Author's response to reviews

Title: Diabetes and tuberculosis: the impact of the diabetes epidemic on tuberculosis incidence

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Author's response to reviews:

Dear Dr da Silva

Thank you for your email of the 13th of August and the two reviewers' comments. We note that the review of William Herman is enthusiastic and recommends acceptance without revision. The review of Reinout van Crevel is also enthusiastic about the manuscript but recommends "minor essential revisions". We are grateful for his detailed and specific comments and have responded to them in the following way:

1. We agree that the data source we have used for the relative risk estimates (Kim et al 1995) has limitations, some of which we had already addressed, but we have now added more detail why we chose this study and on its potential short comings in the section on "limitations and strengths". This includes comment on the diagnostic levels used for diabetes and the very small number of cases of TB in women with diabetes.

2. We have not commented in detail on the fact that in the Kim et al study there was a discrepancy in the 1988 and 1990 examinations in diabetes diagnosis by 30%. In itself this is not particularly surprising as due to a combination of underlying biological variation and measurement error glucose measurements at one point in time will misclassify a large proportion of individuals - similar to using a blood pressure reading at one point in time. We do agree though that it would have been helpful if Kim et al had provided an explanation for the discrepancy, which they do not. However, we have now commented that it is likely that there was significant misclassification of those with diabetes, and that this is likely to have resulted in an underestimate of the association between the two diseases (limitations and strengths section, pg 11).

3. We have also now added to the discussion further comment on the availability of other studies that have assessed the association between diabetes and
tuberculosis. In fact we have recently undertaken a detailed review of these studies and have a paper in press that describes them. We make reference to this paper (ref 23 now inserted).

4. We agree with Dr van Crevel that greater smear or culture positivity in people with diabetes (as found by Kim et al) has not been found in all studies. We have now commented on this in the discussion, and made reference to a paper of his in press (ref 29 in implications section) which describes greater persistence of sputum positivity in those with diabetes.

5. We acknowledge that not all studies have found that diabetes is associated with greater evidence of cavitation on chest x-ray but have not commented on this in the paper as it is not something we refer to in the paper.

6. Finally we have added a little more under the heading of "implications" in the final paragraph of the discussion on the potential implications for public health policy and practice, including some of the implications for future research referred to by Dr van Crevel. As suggested, we illustrate some of these points by referring to current guidance for policy and clinical practice and the extent to which it does, or usually does not, refer to diabetes.

In addition to the response to the reviewers we have made two small amendments of our own, largely in response to new publications coming to light. We have made reference to a new case control (Shetty et al, 2006) from India of risk factors for TB. We have expanded a little the section in the discussion on the assumptions underlying our estimates, particularly the standard assumption for attributable risk estimates that other risk factors for TB are equally distributed between those with and without diabetes. In addition, we have added in reference to a news article published this week in Lancet Infection on the potential importance of the link between TB and diabetes.

Finally, and sadly, we have added into the acknowledgment section that Catherine Stevenson, the first author, died before the final preparation of this manuscript. However, she led this work right up to the penultimate draft submitted here and for this reason fully warrants posthumous first authorship.

We hope that these responses adequately address the comments of the reviewers, but would be happy to respond further if you felt it was necessary.

With best wishes

Nigel Unwin

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