Author’s response to reviews

Title: Recurrent tuberculosis in Finland 1995-2013: a clinical and epidemiological cohort study

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Author’s response to reviews:

Dear Editor,

Thank you reviewing our manuscript entitled “Recurrent tuberculosis in Finland 1995-2013: a clinical and epidemiological cohort study”. Enclosed are our replies to the reviewer’s comments. We hope that, after the revisions made in the manuscript, you will find it acceptable for publication.

Best regards,

Virve Korhonen

Editor Comments:

Although the cohort is extremely large, there are some revisions that need to be made.

Editor comment: The major issue as reported by reviewer 2 is that the highest risk period for relapse (6m - 12m) is excluded from the analyses and treatment failures are not counted. These limitations need to be addressed by providing additional analyses. Without some stratified analyses (providing denominators as well as numerators) and description of missing events, this manuscript provides limited information.
Response: We have now reviewed the raw data in the National Infectious Disease Register (NIDR) for possible recurrent cases being notified by either in physician notification or a laboratory notification (for culture positivity) 6-12 months from the registration date of all TB cases in the study cohort. Based on this review, we found a maximum of 12 cases that, based on the NIDR data only, could be early recurrences between 6 to 12 months from the registration of the first episode. Reviewing patient chart data of these cases within the required manuscript revision timeframe, in order to establish the exact ‘cleaned’ figure, is not possible because of slow administrative processes. The 12 cases would constitute 19% of a total of 62 cases. However, it is likely that clinical review of these cases would decrease the number.

The limitation of potentially failing to identify early relapses (recurrences) is clarified in the last paragraph of discussion section of the manuscript. See a more detailed response on this issue below to reviewer 2.

A table with denominators by risk categories is added to results section (table 2).

Reviewer reports:

Troels Lillebæk (Reviewer 1)

General:


Response: The set of recurrent cases is the same as in our previous study, where the focus was on finding whether the recurrent cases were relapses or reinfections. In the current study, we have analysed clinical factors: the presence of potential risk factors for recurrence, the diversity of treatment regimens administered and particularly the spectrum of treatment outcomes in the first episode preceding recurrence. We have clarified this issue adding text to the last paragraph of the background section.

Specific comments:

Abstract:

Reviewer comment: You write; "Because of a growing proportion of tuberculosis (TB) cases in immigrants and increasing drug resistance of Mycobacterium tuberculosis in Finland, we investigated the epidemiology and risk factors of TB recurrence in a population-based registry
cohort of 8084 TB cases between 1995-2013.” Comment: I do not see why immigrants and drug resistance are used as arguments for looking into recurrence? Perhaps provide a better intro. First of all, you relate recurrence to initial therapy given for episode 1 and the treatment outcome.

Response: We have revised the background paragraph of the abstract according to the suggestions of the reviewer.

Reviewer comment: The abstract is rather "talkative". It can be reduced and appear more sharply and accurately. Just an example, you write: "The rate of TB recurrence, after careful validation of the register data, was low despite the absence of a comprehensive DOT (directly observed therapy) policy. The first two years after a TB episode have a particularly high risk for recurrence. The observed premature discontinuation of treatment calls for improved training of the physicians." Could read: "In Finland, the rate of recurrent TB was low despite no systematic directly observed therapy. The first two years after the initial TB episode had the highest risk for recurrence and the observation of premature treatment discontinuation in nearly one fourth recurrent cases calls for improved training of physicians."

Response: We have revised the conclusion in the abstract according to the reviewer’s advice. We also made minor revisions in the methods and results of the abstract to make the text more explicit.

Reviewer comment: Remove abbreviations not used in the abstract.

Response: The abbreviation (NIDR) not used in the abstract was removed.

Background:

Reviewer comment: Fine intro in Background, but a bit vague finish when you write: "The aim of the present study was to investigate in a national, population based cohort the occurrence of recurrent TB in Finland during the years 1995-2013, and the factors affecting the risk of recurrence, in order to strengthen the TB treatment program in the changing epidemiologic environment." Write more sharply and accurately what you investigate and why? First of all, you relate recurrence to initial therapy episode 1 and treatment outcome. See also general comment.

Response: The aim of the study is clarified in the revised last paragraph of background section.

Methods:

Reviewer comment: You write: "Data on anatomical site of disease (pulmonary/extrapulmonary), radiological, histological and microbiological results, TB diagnosed before 1995, immunosuppressive diseases and medication, substance abuse, exposure to TB, travel to high TB incidence countries, the drug regimen in the first episode, adverse effects and adherence to treatment were extracted from patient charts." Where these data available for all cases? If not, specify for each category the availability. In my experience, these
data are not recorded systematically in patient charts, but may be different in Finland. Also, do you actually use radiological?, histological?, immunosuppressive diseases, exposure to TB, and travel to high TB incidence countries? Leave out if not used or available.

Response: Radiological and histological data were used to validate that both episodes were true TB episodes in culture negative cases. This is clarified in the text in the second paragraph of methods section. Data not used in the study were removed from the text accordingly (second paragraph of methods section). We had all patient charts of 48 out of 50 recurrent TB cases available and all these data used, except substance abuse, were available for 48 cases.

Results:

Reviewer comment: You write: "A history of substance abuse, mostly alcohol, was registered in the patient records in at least one TB episode of 59% of males and none of females; 49% of males had substance abuse recorded in both episodes." How about the rest? No abuse or no information?

Response: Most of the rest did not have any information of substance abuse. This is clarified in the text in the fifth paragraph of discussion section.

Discussion:

Reviewer comment: You write: "We investigated the epidemiology of and risk factors for recurrent TB in Finland in a comprehensive national, register-based cohort of 8084 TB cases from 1995 to 2013, with full clinical data on recurrent cases, …" Again, I am not really sure how much you analysed risk factors. You mention several in the methods, but how many did you actually analyse? For how many did you have complete data? Due to the retrospective design and missing data I don't think you can write you analysed risk factors - but perhaps some specific risk factors with complete or nearly complete data.

Response: We agree with the reviewer. The text was changed accordingly (the first sentence of discussion, the first sentence of abstract and the last paragraph of background).

Reviewer comment: You write: "Patient chart review revealed that in nearly one fourth of the recurrent cases, the physician had discontinued the treatment of the first episode prematurely." This is an interesting and important finding, but you do not really discuss why? Can you explore this point further?

Response: This finding is explored in the text in the third paragraph of discussion section.

Reviewer comment: You write: "Just over one half had a successful outcome according to WHO criteria". This is low, you write it has changed the later years, could be explored.
Response: In the original manuscript (last paragraph of discussion section), we have referred to a successful outcome rate of 76% in our national surveillance for the cohort of 2013. We have expanded this to cover the most recent data with consolidated national surveillance on treatment outcome monitoring (last paragraph of discussion section).

Conclusions:

Reviewer comment: You write: "In the absence of a comprehensive DOT strategy, and with an increasing proportion of cases with foreign origin, the rate of TB recurrence was found to be low compared to most other low-TB-incidence countries." Why the connection to foreign origin should not necessarily be connected to relapse - perhaps even greater awareness on TB in this population segment?

Response: We agree with the reviewer. The connection to foreign origin was removed from the text accordingly (first sentence of conclusions).

Randall Reves (Reviewer 2):

General comments

Reviewer comment: This manuscript is based upon a retrospective review of all 8048 notified TB cases in Finland over an 18-year period 1995-2013. Recurrent episodes were defined those in individuals with another reported episode at least a year after the initial registration. Since most patients were treated for 6 months, the highest risk period for relapse (1st 6 months post-treatment when 69% of relapses have been reported - ref 4) is excluded and treatment failures are not counted. As noted in ref. 23, the US TB surveillance system fails to identify the most common (early) relapses as well. In addition ref. 21 refers to these as "late relapses" for this reason.

Response: We agree with the reviewer that we may fail to identify early relapses/recurrences (months 6-12 after initial registration). We have now reviewed the raw data in the National Infectious Disease Register (NIDR) for possible recurrent cases being notified by either in physician notification or a laboratory notification (for culture positivity) 6-12 months from the registration date of all TB cases in the study cohort. Based on this review, we found a maximum of 12 cases that, based on the NIDR data only, could be early recurrences between 6 to 12 months from the registration of the (first) episode. Reviewing patient chart data of these cases within the required manuscript revision timeframe, in order to establish the exact ‘cleaned’ figure, is not possible because of slow administrative processes. The 12 cases would constitute 19% of a total of 62 cases. However, it is likely that clinical review of these cases would decrease the number.

Furthermore, in routine national TB treatment outcome monitoring surveillance of culture positive pulmonary TB cases since 2007 using WHO and EU monitoring standard, there have been only 0-1 treatment failed cases (0-0.5%) per year in Finland.
The reviewer states that a high proportion of relapses (recurrences) are observed during the 6 months immediately after treatment, based on Reference 4. However, this reference includes two prospective clinical trials with non-standard TB treatment (TB treatment given once or twice a week during the continuation phase) and a considerable proportion of HIV-infected patients.

Our finding is in line with two earlier studies with standard TB treatment (Ref. 3 and 18), where a minority of relapses (recurrences) occurred in months 6-12 after initial registration.

The limitation of potentially failing to identify early relapses (recurrences) is clarified in the last paragraph of discussion section.

Specific comments

Introduction

Reviewer comment: P 3, line 20 - Note that relapse ascertainment in clinical trials (e.g. ref. 4) detects higher rates than surveillance studies for several reasons: inclusion of only smear-positive pulmonary TB and all recurrences including the 1st 6-12 months when 70-90% occur.

Response: We agree with the reviewer that clinical trials detect higher rates of TB recurrence than surveillance studies. However, we disagree on the proportion of early recurrences with reasons described above. We have extended addressing this issue in the last paragraph of discussion section.

Results

Reviewer comment: A table with total denominators (e.g. "controls") by risk categories should be provided, not just the total unstratified number of 8048.

Response: A table with denominators by risk categories is added to results section (table 2).

Discussion

Reviewer comment: Note that compared to similar data from ref 21 (only pulmonary TB) and 23, the 0.6% frequency of relapses is nearly identical, but does likely not include most relapses. Note that treatment failures are not included.

Response: We refer to the preceding responses to the reviewer regarding the importance/proportion of recurrences between 6-12 months after registration and commencement of treatment.

It is correct that we have excluded from this study population treatment failures, which have been rare in national treatment outcome monitoring in Finland in the last 5 years (0-1 cases/Y):
according to WHO and EU treatment outcome monitoring standards, treatment failure is identified just prior to or at the conclusion of treatment, by a positive AFB stain or culture, respectively. In a TB treatment system integrated to general health care, systematic sampling at this time is frequently missing, and in the absence of clear symptoms or signs, it may be difficult to define whether disease recurrence within 6 months from standard treatment conclusion (ie the 6-12 month’s time period) is due to true primary treatment failure or is a recurrence (relapse or reinfection).