Author's response to reviews

Title: Risk factors for poor tuberculosis treatment outcome in Finland: a cohort study

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Author's response to reviews: see over
Title: Risk factors for poor tuberculosis treatment outcome in Finland: a cohort study

Reviewer's report 1
Reviewer: Donald A Enarson

General

This is a well done study that contributes important insights into the quality of care of a rare disease that affects vulnerable groups in relatively wealthy countries. It is important in that it highlights the importance of maintaining competence to provide service to these vulnerable groups.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Abstract

1. Results line 5: I expect ‘conversely’ should read ‘inversely’
   Revised according to proposal

2. Conclusions: Some comment should be made about the ‘systems’ components (the relation of adverse outcome to the type of service providing care).
   Revised: We observed a significant association with unfavourable outcome for the specialty responsible for treatment being other than pulmonary, but not for the volume of cases, which has implications for system arrangements.

3. It may not be certain that adverse outcomes associated with advanced age and with comorbidity might be reduced by earlier case detection.
   Word “probable” added to this context.

4. Page 9 para 2:
   ‘conversely’ should read ‘inversely’.
   Revised according to proposal

Discretionary Revisions (which the author can choose to ignore)

Methods

5. Para 2:
   No mention is made of whether species identification for Mycobacterium tuberculosis was carried out in every case (presumably it was but this should be stated). If this was and there is information available, it would be interesting to know how many cases were rejected because cultures isolated other mycobacteria (a significant problem where tuberculosis is rare).
Species identification was done in every case.
We have added: “Species identification for Mycobacterium tuberculosis was carried out in every case.” (page 5 paragraph 2)
After the preceding sentence, we furthermore added for clarification “There were altogether 660 isolations of mycobacteria other than M. tuberculosis during the study period.”

6. Para 3:
It is interesting to know why 33 patients were excluded when they were still on treatment at 12 months. Was this because they were not adherent? Was it because they had resistant isolates? International (outside Europe) recommendations for evaluation of such patients (if they had susceptible isolates) is that they should be classified as defaulters.

We followed the existing European recommendations, and did not analyze the group ‘still on treatment at 12 months’ further. We agree that the group is interesting, and we will study it in future. No revision made in the manuscript text.

7. Para 3:
It is probably not correct (from a cohort point of view) to exclude the patients who were not treated. It is understandable that some might have died before treatment had begun (in which case, other studies have classified them as ‘diagnosis after death’ and this group can account for as much as one-half of all deaths from tuberculosis). It is particularly important to know more details concerning the 3 patients who were left without treatment. This is an especially important group as far as transmission of infection is concerned. Did they refuse treatment (presumably)? If so, are there any characteristics that might suggest why (for example substance abuse or psychiatric illness)?

We focussed on those who actually received treatment in our study. However, recognising the uncertainty to which the reviewer refers, we carried out an alternate univariate and multivariate analysis including also those not treated (27 cases), but the statistical associations remained the same. There is a sentence on this in the original manuscript in the last paragraph of results (page 10 para 3) (“When we analysed all 656 cases in the cohort with known outcome, including those 27 without treatment, the associations observed in univariate and multivariate analysis as significant were the same as with the 629 cases of the presented analysis.”).
Those three cases left without treatment (but didn’t die) were: 1) Physician suspected a laboratory contamination (there is no note of possible x-ray finding or symptoms), and decided not to treat. However, the laboratory did feel it was a real finding. 2) Nobody noticed a positive culture result for TB. When it was finally noticed (after a couple of months) patient was out of hospital and didn’t admit any symptoms. He was decided not to be treated. 3) A positive sputum culture result was notified by laboratory. There was no mention of possible TB disease or treatment in patient records.
No revision made in the manuscript text.

8. Was any attempt made to determine if death was due to, contributed by or coincidental with the tuberculosis? Certainly there is a great likelihood in such an aged population is that death might be simply coincidental.

During the data collection process we didn’t make an attempt to classify the type of causal relationship between TB and death, as we considered the attempt as very resource-consuming and producing ‘soft’ information because of the high age and multiple comorbidities in a large
portion of our cases. We are, however, going to make a further round of comprehensive data collection to address the issue by acquiring all the death certificates of these cases (we’ll get copies of those from Statistics Finland). However, this is major additional work, and while the result of this extended analysis in our population quite possibly does not bring clear results, we would not like to incorporate it in the current manuscript, but to report separately at a later stage.
No revision in the manuscript.

Results
9. Table 3 certainly indicates system issues related to death that might be included in the conclusions for the abstract. This needs caution, however, because if the patient had comorbidity and this comorbidity was the actual cause of death, the relation of type of service providing care and death may be biased.

We have now included it in the conclusions of the abstract, as indicated above.

10. The relation of adverse outcome and death with treatment group B is interesting and important. It is, however, not clear to me if treatment groups are defined by ‘intent to treat’ (prescription made at the start of treatment) or the actual treatment given. This is important for two reasons. First, group B is clearly less efficacious and not the internationally recommended approach to treatment and second, if the latter scenario is the case, it is possible that the regimen was changed for some reason (?drug intolerance) which may be a reflection of comorbidity (liver disease, cancer) or risk factor (alcoholism) which could be the real explanation of the adverse outcome. (This is actually covered well in the discussion).

In cases with a shift to another group during medication, treatment group was assigned according to the final combination given. We believe that group B treatment was mostly used for the reasons mentioned by the reviewer, i.e. side effects of group A, comorbidity or age increasing the risk of adverse events).
No revision made in the manuscript text.

Discussion
11. First para: This paragraph outlines the important issues raised above concerning systems factors and should be reflected in the conclusions of the abstract.

It is now included in the conclusion of abstract.

What next?: Accept after minor essential revisions
Level of interest: An article of outstanding merit and interest in its field
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:
I declare that I have no competing interests
Reviewer's report 2
Reviewer: Ibrahim Ibrahim Abubakar

Reviewer's report:

General

• This is a very well written paper that presents important data from Finland [not surprising from this group].
• The meticulous way the study has been conducted means that the findings are likely to be valid.
• There are issues around generalisability of the findings for instance, the patient population (small number of immigrants and TB-HIV coinfected patients) and the health system may not be similar to other “similar” low incidence developed countries.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

1. Why was the analysis restricted to culture confirmed cases only? Justification should be given for this.

In Finland, a positive smear is always cultured, and the amount of those cases positive in smear, but negative in culture is almost zero per year. We can link with unique person identifier all atypical mycobacterial findings to clinically confirmed TB cases, and remove these from TB register.

Revised: “Species identification for Mycobacterium tuberculosis was carried out in every case. There were altogether 660 isolations of mycobacteria other than M. tuberculosis during the study period. Only culture positive cases were taken into the study in order to be able to study only the fully confirmed cases.” (page 5 paragraph 2)

In our epidemiological situation, with a high proportion of TB cases >65 years of age, many of the aged have clinical conditions which are hard to differentiate from TB, and there are larger numbers of infections caused by atypical mycobacteria than by M. tuberculosis. Thus, to ensure appropriate specificity for our case definitions, we only focussed on culture confirmed cases of TB. We added to methods “Only culture positive cases were taken into the study in order to ensure appropriate specificity of case confirmation.” (page 5 para 2)

2. The standard outcome categories recommended by EuroTB/WHO have some shortcomings that should be discussed. For instance, a transfer-out where a case is seen by another service and treatment is subsequently completed can not be an “unfavourable” outcome.

Yes. In transfer-out cases in our study, we couldn’t find any data concerning further treatment in patient record copies that contained any further referral organisation that would be reachable in Finland. These cases moved either to another place inside Finland, unidentifiable in the records, or in most cases to another country, in which case we could not follow-up the outcome.

No revision made in the manuscript text.
3. Also not all deaths in TB patients are due to TB – any analysis should acknowledge that deaths in the elderly may be due to factors unrelated to TB. Did the authors have a “cause of death” from death certificates?

This possibility is considered in the discussion section. During the data collection process we didn’t make an attempt to classify the type of causal relationship between TB and death, as we considered the attempt as very resource-consuming and producing ‘soft’ information because of the high age and multiple comorbidities in a large proportion of our cases. We are, however, going to make a further round of comprehensive data collection to address the issue by acquiring all the death certificates of these cases (we’ll get copies of those from Statistics Finland). However, this is major additional work, and while the result of this extended analysis in our population quite possibly does not bring clear results, we would not like to incorporate it in the current manuscript, but to report separately at a later stage.

No revision in the manuscript.

4. Also combining various measures into one composite “unfavourable” outcome category inevitably hampers the ability to understand the risk factors for each outcome category. For example, the factors associated with loss to follow up [e.g. social risk factors] may be different from those associated “physicians discontinuing treatment” [e.g. adverse effects].

We agree with the reviewer in that the significance of different adverse outcomes for system improvements are different. However, the statistical power for identifying subgroup-specific associations would be insufficient in this size of a cohort. Therefore, we kept these categories together in analysis, and make an attempt to exploit simple descriptive data to support decisions improving different system parameters.

No revision in the manuscript.

5. Speciality responsible for treatment:
What is the difference between internal medicine and general medicine?

Internal medicine is within hospitals treating “more specialized cases”, but general medicine is in the primary care (this is added to results, page 9, paragraph 3).

6. Change of speciality – in what direction was this? Is this to internal medicine or from internal medicine? I suspect the implication on outcome will differ – very ill patients with other co-morbidities will be moved to specialties such as palliative care, while relatively fit patients who have uncomplicated TB will be transferred back to respiratory physicians.

Change of specialty included any change from one speciality to another during treatment (it can be to/from internal medicine, but in most cases treatment was started by pulmonary unit). This is reformulated in text. (page 7, paragraph 3)

7. The relative contribution of “use of appropriate treatment regime” versus “speciality of physician ending treatment” should be discussed.

It is now discussed on page 13, paragraph 1: “The experience in the treatment of tuberculosis may therefore be greater in most pulmonary units than other specialty services. However, the volume of cases treated was used as a separate parameter in analysis. On the other hand, it is possible that the
patient records do not fully cover all relevant comorbidities, which may be more common in other services than pulmonary. ”

8. The criteria for choosing factors to include in the multivariate model are not clear.

Revised: “Any variable for which the univariable test had a p-value <0.20 was included in the multivariable analysis.” (page 7 paragraph 1)

9. “Pauses of treatment” is likely a proxy for treatment interruption (physician or patient) i.e. is the authors controlling for an outcome measure as a risk factor.

We are aware of the potential for using the terminology in a way which may not be explicit to all readers. We wanted to keep ‘Pauses of treatment’ separate from ‘Treatment interruption’, because pauses could also be due to other factors like side effects. Pauses of chemotherapy were recorded only when lasting at least one week (this is from page 6 para 1), but less than the official limit of ‘Treatment interruption’. No revision in the manuscript.

Other weaknesses should be acknowledged.

10. Sample size – due to relatively small number of deaths, the power of the study to investigate outcomes such as death is limited.

This is now added to discussion on page 11, paragraph 3.

11. The study is retrospective. Therefore, despite the meticulous conduct, it is possible that not all factors such as co-morbid conditions were recorded in the case notes. A further limitation is the number of confounders available from clinical records.

This is now added to discussion, page 11, paragraph 3.

Minor Essential Revisions (such as missing labels on figures (it is at the end of text and tables), or the wrong use of a term, which the author can be trusted to correct)

12. Page 3. first paragraph
WHO – in full the first time it is mentioned

Revised

13. Drugs abbreviations such as INH, HRE, HRS should be defined in full.

Revised

Discretionary Revisions (which the author can choose to ignore)

14. Page 3. first paragraph “succeeds” should be “succeed”

Revised

15. WHO has published….should read “The WHO published recommendations for assessing the outcome of tuberculosis treatment in 199x, revised recently.”
Revised

16. Page 3. second paragraph
patient should read “patients”

Revised

17. page 4. last sentence.
“during study period” should read “during the study period”

Revised

What next?: Accept after minor essential revisions
Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:

I declare that I have no competing interests
Reviewer's report 3
Reviewer: Andrew C Hayward

Reviewer's report:

This is valuable and original piece of research which is certainly worthy of publication. There is very little previously published work on outcomes of TB management in low incidence countries or analyses of risk factors for poor outcome.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)
Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

1. There needs to be some discussion of the generalisability of the findings. Finland is unusual in that very little of the TB is in migrants, I also suspect that homelessness, imprisonment and drug use are not major issues in Finland and that relatively few TB patients have these risk factors. The authors have combined unemployment, imprisonment, homelessness and drug use into a single category so it is not possible to tell how important these factors are. They report no association between social risk factors and outcome which is likely because their social risk factor group is dominated by unemployment rather than more extreme social issues. In our recent analyses in London we have found imprisonment, drug use and homelessness to be the most important predictors of poor outcome. Story A, Murad S, Verheyen M, Roberts W, Hayward AC. Tuberculosis in London - the importance of homelessness, problem drug use and prison. Thorax. 2007 Feb 8; [Epub ahead of print]) It is important to make the point that whilst these social issues are not a major issue in Norway they are important in other settings.

We added in discussion, page 14, para 2: “No association was found in our study between social risk factors and outcome, but that may depend on the dominance by unemployment rather than more extreme social issues which are rare in our TB cases. In a recent analysis in London, imprisonment, drug use and homelessness were found to be the most important predictors of poor outcome [35].”

2. The findings about service size and speciality may also not be generalisable outside of their setting. In London we certainly find that smaller centres cannot cater well for the needs of ethnically and socially diverse populations as they are less likely to be geared up to give directly observed therapy, provide interpreters or help to deal with complex social issues. The authors should therefore qualify their statement about centre size to make it explicit that this finding is relevant for low incidence countries with relatively little TB associated with immigration, homelessness, drug use and imprisonment but may not be relevant for other settings.

This in now added to discussion on page 13, para 1.

3. Most of the results are highly statistically significant but given the large number of significance tests carried out I would advise against overinterpreting factors that are associated with poor outcome. I do not think formal bonferonni corrections are necessary but
the authors should be aware that p values that are relatively close to 0.05 could well have occurred by chance. For example the apparent lower risk of death in those with previous TB p=0.044 is likely to be a chance finding.

In the discussion, page 14, para 1, we have added: “although of borderline statistical significance”.

4. In the abstract conclusions it is not apparent why high death rates in immunosuppressed and elderly patients suggests the need for low thresholds of suspicion, rapid diagnostic tests or early empiric treatment. If the authors had demonstrated that the higher death rates in these groups were due to diagnostic delay this might be a valid conclusion but diagnostic delay was not examined.

These thoughts are suggested as possible (added on page 15 para 1) approaches to control poor outcomes.

5. I think some of the risk factors examined may also have formed part of the outcome definitions (e.g. short treatment is presumably the same or highly similar to "default" or to "physician stopped treatment early" which form part of the unfavourable outcome definition) -also short treatment is inevitable if you die early in the course of disease so will inevitably be associated with death -this could account for the very high odds ratios seen -short treatment should therefore not be included in table 3

Treatment duration is removed from table 3.

Discretionary Revisions (which the author can choose to ignore)

What next?: Accept after minor essential revisions

Level of interest: An article of importance in its field

Quality of written English: Acceptable
Statistical review: Yes, and I have assessed the statistics in my report.
Declaration of competing interests:

'I declare that I have no competing interests'