Author's response to reviews

Title: HIV prevalence in the Israeli tuberculosis cohort, 1999-2011

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Author's response to reviews: see over
To:

Editor in Chief
BMC Public Health

Dear Editor,

Re: Tuberculosis and HIV co-infection in Israel, 1999-2011

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Dear Professor,

We I wish to thank BMC PH for a thoughtful, comprehensive, and constructive review of our manuscript. We have fully addressed every comment and question raised. In our view, this process has substantially strengthened the manuscript. Respectfully, we are resubmitting this version within the requested timeline. If there are additional questions, please do not hesitate to engage us. We have included a redlined version to aid in your re-review.

Sincerely Yours,

Zohar Mor, by the names of all Authors
Reviewer: Valeria Saraceni
Reviewer’s report:
Major Compulsory Revisions
1 – Title: A prevalence study should not be called a cohort study. I’d suggest the authors another title: HIV prevalence in the Israeli Tuberculosis cohort, 1999-2011.
Authors: Corrected, as suggested.

2 – Abstract: 4th paragraph: the authors stated; “and higher risk of dying during treatment than HIV-negative tuberculosis patient”. There’s no measure of risk performed in their study. They didn’t even tell us how many had death as outcome, as their outcome was defined as “Treatment outcomes were defined by the WHO [7], and patients who were cured or completed the treatment were considered success.”
Authors: We measured death during treatment. Death during treatment, as one of the treatment outcomes, was cited in Table. However, as no risk analysis was performed we changed the text to: "more likely to die during treatment", see row # 20 in the Abstract, row # 127 in the Results and rows #181 and 215 in the Discussion.

3 – Methods:
3.1 – Line 2 in this section: TB infections should be replaced as active TB disease, as classically, TB infection refers to latent TB infection, not the actual disease.
Authors: Correct, as recommended. See row #75.

3.2 – P.6 last paragraph: “The follow-up study period...” – I strongly suggest to take out follow-up, as nothing is this study suggests an actual follow-up.
Authors: The text was changed to: “All TB patients in Israel were followed”, see row #103.

3.3 – Same location: Line 4: “P>0.05 was considered statistically significant.” I’m positive there’s a typo here, as it should be P<0.05 to be considered statistically significant.
Authors: Corrected, as suggested, row #107.

In this section, there’s no mention to any measures of association in the study to assess risk of death. I’d suggest a stronger analysis to asses this.
Authors: Death is one of the outcome of treatment as classified by the WHO. In this updated version, we describe the difference in the rate of death during treatment between the two groups, and we no longer use the term "death rate”.

4 – Results:
4.1 -Any other number of cases (samples) should be denoted as “n”. The total population from where the cases derived would be “N”.
Authors: The study includes all TB patients in Israel, and therefore it may be considered as the entire population rather than a sample.

4.2 – Last line in the 1st paragraph: “outcomes and higher risk of dying during
treatment”. Again, no measure of risk assessment was found in the paper. The phrase should be rewritten accordingly. There’s only the comparison of proportions, which is not a measure of risk. **Authors:** Corrected, and changed to: “more likely to die during treatment”, see row #127.

4.3 – Figure 2 does not add to the paper. In fact, I’d suggest to take it out. **Authors:** The figure was deleted, as suggested.

5 – Discussion:
5.1 – 3rd paragraph: Reference 14 is not recent and doesn’t assess the issue of timing of ARV initiation in TB patients with the latest findings in this field. The reference should be replaced by a more recent, like WHO recommendations on this issue. **Authors:** The reference was replaced with the more recent: CDC. Managing Drug Interactions in the Treatment of HIV-Related Tuberculosis [online]. 2013. Available from URL: http://www.cdc.gov/tb/TB_HIV_Drugs/default.htm Consequently, the recommendation was changed to: "be treated with ART 2 weeks after initiation of TB-treatment", see row #158 (ref #16).

5.2 – Page 9, 1st paragraph: “It is possible that the lack of association between extrapulmonary TB and HIV was a result of analyzing only EPTB cases, rather than concurrent pulmonary and extra-pulmonary TB in HIV patients, resulting in reporting bias.” If the authors are in agreement that they’ve introduced a bias here, how would they treat this in their results? **Authors:** It is possible that classifying concurrent pulmonary and extra-pulmonary TB as EPTB would yield a greater number of patients with EPTB in comparison to EPTB patients only, allowing for statistical significance. We respectfully think that the reader are able to conclude it themselves and prefer not to include the suggested remark in the text, as it may disrupt the attention of the readers from the main subject.

5.3 - Page 9, 2nd paragraph: “TB/HIV co-infected patients are more susceptible to MDR-TB, either through nosocomial transmission, as they visit medical settings more commonly, due to malabsorption of TB medication as the ART may cause rapid gastrointestinal passage,” – I don’t understand this comment: Do patients visit medical settings because of malabsorption of TB meds? Does this increase the risk of MR-TB by visits to health centers, or does this increase because of lower serum levels of TB meds? I’d like to see a reference here, in order to make it clearer for the reader. **Authors:** There was a typo, and the word "or" should have been included before "due to malabsorption". The full sentence is now: "TB/HIV co-infected patients are more susceptible to MDR-TB, either through nosocomial transmission, as they visit medical settings more commonly; or due to malabsorption of TB-medication, as the ART may cause rapid gastrointestinal passage; or by poor response to TB treatment as a consequence of other social difficulties, such as being a migrant or drug-user [18], see rows #171-175. The reference was added: Lazarus JV, Olsen M, Ditiu L, Matic S: Tuberculosis–HIV co-infection: policy and epidemiology in 25 countries in the WHO European region. HIV Med 2008, 9:406-414.
5.4 - Page 9, 3rd paragraph: “As TB/HIV mortality rate was higher than TB patients who were HIV-negative,...” Again, I wasn’t able to find mortality rate, which is a measure of incidence.
**Authors:** The sentence was changed to: “As higher rate of patients who were co-infected with TB/HIV died during treatment”. See row #181.

5.5 – Page 9: the last sentence, which continues on page 10 “This...”, is very hard to understand. It should be rephrased.
**Authors:** It has now changed to: “The "3 Is" strategy should be augmented with ART early following TB diagnosis in order to support restoration the immune system”, see rows #187-189.

5.6 – Page 10: Last paragraph: “First, there were no accurate data regarding the proportion of TB patients who were tested for HIV.” The authors used reference #8 to assess this topic in page 6, where I thought they were quite sure of the high coverage. How do you explain that?
**Authors:** The department of TB and AIDS, in which both the 1st and 3rd author are managing, receives notification from all the AIDS and TB treatment centers in Israel, and cross-match the findings. These authors also run periodic internal surveillance studies to make sure no patient was missed. However, we can never be 100% sure that all the data we receive reflect "real life". Additionally, the ECDC office requests the different countries to complete an estimation of the number of TB patients who were tested for HIV. We therefore specifically mention in row #206 that the rate of 88.4% is estimated, and this is the way the ECDC asks countries to complete.

Minor Essential Revisions
Some misspelling found throughout the paper, as coinfection, benchmark, antiretroviral, that would benefit from a review.
**Authors:** Corrected, as recommended.

**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 interest
The authors have reported the results of a cross match of the National TB and HIV Registries in Israel. The study covers the period 1999-2011 and is descriptive in nature. Unfortunately, there are some quite serious limitations with the data as presented and the analysis. These are summarized below.

Major:

1. The HIV Registry appears to be a Registry of all laboratory proven cases of HIV/AIDS. It would not appear to include those that were HIV tested and negative. The average estimated HIV testing coverage of TB patients during the study period is reported to be very high (88.4%). The reference for this is a TB surveillance and monitoring report in Europe. What is not known is the date of the HIV test relative to the date of diagnosis of TB. Can the authors indicate whether the positive HIV test result was reported before or during treatment of TB? The HIV co-infection rate was remarkably low in 1999. Was this because testing coverage was very low that year?

Authors: This study includes only TB patients who were reported with HIV "before" TB treatment was initiated (i.e., does not include those who were recovered from TB and reported with HIV after their TB-treatment was completed). We added this sentence in the Methods: "between TB-patients who were co-infected with HIV and TB-patients who were HIV-negative", see rows #106-107. Indeed, it was estimated that 88.4% of all TB patients were tested for HIV, however, we also crossed-matched all National TB registry with the National HIV/AIDS registry to response for those TB patients who were not tested for HIV in the clinics.

As most TB/HIV co-infection cases originated in Africa, it is probable that the increasing migration waves to Israel after 2000 (especially from Africa) is responsible for the rise in co-infection rate during these years. It has been now added in rows #145-147 in the Discussion: "...especially originating in Africa, as 34,127 Jewish Ethiopian legal migrants and 37,646 illegal migrants from the horn of Africa (Eritrea, Sudan and Ethiopia) arrived in Israel after 2000."

2. Since the HIV co-infection rate is very much dependent upon the country-of-birth of new immigrants, it is quite conceivable that any trend in HIV co-infection rate of TB patients relates to the relative contribution of arrivals from high vs low HIV prevalence countries over time. Are the authors able to relate their trend in HIV co-infection rates to trends in country-of-birth of new arrivals?

Authors: Most of TB/HIV co-infections originated in countries characterized by high prevalence of TB and HIV, especially Africa. In this updated version, we now divided in Table 1 those who arrived in Israel from Ethiopia and those from the horn of Africa. See the updated Table 1 and row #135 in the Results.

3. The authors have compared HIV positive to (presumed) HIV negative TB cases using chi-square and Student’s-t test for categorical and continuous
variables, respectively. This limits any conclusions that might be drawn from the analysis. For example, it appears that HIV positive cases were more likely to be culture-positive because they were more likely to be adults (>17 years of age - children being much less likely to be culture-positive). Likewise, HIV-infected cases were more likely to die during follow-up (we are not told how a TB death was defined - the follow-up period was reported to last from January 1, 1999 until December 31, 2011) but since most HIV co-infected cases were foreign-born from high HIV prevalence countries and those same countries could have high MDR-TB prevalence rates, it is not clear whether death is related to HIV or MDR-TB. Thus, it is not possible to know whether HIV is an independent risk factor for TB death. Odds ratios with 95% confidence intervals would be better.

Authors: We performed univariate analysis generating odds ratio and 95% confidence interval (see rows# 108-110 in the Methods), as recommended. We further included all relevant dependent variables achieving statistical significance in the multivariate analysis (rows # 110-112 in the Methods). This allow us to show more accurate results, which are now appear on rows #127-129 in the Results, rows #138-140 in the Discussion, rows # 212-213 in the Conclusion and rows #21-23 in the Abstract. In short, the multivariate analysis demonstrated that TB diagnosis short time after arrival in Israel, older age, being born in Ethiopia, having positive sputum culture and multi-drug resistant TB are variables that predict TB/HIV co-infection.

4. Since only 9 of 254 TB cases were younger than 18 or older than 64 years of age (3.5%), it may be better to restrict their comparison of HIV positive to HIV negative TB cases to the age group 18-64 years.

Authors: We took off all TB patients who were younger than 18 years of age, but included those who were older than 65. We preferred to keep them in the analysis, as Israel receives older Jewish migrant, and also they are at higher risk of developing TB than the general population.

5. The authors disease site analysis does not include cases with both pulmonary and extra-pulmonary disease. Many HIV co-infected TB patients would be expected to have both.

Authors: Those with combined pulmonary and extra-pulmonary TB were considered pulmonary, as per WHO classification.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being Published Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests: no competing
Reviewer's report
Title: HIV prevalence in tuberculosis patients in Israel, 1999-2011: A retrospective cohort study
Version: 2Date: 18 November 2013
Reviewer: Haim Bibi
Reviewer's report: minor essential revisions that the authors can be trusted to make.
Authors: Done, as recommended.

Level of interest: An article of importance in its field
Quality of written English: Needs some language corrections before being published
Statistical review: No, the manuscript does not need to be seen by a statistician