Reviewer's report

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

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Reviewer: Nobuyuki Nishikiori

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Major Compulsory Revisions

1. The incidence estimate

Although the major objective of the study was to determine the incidence of TB in the study area, the reviewer recognized several limitations and the lack of discussion before arriving the estimation. These are critically important because the central thesis of the paper appeared to be a high incidence of TB in the area.

1a. Study design

Using hospital-based statistics for calculating incidence requires careful discussion on various sources of biases (facility bias, ascertain bias, diagnostic bias, etc) that can drive an estimated incidence in any direction. Further more, estimating coverage population is always a huge challenge (discussed below). From the title and the design section, it is understood that the study is a prospective observational study, rather than retrospective hospital record review. Then following points were not very clear to the reviewer:

- Whether the operating procedures (for patient enrolment, testing, case definition, supervision, record keeping, etc) were predetermined before the study started? If it is the case, the reviewer wondered why there was so low rate of sputum collection and why better diagnostic criteria for smear negative (or clinical) TB had not been set in advance?

- Why did the study include inpatients who were already on treatment if the purpose of the study is to determine the incidence? It gave confusion to the analysis (as discussed below).

- How was the study period of 16 weeks determined? Was there any sample size calculation done before the study started?

1b. Estimation of coverage population

There seems to be a number of issues in estimating the coverage population.

- Catchment area was defined as West Kikori rural ward, East Kikori rural ward
and only Baimaru Station of Baimaru ward. Was there any attempt in confirming
the catchment area (e.g. analyzing geographical distribution of hospital
users—not only patients)? What about the other hospital operating in Kikori
hospital? Was there a possibility that the Kikori hospital was attracting many
patients out of catchment area because of the services or fee policy? Was there
any analysis of TB cases in the other hospital or provincial TB case notification?
- The study took the GPS points of patient home (Methods section) but it is not
clear how it was used in the analysis or by any way contributing to defining the
catchment.

- In addition, the study examined time-distance between patient home and
hospital. Is this information also consistent with the defined catchment area? All
those patients coming from the areas > 1day travel distance were within the
defined coverage area?

- Estimating the population is amongst biggest challenges. The study used the
2000 census population and simply applied an estimated annual population
growth from the 2011 census (1.2%; no verifiable source cited) for over the
period of 12 years (i.e. powered by 12). It is not clear whether the annual growth
rate is for national figure that might not be appropriate because the annual
population growth can be substantially different place to place. (for example, an
estimate of annual population growth rate from the CIA fact book was 1.89%
which makes 8.5% difference in a population estimate if it is applied over 12
years).

- Moreover, besides the annual population growth from the population statistics,
migration can be a significant factor to influence disease incidence (in both
directions – “healthy migrant effects” and/or influx of disease prone population).
The study explained in the background “resource development ventures with
projects extending into the Gulf province have raised concerns that TB is
prevalent in the area and this was brought to our attention.” Did this imply that
the resource development ventures had been operating in the area some time in
the recent past? If so, what was their impact in demography (population size and
structure, migration, changing risk factors, risk behaviors, etc)?

- Despite these many issues in the incidence estimate, the discussion section
paid almost no attention to the limitations of the estimate. Although there should
be ways to effectively and wisely use the precious hospital-based data to inform
public health actions, the use of hospital-based data always requires careful and
scientifically rigorous considerations in terms of methodology, limitations, and
interpretation.

1c. Case definitions / classification

- TB incidence should be disaggregated. Particularly the incidence of
bacteriologically confirmed cases should be presented at least. It is important to
note the facts that only 74 out of 146 cases (50.7%) had clinical specimen and
the criteria for clinical diagnosis was weak – defined as “when a health worker or
clinician diagnosed TB based on symptoms and signs and decided to treat the
patient with a full course of TB therapy”. With these limitations, the primary
outcome of the interest should be an incidence estimate of bacteriologically
confirmed (in this case smear-positive) TB. Since the authors did not provide appropriate disaggregation by smear status for the 97 NEWLY diagnosed cases (figure 2), it is hard for readers to assess the estimated incidence in terms of breakdown between smear-positive, smear-negative, and clinically diagnosed proportions. The Figure S-1 (supplementary file) was useful in terms of disaggregation by smear status but mixing new cases with existing cases (diagnosis prior to the study) makes the entire picture so confusing. The Figure S-1 needs to disaggregate “new case” and “existing inpatients prior to the study” at the very first level.

- Additional note on the issue of patients diagnosed before the study: The reviewer assumes that the existing patients who were on treatment as inpatients must have been a qualitatively different population from those who are newly diagnosed and prospectively enrolled. Mixing up these two groups (treated as one group of N=146) makes interpretation difficult. For example, many factors could have been associated with longer hospital stay (=likelihood of enrolment in the study is higher compare with the patients discharged earlier) such as MDR-TB, pediatric cases, co-morbidities (including HIV, diabetes, malnutrition and alcoholism), travel distance to home, types of TB disease including more severe forms, etc. In order to clarify the characteristics of the TB patients, analysis should be separately reported for newly diagnosed patients.

1d. Statistical issues
- The paper did not provide sufficient information to assess the soundness of the statistical analysis. For example, it is described that two methods for calculating confidence limits for binomial proportion (Wilson score interval and Agresti-Coull) but only one set of confidence limits were presented.
- It is also not clear how the number of TB cases from the 16-week period (N=70) was annualized. A simple proportional inflation (i.e. divided by 16 and multiplied by 52) of a case number would lead to the underestimation of confidence interval because the observational period is short (i.e. person-year denominator is small).
- Since the outcome of the interest is rate and observational period is short, statistical methods for rate calculation can be more appropriate, rather than the methods for binomial proportion.

2. Interpretation of characteristic and risk factors
- Due to the nature of the available data and analysis, it is not appropriate to claim association between risk factors and TB. For example, even though many patients came from a household with a large number of family members, what is the comparative baseline to claim the TB is associated with overcrowding? Similarly, for household smoke, how can we judge 71.2% exposure is higher among TB patients (compare to whom)?
- Also as discussed above, the analysis of the mixed group (N=146) makes interpretation more difficult. The characteristics and risk factors need to be presented separately for those patients newly diagnosed (prospectively) and for those INPATIENTS who were on treatment prior to the study.
- With above reasons, it is preferable that the authors revisit the sentences such as:

---“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.”

---“Drivers of clinical disease in Kikori might include malnutrition and exposure to household smoke.”

---“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.)

---“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%. )

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

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

Nothing to declare.