigma, economic factors, and time to reach the health facility were among the main determinants of delayed access to healthcare system"

"In addition, a long delay until diagnosis, favours disease progression and therefore symptom appearance."

"In general, female patients are reported to encounter greater barriers (financial, physical, and health literacy) to receive appropriate medical care and treatment"

"In the present study, several aspects have been investigated as key factors contributing to PD and HSD delay in TB patients."

In the present study, several aspects have been investigated as key factors contributing to PD and HSD in TB patients. However, further studies addressing other components of delays<sup>7, 32, 38</sup> ~~and other stakeholders~~ may be necessary to understand all factors that are closely associated with delay in the diagnosis and treatment of TB.

"In conclusion, this study detected several modifiable factors associated with longer delay in TB patients, both attributable to patients and health system service. Interventions designed to empower the general population and stakeholders, by increasing knowledge and awareness and screening of active TB in migrants upon arrival are key actions to reduce PD and HSD ~~TB delay~~ and achieve TB control"

Foreign born patients represent 50% of all cases of TB in Italy: which year was this?

Response: Please see the sentence where we added the year to which the reference refers.

"The number of TB cases in foreign-born represents about 50% of total cases in Italy (data until 2008).<sup>21</sup>"

The section comparing different delays from this study with literature could be presented in a Table.

Response: According to reviewer's suggestion we added the following sentence in the discussion and a new table (Table S1) in the supplementary material

“Table S1 shows the above mentioned median values and the prevalence of delay that would have been detected in our study, by using them.”

**Table S1. Median delays from literature and prevalence of delay in the present study**

Delay/ prevalence of delay	Pezzotti et al. 2015 (Italy) <sup>13</sup>	Saldana et al., 2013 (UK) <sup>19</sup>	Tattevin et al., 2012 (France) <sup>25</sup>	Farah et al., 2006 (Norway) <sup>26</sup>	Jurcev- Savicevic et al. 2013 (Croatia) <sup>27</sup>
Median PD (days)	31	29	14	28	
Prevalence of PD*	64.5	50.2	59.7	50.2	
Median HSD (days)	15	30	-	33	15
Prevalence of HSD*	40.9	29.3	-	25.3	40.9
Median TODD (days)	-	62	-	63	-
Prevalence of TODD*	-	42.3	-	40.9	-

\*Prevalence of delay that would have been retrieved in our study by applying median values of delays from other studies

The section on biases could be improved by incorporating the direction of biases (over or underestimation of OR), and whether biases affect homogeneously the whole sample or not.

Response: According to reviewer’s suggestion we have improved the section on bias, as follow:

“Our study has some limitations, some of them specific to the cross-sectional study design. A selection bias should be considered. In fact, the mediator was not often available in hospitals, thus, foreign-born patients recently arrived in Italy, may have experienced difficulties during the interview, resulting in refusal or in missing data. In any case, no difference has been detected for country of birth among responders and non-responders and the completion rate for the questions included in the analyses was at least 80%. Also, the low education level of the overall population may have contributed to an information bias. However, since a higher frequency of low educational level was shown in foreign-born patients than in patients born in Italy, a differential misclassification could be supposed and thus the direction of the bias is unpredictable. Furthermore, as the onset date of symptoms was self-reported, it may have been affected by recall bias that could have occurred heterogeneously in the whole sample.”

Since authors state that collinearity might exist between variables, perhaps they could analyze the extent of it.

Response: As stated in limitations, we were not able to analyse the extent of collinearity of variables.

Comment: It could be interesting to include a discussion on why some patients see different providers.

Response: According to reviewer's suggestion we better discussed the relationship between multiple visits and health system delay in the discussion section, and amended the sentence in limitations as follow:

"Furthermore, repeated visits, especially with different healthcare workers in different health facilities, has been retrieved as predictor of HSD in other studies,<sup>15 17 39-41</sup>

however we did not find this association in the final model. It has been reported that generally, patients see different healthcare providers in case of poor clinical suspicions of signs and symptoms, failure to request for proper investigations, refer patients to specialized TB centre for further investigations,<sup>42</sup> or when receive inappropriate antibiotic that can modify the clinical picture of the disease.<sup>41</sup>"

15. World Health Organization. Diagnostic and treatment delay in tuberculosis. WHO; Geneva, 2006. <http://applications.emro.who.int/dsaf/dsa710.pdf> (accessed 26 Apr 2014).
17. Sreeramareddy CT, Qin ZZ, Satyanarayana S, et al. Delays in diagnosis and treatment of pulmonary tuberculosis in India: a systematic review. *Int J Tuberc Lung Dis* 2014;18(3):255-66. doi: 10.5588/ijtld.13.0585
39. Osei E, Akweongo P, Binka F. Factors associated with DELAY in diagnosis among tuberculosis patients in Hohoe Municipality, Ghana. *BMC Public Health* 2015;15:721. doi: 10.1186/s12889-015-1922-z
40. Takarinda KC, Harries AD, Nyathi B, et al. Tuberculosis treatment delays and associated factors within the Zimbabwe national tuberculosis programme. *BMC Public Health* 2015;15:29. doi: 10.1186/s12889-015-1437-7
41. Sabawoon W, Sato H, Kobayashi Y. Delay in the treatment of pulmonary tuberculosis: a report from Afghanistan. *Environ Health Prev Med* 2012;17(1):53-61. doi: 10.1007/s12199-011-0219-9
42. Kiwuwa MS, Charles K, Harriet MK. Patient and health service delay in pulmonary tuberculosis patients attending a referral hospital: a cross-sectional study. *BMC Public Health* 2005;5:122. doi: 10.1186/1471-2458-5-122

"Furthermore, in our regression model we did not take into account for the potential collinearity of explanatory variables, which could explain complex relationship involving several risk factors at the same time, for example the use of unspecific antibiotics and multiple visits with healthcare providers".

Along strategies authors propose, they could also include "alleviating stigma around TB".

Response: According to reviewer's suggestion, we have amended the sentence as follows:

"Strategies should mainly target alleviating stigma around TB, and ~~improve~~ improving TB-related health literacy and access to care among the general population, education of GP, earlier referral of TB suspects to the hospital, where appropriate investigations for final diagnosis are readily available, and limiting the use of unspecific treatment in patients with respiratory symptoms."

#### Reviewer: 2

Reviewer Name: Dr AB Vedio

Institution and Country: Sheffield Teaching Hospitals NHS Foundation Trust and Academic Unit of Cardiovascular Disease, Infection and Immunity, University of Sheffield, England, UK

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

Please leave your comments for the authors below

I want to thank the authors for reviewing the manuscript, it is much improved and most comments have been responded to. I am happy to recommend the study for publication, although not before certain grammar mistakes are corrected. For example:

Discussion, page 12 of 30, lines 17 to 21: "It is likely that patients who contact the health system later could have more severe symptoms facilitating TB suspicion and prompt diagnosis,<sup>14</sup> thus the higher the PD, the lower the HSD, and vice versa." (replace lately with later and suspect with suspicion)

Response: We thank the reviewer for his approval for publication. We have reviewed the manuscript and corrected the grammar mistakes.

According to the Reviewer suggestion, the sentence has been amended as follows:

It is likely that patients who contact the health system lately could have more severe symptoms facilitating TB suspicion and prompt diagnosis..."

Reviewer: 3

Reviewer Name: Constantinos Siettos

Institution and Country: National Technical University of Athens

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

Please leave your comments for the authors below

The authors accomodate adequately my comments, hence I recomend its acceptance.

Response: We thank the reviewer for his approval for publication

We wish to thank you, the Reviewers and the Editorial Board for useful comments and suggestions which really helped us in ameliorating the quality of our manuscript, that we hope will be now suitable for being accepted for publication. Looking forward to hearing from you, we thank you very much again,

### VERSION 3 – REVIEW

<b>REVIEWER</b>	Johann Cailhol Université Paris Nord, France
<b>REVIEW RETURNED</b>	26-Mar-2018

<b>GENERAL COMMENTS</b>	<p>Thank you very much to authors for providing detailed answers and corrections according to our suggestions.</p> <p>There is still one comment which remained insufficiently addressed, which is the issue of missing data. Since it appears that 10-20% of data were missing depending on the variable, the appropriate method for handling these may not be just to ignore them (I assume authors used the pairwise deletion method). There are sophisticated statistical methods to ensure that missing data will not incur bias (I attached one example of a paper describing these methods). Perhaps the authors could use one of the methods described in this paper.</p> <p>The reviewer provided a data. Please contact the publisher for full details.</p>
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### VERSION 3 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Johann Cailhol

Institution and Country: Université Paris Nord, France

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

Please leave your comments for the authors below

Thank you very much to authors for providing detailed answers and corrections according to our suggestions. There is still one comment which remained insufficiently addressed, which is the issue of missing data.

Since it appears that 10-20% of data were missing depending on the variable, the appropriate method for handling these may not be just to ignore them (I assume authors used the pairwise deletion method). There are sophisticated statistical methods to ensure that missing data will not incur bias (I attached one example of a paper describing these methods). Perhaps the authors could use one of the methods described in this paper.

Response: We thank the reviewer for this comment. We acknowledge that missing data are a challenge which could affect the quality of the evidence, limit power, and reduce generalizability, causing a distortion from the truth (Hardy et al., 2009). There is no general consensus from the literature regarding an acceptable percentage of missing data in a data set for valid statistical inferences, yet. Cut-off values have been proposed ranging from 5% to 20% (Schafer, 1999; Peng et al., 2006).

Taking into account reviewer's recommendation and the suggested paper, we have followed the proposed steps in Reporting and Managing Missing Data in Quantitative Analyses (Schlomer et al., 2010), and reported the key elements, where applicable, throughout the manuscript. In particular, in the revised version of the manuscript we have now reported the amount of missing data for each variable included in the multivariable analyses as the percentage of complete data (in the supplementary Table S1) and provided in the text the range of missingness that is from 0.4% to 21.7%.

In our study, at the stage of the analysis plan, we did not include the evaluation of pattern of missing data and we handled missing data for the characteristics included in the analyses, through deletion method.

Finally, we have discussed the potential impact of missing data on the interpretation of study findings among the limitation.

Thus, the following sections, throughout the manuscript have been modified as reported below:

#### Methods - Statistical analysis

The response rate and descriptive statistics were used to characterise the sample using frequencies, means, medians and interquartile ranges (IQRs). Valid percentage was reported when missing data were was missing (pairwise deletion method). Furthermore, the magnitude (proportion) of missing data was quantified and reported in Supplementary Table S1.

..... All variables with  $P < 0.1$  on univariate analysis were included in the multivariable logistic regression analysis, using a backward-stepwise selection procedure. The analysis was only run on cases which have a complete set of data.

#### Results

Completion rate for all questions included in the analysis was  $\geq 80\%$ . Missing data ranged from 0.4% to 21.7% (Table S1).

#### Discussion

Our study has some limitations, some of them specific to the cross-sectional study design. A selection bias should be considered. In fact, the mediator was not often available in hospitals, thus, foreign-born patients recently arrived in Italy, may have experienced difficulties during the interview, resulting in refusal or in missing data. In any case, no difference has been detected for country of birth among responders and non-responders and the completion rate for the questions included in the analyses was at least 80%.

Missing data are a challenge which could affect the quality of the evidence, limit power, and reduce generalizability, causing a distortion from the truth.<sup>42 43</sup>

There is no general consensus from the literature regarding an acceptable percentage of missing data in a data set for valid statistical inferences, yet. Cut-off values have been proposed ranging from 5% to 20%.<sup>44 45</sup> In our study we retrieved a certain amount of missing data, up to 21%, and observations with missing data have been excluded in the multivariable analysis, hence reducing the final sample size. In addition, the pattern of missingness was not explored. Thus missing data may represent potential bias in our findings. The questionnaire used for data collection could have been a plausible cause for missing data in our study, because of the length of the survey, and the unavailability of translation in languages other than English and French. Thus, to prevent missing data in further studies, the data collection tool should be designed and adapted to the needs of the target population, piloted and monitored during the study.

42. Hardy SE, Allore H, Studenski SA. Missing data: a special challenge in aging research. *J Am Geriatr Soc* 2009;57(4):722-9. doi: 10.1111/j.1532-5415.2008.02168.x
43. Schlomer GL, Bauman S, Card NA. Best practices for missing data management in counseling psychology. *J Couns Psychol* 2010;57(1):1-10. doi: 10.1037/a0018082
44. Peng CY, Harwell MR, Liou SM, et al. Advances in missing data methods and implications for educational research. In Sawilowsky SS, editor, *Real Data Analysis*. New York. 2006. p. 31-78
45. Schafer JL. Multiple imputation: a primer. *Stat Methods Med Res* 1999;8(1):3-15. doi: 10.1177/096228029900800102

Having now prepared a completely revised version of the manuscript, according to the Reviewer's comment and suggestion, we are pleased to submit the revised Article for publication on the BMJ Open.

We wish to thank you, the Reviewer and the Editorial Board for useful comments and suggestions which really helped us in ameliorating the quality of our manuscript, that we hope will be now suitable for being accepted for publication. Looking forward to hearing from you, we thank you very much again,

#### VERSION 4 – REVIEW

<b>REVIEWER</b>	Johann Cailhol Paris Nord University none declared
<b>REVIEW RETURNED</b>	20-May-2018
<b>GENERAL COMMENTS</b>	I wish to congratulate the authors, who reviewed the paper thoroughly according to the reviews provided.