Author’s response to reviews

Title: TB incidence and characteristics in the remote gulf province of Papua New Guinea: a prospective study.

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Dr. Kevin Cain
Editor, BioMed Central
BMC Infectious Diseases

Dear Kevin,

Re: Revision of manuscript: 4970374381094865, TB incidence and characteristics in the remote gulf province of Papua New Guinea: a prospective study by Cross et al.

Thank you for giving us the opportunity to provide a revised manuscript and we also thank the reviewers for their critical appraisal of our work. We have included 1 new Table and 3 new Figures incorporating new data that substantiate our conclusions and address issues raised by our reviewers. We provide a point-by-point response to questions / issues raised by the reviewers and editor below. We have paraphrased reviewer questions in italics and our response is in “regular font”.

Reviewer: Daniel O’Brien:
1. Only 29% of cases were followed up – are the rest defaulters?
The reviewer is referring to patients that where commenced on therapy during the study period. In this remote region of PNG, follow up of TB cases is arranged on a case by case basis were practical. Patients that live near the hospital are given follow-up appointments, some are referred to local health facilities or outreach programs and others are provided with a full course of therapy to complete at home. By definition, the latter group, are not “defaulters” as they had their treatment supplied in full and formal follow-up could not be organized through the hospital. However, it is possible that some of these patients may stop their drugs on discharge but the current study was not able to address this issue. We now clarify this in manuscript in the Methods / Setting section. The reviewers comment prompted us to revisit the number of patients classified as defaulters / failed therapy and we found that several cases were inadvertently placed in the incorrect boxes in Figure 2 (now Figure 3 in the revised manuscript). We have corrected this in the revised manuscript and provide an updated incidence.

2. Is it possible that knowledge of a TB study may have caused more patients to attend the hospital and inflated incidence?
This is a concern we initially shared but retrospective review of hospital records over several years prior to the commencement of our study shows that our prospectively calculated incidence figure concurs with the number of cases in all the proceeding years (2004, 2005, 2006 etc). We now highlight this in the discussion (page 11).

3. Discretionary revision – separate treatment follow-up from TB clinical manifestations.
We are constrained by manuscript length restrictions.

Reviewer: Nobuyuki Nishikiori:
1a(i). Why were there not better rates of sputum collection, diagnostic tests etc. set up in advance?
Our study deals with a very remote area of PNG and we planned to follow standard of care
diagnostics and treatments in that region. We elaborate on this issue in our Methods / Setting section. To introduce novel and unsustainable protocols, diagnostics and treatments would have created major ethical issues. Importantly, and we believe this is the strength of our study, we replicated the current standard for PNG TB case reporting, used by the WHO, and we show that the TB incidence reported by the WHO is a gross underestimate for certain regions in PNG. Creating new diagnostic protocols would have biased our study substantially (facility bias, ascertainment bias, diagnostic bias etc.) and it would undermine current WHO TB case definitions used in developing countries.

1a(ii). Why did the study include inpatients if the study was to determine incidence in a prospective study.
We only used **prospectively** accrued patients to determine incidence. We emphasize on page 11 of the revised manuscript that “to estimate TB incidence we only included cases that were diagnosed and commenced on treatment during the study period”. See also point 1c(ii) below.

1a(iii). How was the study period of 16 weeks determined?
Review of hospital records in the preceding years (2004 onwards) showed that any 16-week period was sufficient to extrapolate annual case numbers. We detail this in the revised manuscript on page 11 and also in Figure S-4.

1b(i). How was the “catchment area validated”?
The catchment area for the hospital was validated by assessing the geographic distribution of TB cases in previous years. We also confirmed that all obstetrics patients at the hospital over the 16 week period resided in our defined catchment area. We now provide these details in our revised manuscript (page 6).

1b(ii). Why were GPS coordinates obtained for patients?
GPS coordinates were used to confirm that all cases resided in our catchment area. We now provide a map of the region and a map showing the distribution of all cases resistant cases and isolates that were genotyped (Supp Fig 2 and 3).

1b(iii). Were patients coming from areas > 1 day travel time within the defined coverage area?
Yes, see 1b(ii) above.

1b(iv). Validation of population estimates and elaborate on the limitations in the discussion section.
As cited we used public PNG census data from 2009 (including national growth rates) and all available (limited) Census data from 2011. Complete census data for 2011 has not been released. The published National Statistical Office of Papua New Guinea population growth rates, sourced at:
[http://www.spc.int/prism/country/pg/stats/Pop_Soc_%20Stats/popsoc.htm](http://www.spc.int/prism/country/pg/stats/Pop_Soc_%20Stats/popsoc.htm)
clearly shows a higher growth rate in urbanized areas compared to economically challenged remote and rural areas. We used the population growth rate for the Gulf Province in calculating TB incidence estimates. The same statistics show that rural-urban migration is very low. The remoteness of Kikori and the economic poverty in the area precludes substantial migration out of the region. Resource development ventures in rural areas may increase the population size but this would cause an underestimation of TB incidence, contrary to the reviewer’s bias. In the revised manuscript we provide details on
the estimation of population size (Methods) and in the discussion we acknowledge that this is an estimate of the true figure (which in an unbiased appraisal could be smaller or larger than the true population). On page 11 (discussion) we now clearly advise the reader of this potential limitation.

1c(i). The authors did not disaggregate the smear status of the 97 cases used to estimate the incidence.

This is a good and important point raised by the reviewer. We have now revised Table 1 such that only prospectively accrued patients (and prospectively collected specimens) are represented in the Table. This data now correlates with patient numbers used in the estimation of incidence.

1c(ii). Bacteriologically confirmed cases should be used in the calculation of incidence.

Accepted WHO country specific TB incidence reporting is based on the WHO accepted definition of a TB case (the same definition we have used in our study). WHO does not report TB incidence based on bacteriological confirmation. The reviewer’s request is contrary to reporting convention and undermines WHO global guidelines. The reviewer also refers to our definition of TB cases as a “limitation”. We refer the reviewer to the WHO definitions for TB cases (Ref 5). We have used the WHO internationally accepted criteria for the definition of cases. To deviate from such reporting convention would undermine all previous TB studies and the WHO TB incidence data. For some countries WHO does provide an appendix detailing bacteriologically confirmed cases but this should not be confused with TB incidence and indeed for all developing countries there is little correlation between TB incidence and bacteriologically confirmed cases. For example in the latest WHO 2013 Global report, bacteriologically confirmed incidence is 1.6 per 100,000 population in PNG – clearly an aberration reflecting the resource poor setting. Nonetheless we now provide a figure for the incidence of bacteriologically confirmed TB (page 11).

1c(iii) The patients included in the TB characteristics data Table that were inpatients at the time of the study may differ from the characteristics of those patients accrued over the study period.

By definition TB inpatients included in our description of “TB characteristics” were still in hospital at the time the study commenced and were in their intensification phase of treatment (as per standard of care in the region), i.e. they had been diagnosed with TB no more than 2 months prior to the study. The reviewer erroneously assumes these inpatients are being hospitalized because of complications or for other medical matters. We have clarified this point in our revised methods section (page 8). These patients do not represent classical retrospective reviews – as all patients were prospectively interviewed and were undergoing intensification phase treatment hence there were no issues of recall or ascertainment bias. Importantly we have now removed these cases from Table 1 so that only prospectively accrued specimens are represented. These patients were included in the “TB Characteristics Table” as they were prospectively followed during the study period. The characteristics of inpatients and newly diagnosed patients were qualitatively similar and hence the groups were not tabulated independently as this would have represented a duplication of the same qualitative data. Also inpatients diagnosed prior to the commencement of the study were not included in any statistical analyses only prospectively accrued newly diagnosed patients were used for incidence determination.
Id(i) Two methods for calculating confidence limits for binomial proportion our quoted but only one figure is given.
Both methods were used and both gave the same result.

Id(ii) Can the extrapolation of cases from 16 weeks to 1 year be validated?
In the original manuscript Supp Figure 2 (now Supp Figure 4 in the revised manuscript) shows that the retrospective yearly TB cases from 2004 onwards concur with our extrapolated value for 2011. This validates the number of cases.

Id(iii). By using the aforementioned statistics the confidence interval may be underestimated.

2(i). Should the characteristics of only 97 prospective cases be shown rather than 146 total. (This appears to be a repetition of question 1c(ii) above).
The inpatients at the time the study was commenced were prospectively accrued and followed hence we have included them in the Table of characteristics as the represent the same population of cases. See 1c above.

2(ii). The authors make claims of causal associations between factors such as overcrowding etc and the incidence of TB, what is the comparator?
We do not make any such claims. We provide a qualitative description of case demographics and make no comparisons, as there are none to make. We clearly do not attempt to correlate any of the characteristics with a relative risk of TB as this was not the point of the study and nor could we do this. In our results section we clearly describe the characteristics but make no inferences. In our discussion we speculate that some common factors (such as overcrowding etc) may contribute to the high incidence (and this is substantiated by references). We clearly state in the discussion that we do not understand the cause of the high incidence in Kikori. We have revisited the sentences quoted by the reviewer and revised them as follows:

Old: ---“Our study highlights that overcrowding, spitting as a cultural phenomenon, and the heavy AFB density in most cases, could translate to a high infectious load which results in a cycle of infection, repeated exposure, onset of clinical disease, and further transmission of disease.”
Revised: “Factors such as overcrowding, spitting as a cultural phenomenon, and the heavy AFB density in most cases, could contribute to a high infectious load which may lead to cycles of infection, repeated exposure, onset of clinical disease, and further transmission of disease.

Old: ---“Drivers of clinical disease in Kikori might include malnutrition and exposure to household smoke.”
Revised: It is unclear what the major drivers of clinical disease in Kikori are but some factors that may contribute to disease development include malnutrition and exposure to household smoke.
Old: ---“Delayed presentation is evident in our study as illustrated by the number of complicated presentations including disseminated TB, and the duration of symptoms.”
(* The reviewer fully understood the importance of this information. But from the epidemiological point of view, this again needs to be confirmed by checking the prevalence among new cases.)

Revised: We now show prevalence amongst the 97 cases in Table 1.

Old: ---“the finding of three rifampicin resistant isolates amongst 37 strains tested (8%) is of concern and a systematic study of patterns of drug resistance to anti-tuberculosis agents is urgently required in this patient cohort.”
(* The reviewer believe the claim is completely valid but need to know which categories of patients the three specimen came from—new, chronic, retreatment, relapse? It is difficult to interpret just this 8%. ).

Author response: In our “Results” section (page 10) we clearly elaborate on the history of the three resistant cases – “One out of the three patients with rifampicin resistance had previously been treated for TB and had defaulted on therapy. The other 2 patients had no history of TB treatment.” Therefore we have not repeated this statement in the “Discussion” section. Additionally, in revised Table 1 we clearly highlight the resistant cases.

Editorial requests:

1. Provide a description of eligibility criteria, screening and enrollment.
We acknowledge that these were not described sufficiently in the original manuscript and we now provide a more detailed description of these elements in the methods section under study design.

2. Provide a bacteriological incidence and recognize in the discussion that there may have been overdiagnosis.
We now provide a bacteriological incidence in the results section. Please see our comments to 1c(ii) above. Using a bacteriological incidence in lieu of the accepted WHO reporting criteria for TB (in the case of developing countries) is contrary to Global reporting practice for such countries. In our study we have used the WHO standard accepted criteria for TB diagnosis and (the same methods used to report TB incidence across all developing countries). We believe that a balanced approach needs to be taken and that there is equal probability that our calculated incidence rate could be lower than the true incidence. Nonetheless we alert the reader (in our discussion) that our reported incidence may be greater than the true incidence due to TB overdiagnosis (page 16, discussion, first paragraph). In the Kikori setting, and indeed for all of PNG and developing countries, bacteriological confirmation is only practical for pulmonary disease (50% of cases). We were able to obtain bacteriological confirmation for 32/40 pulmonary cases. Given that approximately 50% of TB in developing countries is extrapulmonary reliance on sputum microscopy would grossly underestimate incidence (and this is the clear position of WHO).

3. To study incidence you need to exclude people that were already diagnosed inpatients at the start of the study.
Only patients that were prospectively diagnosed with TB were used in the incidence
calculation. We now make this very clear in the Methods and Results section. See question 1c(i, ii and iii) above. We have only included prospectively accrued specimens in Table 1.

4. Transfer supplemental figure 1 to the main paper.
Thank you for the suggestion we have now done this.

5. Address reviewer concerns regarding statements that are made in the discussion.
We have revised the relevant sentences in the discussion and a full itemized list is provided in 2(ii) above.

6. Why are patients being hospitalised for so long and could this promote transmission – discuss in manuscript.
Standard of care for TB treatment in PNG is that patients are hospitalized for 2 months for the intensive phase of therapy (in a resource poor setting it is not possible to perform repeated AFB smears to follow clearance / control). One of the rationales for the hospitalized treatment for intensive phase therapy is to ensure an element of directly observed therapy and to monitor for side effects / toxicity in the absence of good outpatient blood pathology services. TB cases are segregated / isolated in a designated TB ward that is physically separated from all other hospital wards. We now provide a better description of this practice in our settings / methods section.

7. A map of PNG and the region should be included in supplemental figures.
This is a good suggestion and we now provide map in the supplemental figures.