Author's response to reviews

Title: Clinical presentation, demographics and outcome of Tuberculosis (TB) in a low incidence area: a 4-year study in Geneva, Switzerland

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Author's response to reviews: see over
Geneva, October 5, 2009

Submission of a manuscript entitled: Outcome of Tuberculosis (TB) in a low incidence area: a 4-year study in Geneva, Switzerland.
Authors: O Kherad, F Herrmann, JP Zellweger, T Rochat, JP Janssens

Revised version

Dear Editor,

Please find attached a revised version of our manuscript. Please notice that the title of the manuscript has been modified at the request of one of the reviewers.

Furthermore, you will find below a point-by-point reply to all the reviewer’s comments:

**Editorial requests**

1. **Author’s contributions have been added as requested**
2. **We also modified the abstract following your guidelines and we added a “background” section**
3. **Informed consent was not available considering the retrospective design of our study. The risk of identification of patients was however negligible and the Ethics Committee of Geneva University Hospital approved the study protocol.**
4. **We already replied to a question relating to the manuscript of E Langenskiold (email 7 August 2009), which was a completely different study focusing on contact tracing procedures only.**

We hope you will find the revised version of this manuscript suitable for publication in BMC infectious disease.

Yours sincerely,
Reviewer 1: Robert Colebunders

1. Methods: Intrathoracic and Extrathoracic definition

Intrathoracic and extrathoracic have been replaced by intrapulmonary and extrapulmonary TB all along the manuscript as requested (and numerical values checked accordingly).

2. Definition of cure rate and success rate according WHO-definitions

Microbiological evidence of cure (smear conversion of S+ cases) was not systematically available for all patients, the most frequent cause being failure to obtain secretions in spite of induced sputum. “Successful outcome” as suggested by WHO is therefore defined as clinical cure and/or treatment completed.

3. Definition of WHO objectives.

Modified in the text as requested

4. Discussing treatment outcome

Treatment regimen for TB has been specified (p6)

5. Treatment delay

Treatment delay refers to time elapsed between first symptoms recalled by the patient and beginning of treatment. This has been specified in the text (p9)

6. Results: Confusion with PTB (158 in table 2 but 152 in text)

As requested and above mentioned, we replaced ITB and ETB and by pulmonary and extra-pulmonary TB: discrepancy between text and table has been corrected.

7. Be careful expressing OR as probabilities

Modified as requested (p9)

8. Cave with interpretation and generalisation of results
We agree that some of our confidence intervals are wide due to low sample size and we added a comment in the “study limitations” § of the discussion.

9. Fourth paragraph of page 8 and figure confusing as no correspondence

Footnote of figure 3 and text were revised to clarify this point.

10. Abbreviation of BA and BAL

Modified as requested in page 9

11. Outcome: 42 cases incomplete (p10) and table 4

Corrected: in 42 cases follow-up was unsuccessful

12. Discussion: structure of sentence under 1/ and 3/

These sentences have been modified as requested

13. Several references missing

To the best of our knowledge, we did not identify other European studies reporting outcome of TB. However, we added the reference of the internet site “EuroTB” which summarizes and up-dates TB outcome in different European countries. Furthermore, the last reference has been completed.

14. Tables 1 subheadings and Table 2

We added subheadings in Table 1 as requested and we modified subheadings (pulmonary and extra-pulmonary TB) in Table 2. Footnote of table 2 states that smear results combine sputum examinations and bronchoscopy

15. English mistakes

All changes suggested were included in the revised version of the manuscript.
Reviewer 2: Einar Heldal

Major compulsory revisions.

1. We did in fact search for factors associated with treatment failure or relapse but, considering sample size, we did not perform a multivariate analysis. We modified the sentence in the introduction by specifying that the aim of study was also to identify factors associated with unsuccessful outcome. We performed a multivariate analysis adjusted for different variables and we specified these variables in the text (p11, outcome).

2. Relapse rate was computed and included as requested (0.24 per 100 patient-years) (Abstract and page 11).

3. As mentioned in “study limitations” §, our cohort corresponds to 78.5% of all cases notified in Geneva during study period.

4. During our study period, 30 cases with a presumptive diagnosis of TB but without any microbiological and/or histopathology confirmation were excluded. This information has been added in p 6. None died before treatment started.

5. Yes, we specified this information in p 6.

6. This information has been clarified in p6.

7. The completeness and quality of date of the database were excellent without missing values excepted for sputum analysis as explained in the “study limitations” §

8. We changed outcome according to WHO criteria and now the outcome described in p6 corresponds to table 4.

Discretionary revisions

9-10. The title and the abstract of the manuscript have been modified as requested.

11. We replaced extra-thoracic by extra-pulmonary TB as requested by all reviewers.

12. Table 1 has been modified as requested. Of note: we had no missing values.
13. HIV testing was performed in all cases after informed consent (specified in text p6).

14. There was no S+/C- cases

15. As mentioned in footnote, diagnosis was based on positive culture of samples from other organs involved.

16. Modified as suggested. Concerning the unfavourable outcome (=unsuccessful) we performed a multiple regression logistic analysis adjusted for different variables as mentioned in p 11. However considering the small number of fatal issues, we did not perform a multivariate analysis for this specific outcome.

17. These authors redefined criteria for “success” (i.e.: cure or treatment completed, TB incidental to death, patient still on initial treatment after 12 months as a result of drug intolerance, side effect, failure to convert culture or smear from positive to negative and poor clinical response on treatment) and “failure” (uncompleted treatment, TB cause of death, patient still on treatment for reasons others than mentioned under “successful outcome”, lost to follow up, stopped treatment, unknown data) from a clinical perspective.

18. Modified as requested.
Reviewer 3: Bernard Vandercam

Background

1. 9 millions new cases, mentioned in text
2. We gave more details about treatment and DOT in our area in chap “methods”. The incidence of INH resistance is 4.9% and this information has been added in p 6.

Results-Patients

3. The real range is 15-92. Modified as requested in text.
4-5. The retrospective design of our study did not permit to obtain information about duration of stay in Switzerland or mode of acquisition of HIV
6. Asylum seekers were screened by X-ray. Added in text p 9.
7. As mentioned in manuscript, only 3 cases co-infected with HIV were already under HAART at admission. For the others patients co-infected with HIV, standard practice at our hospital was - during study period - to treat with HAART two months after the beginning of anti-tuberculosis treatment.

Treatment and side effects

8. 2/3 of the cases were due to liver test abnormalities (any level above upper limit of normal values with GI symptoms ) which doesn’t correspond to our definition of biological hepatitis (cf definition p7) = an elevation of ASAT and/or ALAT 5 times above upper limit of normal values.
9. All cases reported polyneuropathy (specified in the text p11)

Diagnosis and diagnostic procedure

10. We gave more details about these procedures in p 7.

Outcome

11. All five cases of MDR-TB were considered cured. (Added p 11)
12. Luckily in our area, there is an easy access to health care even for subjects with no legal status and/or no insurance coverage; whenever necessary, funding through public or non-profit organisations covers costs of TB treatment and investigations; because the Canton of Geneva is rather small, there are no real difficult to reach populations.