

## **Understanding and addressing the tuberculosis case detection gap: national inventory studies to improve estimates of incidence and strengthen surveillance**

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**Running title:** Understanding and addressing the tuberculosis case detection gap

**Keywords:** Tuberculosis; surveillance; SDGs; incidence; under-reporting

**Word count:** 1570

**References:** 21

## Background

Global targets for the reduction in tuberculosis (TB) disease burden were set within the context of the United Nations Millennium Development Goals (MDGs), spanning the period 2000-2015.<sup>1</sup>

The targets were that TB incidence should be falling and that TB prevalence and mortality should be reduced by 50% compared with 1990 as the reference year at global, regional, and national levels compared with 1990 rates. Building on the MDGs, have been followed by the recently adopted Sustainable Development Goals (SDGs) with 2030 as their end date.<sup>2</sup> include as a target within the health-related SDGs is to end the tuberculosis-TB epidemic, as measured by TB incidence, by 2030.<sup>2</sup>

The World Health Organization's (WHO)'s post-2015 global TB strategy, also has the goal to end the global TB epidemic, with corresponding targets of a 90% reduction in deaths and an 80% reduction in the TB incidence rate by 2030.<sup>3</sup> The accurate understanding and measurement of TB incidence, one of the high level indicators consistently used by the global health community since 2000, is pivotal to monitoring progress against targets, and assessing whether investments in TB care and prevention reap benefits.

The level of and trends in TB incidence and prevalence can be measured directly by performing incidence surveys, population measured through population cohort studies and periodic prevalence surveys, respectively. There is general agreement that cohort national cohort studies are too expensive and impractical to directly measure TB incidence to conduct TB incidence surveys these studies at a national scale and implement, while many countries do not meet the recommended criteria to conduct a national TB prevalence surveys to directly measure to generate estimates of TB disease burden. Ideally, data on TB incidence should be obtained from routine national TB notification surveillance registers, e.g. the National TB Programme (NTP) register. In settings with such state-of-the-art routine surveillance systems in place, the number where most, if not all of, new TB cases are diagnosed and registered, TB cases notified to the system reflects National TB Programme (NTP) of the Ministry of Health provide a good proxy for TB incidence provided that all TB cases are registered. There is general agreement that it would be too expensive and impractical to conduct TB incidence surveys at a national scale to generate

**Commented [SC1]:** Sub-headings will not be part of the official submission of this manuscript, as they are not allowed for viewpoints. I am leaving them in for now, to help everyone understand the structure easier, and help our discussion.

**Commented [IA2]:** Maybe I am missing something here. The term incidence survey is not generally used by epidemiologist simply because a survey usually entails collection of information in a one off exercise – and not the process required to detect new cases which really needs a population cohort study.

BABIS: I agree, text has been changed accordingly.

**Commented [BE(3)]:** We need to avoid under-selling the importance of surveys here. Maybe another way to say it is...

BABIS: I agree, text has been changed accordingly.

~~estimates of TB disease burden. This leaves us with~~ Instead, the ultimate goal for measuring the level of, and trends in, TB incidence is from a state-of-the-art national surveillance systems. However, there can be various TB case detection gaps causing differences between the officially reported number . Most often than not however case detection gaps plague national TB surveillance systems at different stages throughout the patient cascade. Incident TB cases could be missed from national TB surveillance systems: in settings with no universal health coverage and hence no access to diagnosis; due to errors in correctly identifying individuals as having presumptive TB; due to errors in diagnosis of TB; due to TB patients not receiving anti-TB treatment; and due to no notification of TB cases and actual number of TB cases in a country. When people have no access to health care they have a zero probability to be registered. But even with access to health care they may not or incorrectly be diagnosed and therefore not registered. After a correct diagnosis of TB, patients may not receive treatment and unknown to the national TB register when starting diagnosed or on treatment is the opportunity for reporting. Finally, after treatment the physician may not notify the patient case to the national authorities, especially physicians outside to the NTP.<sup>4,7</sup> The total case detection gap is the sum of the accessibility, diagnosis, treatment and notification gaps.<sup>4,7</sup> Population cohort and periodic prevalence surveys can (partly) address accessibility, diagnosis and treatment gaps. An A customised and more cost-efficient alternative to population cohort studies and periodic prevalence surveys to assess that could inform the notification gap, hence measure underreporting corrected TB incidence extend of such gaps, are TB inventory studies, using record-linkage of the national TB register with various other case-based TB-related registers. Based upon the overlap data after record-linkage.

TB inventory studies have two broad study objectives, one involving the direct measurement of TB under-reporting and the other, under certain conditions, the estimation of TB incidence through capture-recapture analysis, under certain assumptions can subsequently estimate TB incidence, i.e. including the number of TB patients not present in the registers used for linkage.<sup>8</sup>

A national system will provide an accurate estimate of the incidence of diagnosed TB cases if it has national coverage and if there is no underreporting in settings with universal health coverage and

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Commented [IA4]: And no underdiagnosis..

BABIS: I agree, text has been deleted.

documentation of the detection gap from small-scale operational research studies. In such settings with such surveillance systems in place, the number of new cases captured by and notified to the system provides a good proxy for TB incidence provided that all TB cases are diagnosed. In the absence of such characteristics, knowledge about the level of underreporting or in cases where there is underreporting, specific data are required to correct for the detection gap of known weaknesses of cases that are missed by the TB surveillance system. These data include information on the underreporting of cases from the private and, in some cases, public sectors<sup>4</sup> and the under diagnosis of cases missed due to lack of access to diagnosis<sup>5</sup>, misdiagnosis of patients who do seek care<sup>6</sup> or laboratory errors<sup>7</sup>. TB inventory studies offer a customised solution to producing relevant data on the underreporting gap, since they directly measure under reporting and under certain conditions also estimate incidence through capture-recapture analysis.<sup>8</sup> (CR) analysis.<sup>8</sup>

## Methods

There are two broad categories of design for national TB inventory studies: the retrospective design, most often possible in resource-rich settings with an established surveillance and national, case-based TB-related surveillance system, as well as other national health TB-related, case-based databases, such as health insurance, laboratory, hospital admission or pharmacy registers, often in resource-rich settings, – and the prospective design, which requires a creates most often possible in resource-limited settings, which involves the creation of study registers, e.g., in from a representative sample national sample of health-care providers who diagnose and/or treat TB, – such as private practitioners and non-NTP public practitioners, often in resource-limited settings.<sup>8</sup> as well as prospective data collection for TB cases diagnosed during the study period.<sup>8</sup> For both designs, linkage of the study registers with the national official TB surveillance database records with the other study databases is required. This can be done either deterministically, with a unique identifier (e.g. national ID number), or probabilistically with a combination of patient characteristics (e.g. age, sex, postcode). There Inventory studies require extensive data management and analytical skills, particularly true when CR analysis is attempted, that may not be available in NTPs. Local research partners and international technical assistance are also two broad often needed to

**Commented [IA5]:** Which data?

BABIS: I agree, text has been changed accordingly.

**Commented [MvdW6]:** I suggest to order this logically. So in that case under reporting by private and public sector would come last.

BABIS: Done

**Commented [MvdW7]:** I believe that these problems will not be solved by inventory studies.

BABIS: Don't agree, already explained that inventory studies do in fact address case detection gaps.

**Commented [IA8]:** I am curious about the structure of the paper. If the next section is described as "methods" then I would expect the last section of the introduction to outline the objective of the paper.

BABIS: added objectives of studies at the end of background section.

~~support study objectives, one involving the measurement of TB under-reporting and the other the estimation of TB incidence through capture-recapture analysis.~~ implementation.

**Commented [IA9]:** But this describes the objective better. I would suggest moving this to the introduction to replace the last sentence.

BABIS: Moved to introduction as suggested.

In principle, all countries with an unknown level of underreporting are eligible for inventory studies. However, ~~these type of studies~~ they may be most relevant for ~~Countries~~ countries where ~~there is~~ substantial underreporting ~~under-reporting~~ is expected, e.g. because reporting of TB is not mandatory or is mandatory but not enforced, or due to a large private or non-NTP public sector with weak ~~or~~ or no linkages to the official TB surveillance system. ~~reporting of TB is not mandatory — or it is mandatory but not enforced — or the public sector is not reporting cases to the national TB programme (NTP), are eligible for a TB inventory study.~~ For ~~Countries~~ countries with a strong surveillance system ~~are also eligible for~~ inventory studies ~~will may to could~~ produce clear and quantifiable evidence, ~~if required,~~ that ~~notified-TB cases~~ case notifications are a good proxy for TB incidence, although violation of the basic assumptions for reliable outcomes, such as perfect record-linkage for inventory studies and, in addition, independence of registers for capture-recapture studies.<sup>9,10</sup>.

Alternative types of investigations have been suggested to measure TB under-reporting. A nested investigation within a national prevalence survey identifies all those TB cases on antibiotic treatment at the time of the survey. A measure of under-reporting can be drawn through record linkage of the identified TB patients on treatment from the survey with all those in the official TB surveillance system. ~~Another investigation involves identifying TB patients from a cross-sectional household level survey and establishes establishing how many of those are not under treatment from the national TB programme at the time of the survey.~~ While results from such investigations are informative for hypothesis building purposes, there are important limitations involved in their design such as misclassification and recall bias.

**Commented [MvdW10]:** Now the detection gap and underreporting is both used. I suggest to choose one.

BABIS: Text has been changed.

**Commented [IA11]:** But this does not measure underreporting – it is likely assessing both underreporting and underdiagnosis except if the survey only enquires about diagnosed cases.

BABIS: Text has been changed.

## Results

There has been considerable momentum during the last ~~10~~ten years have seen in the implementation of national inventory studies to measure TB under-reporting, and in many cases in

~~combination~~ combination with capture-recapture analysis, in countries including the Netherlands<sup>9</sup>, the UK<sup>10</sup>, French Guiana<sup>11</sup>, Egypt<sup>12</sup>, Yemen<sup>13</sup>, Iraq<sup>14</sup>, Pakistan<sup>15</sup> and Kenya<sup>16</sup>. Hypothesis-generating investigations to assess the level of TB ~~under-reporting various TB~~ case detection gaps were also completed in India<sup>17</sup> (cross-sectional survey of households) ~~and -),~~ Indonesia<sup>18</sup> and Viet Nam<sup>19</sup> (nested within a national prevalence surveys among adults). The level of TB under-reporting found was quite context-dependent ranging around 15% in European countries, 20% in Africa, 30% in the Eastern Mediterranean region, and 50% in countries in Asia with a large private sector. These data have all informed national estimates of TB disease burden.<sup>20</sup>

Results from inventory studies provide the platform and evidence to make programmatic changes to better address TB. Studies in Pakistan and Vietnam, settings with rapid growth of the private sector and the availability of TB drugs in private pharmacies, identified the need to strengthen TB surveillance in both countries and to scale up public-public and public-private mix (PPM) interventions to address high levels of under-reporting from that sector. In both countries, study results informed the national strategic plans and guided investment in concept notes submitted to the Global Fund. Inventory studies have also provided evidence to NTP programs on where to target their efforts to strengthen surveillance. For example, results from a study in Kenya found differences in the level of under-reporting by region.<sup>16</sup> Under-reporting was also more likely in patients who were older, had scanty smear results, and were diagnosed at large or private facilities. Results were used by the NTP to inform the development of systems to improve linkages between laboratories and TB facilities and to track diagnosed patients who do not return for treatment in areas with the highest levels of under-reporting. In countries such as the UK, capture recapture studies have informed specific modifications to the surveillance system to decrease under-reporting. For example, laboratory reports are automatically flagged to local teams to encourage the clinical reporting of cases supported by an automated record linkage programme in the surveillance system.

## Discussion

The role of TB inventory studies is critical in quantifying how much of a gap in under-reporting of TB there is in a country and where that gap is in terms of the type of health care providers who diagnose the disease. Next to that, these studies produce national level data that improve the estimates of the level of and trends in disease burden and make monitoring of progress towards international targets for TB a more robust and methodologically sound exercise. The contribution of national inventory studies is particularly important for childhood TB where they are currently the only option to provide direct measurements that improve our understanding of burden due to TB and this way contribute to better scale up response.

Lesson learnt from these studies were... Results from the Inventory studies provide the platform and evidence to make programmatic changes to better address TB. Studies in Pakistan and Vietnam, settings with rapid growth of the private sector and the availability of TB drugs in private pharmacies, identified the need to strengthen TB surveillance in both the countries and to scale up public private mix (PPM) interventions to address high levels of under-reporting from that sector. These In both countries, study results informed the country's national strategic plans and guided investment in the country's concept notes submission submitted to the Global Fund. Inventory studies have also provided evidence to NTP programs on where to target their efforts to strengthen surveillance. For example, results from a study in Kenya found differences in the level of under-reporting by region.<sup>16</sup> Under-reporting was also more likely in patients who were older, had scanty smear results, and were diagnosed at large or private facilities. Results were used by the NTP to inform the development of systems to improve linkages between laboratories and TB facilities and to track diagnosed patients who do not return for treatment in areas with the highest levels of under-reporting. In countries such as the UK, capture recapture studies have informed specific modifications to the surveillance system to decrease underreporting. For example, laboratory reports are automatically flagged to local teams to encourage the clinical reporting of cases supported by an automated record linkage programme in the surveillance system.

**Commented [MvdW12]:** I actually think that the first and the second sentence of this section are the same but differently phrased. If you know the underreporting you know the estimated incidence given that there is no problem in TB detection.

**Commented [A13]:** Perhaps the second sentence can be more about monitoring trends

BABIS: Text has been changed accordingly.

**Commented [CS14]:** One of the major points that should be made is that inventory presents are one of the only options to better improve the numbers for children who are presently not included in prevalence surveys, and therefore allows programs to better scale up its response to childhood TB

BABIS: Added.

Promising recent interest from funding agencies such as the European Centre for Disease Prevention and Control has resulted in the planning of much needed national TB inventory studies in countries in Asia<sup>31</sup> and Europe<sup>22</sup>. Reasonable budget estimates for these surveys are around USD 200,000–400,000 for prospective and USD 50,000–100,000 for retrospective designs.

The role of TB inventory studies is critical in quantifying how much of a gap in TB case detection there is in a country and where that gap is in terms of the type of health care providers who diagnose the disease. On the one hand ~~Next to that, these studies produce national level data that improve the estimates of disease burden and make monitoring of progress towards international targets for TB a more robust and methodologically sound exercise. On the other hand~~

Furthermore, the results and lessons learnt from inventory studies provide invaluable insight ~~in terms of programmatic implications~~ for national TB programmes with respect to health care seeking behaviour of TB patients and reporting practices of health care providers that diagnose TB. ~~The results will can also Furthermore, there are associated benefits of inventory studies that strengthen national TB surveillance systems, especially the prospective design, in which a representative national sample of health-care providers who diagnose and treat TB are selected, will provide information on the distribution They promote the exhaustive mapping of health care providers in the country and will provide a clear understanding of the different types of facilities that diagnose and treat TB. This type of study Inventory studies may they support the establishment or expansion of public-private and public-public mix PPM recording and reporting by building links with sectors that are not normally a part under the purview of the NTP, e.g. such as paediatric specialists. Both retrospective and prospective inventory studies; they provide the evidence to NTP programs to on where to target their efforts to strengthen surveillance; or private laboratories; they showcase the benefits of case-based electronic TB surveillance solutions; they provide a better understanding of existing diagnostic and case management practices in the non-NTP sector; they promote the institutionalisation of components of inventory study type investigations as part of annual quality checks of the TB surveillance system; and; lastly they improve data linkages between the NTP and non-NTP (including laboratories) sectors where the prospective design is implemented the studies~~

**Commented [MvdW15]:** Suggest to add this and then remove reference 22. Maybe you can do the same for reference 21.

BABIS: Done

**Commented [BE(16):** Mentioned in above paragraph

BABIS: Now deleted

**Commented [BE(17):** I don't have a reference, but I know that CDC is planning to support China in the development of a tool for staff to do routine checking of under-reporting based on their pilot inventory study there.

BABIS: thanks for the information, nothing changed.

**Commented [BE(18):** This could be dropped as it is mentioned in examples in above paragraph/

BABIS: Dropped



provide detailed mapping of health-care providers in the sampled areas and a clear understanding of the different types of facilities that diagnose and treat TB in the country.

Promising recent interest from agencies such as the European Centre for Disease Prevention and Control and UNITAID has resulted in the planning of much needed national TB inventory studies in countries in Asia<sup>24</sup>Asia and Europe<sup>22</sup>Europe. In general, inventory and capture-recapture studies are less costly than other population-based sampling methods relevant to TB. Reasonable budget estimates for these surveys are around USD 200,000 – 400,000 for prospective and USD 50,000 – 100,000 for retrospective designs.<sup>8</sup>

Limitations to these studies include: failure to establish linkage of records that appear in a non-sampled area or that were recorded outside the timeframe of the study resulting in misclassification of reported (or not reported) TB cases; change in recording and reporting practices of health care providers during study implementation; errors with record linkage; unmet conditions necessary for the successful implementation of capture-recapture analysis<sup>23</sup>; analysis most importantly the independence of case source registers.<sup>21</sup> Lastly, in resource-limited settings where the retrospective design is not possible and a large percentage of the population lacks access to basic health care, inventory studies are also not designed to assess the diagnostic gap, i.e. the number of individuals may not be useful in that only a small percentage of TB cases can be identified or diagnosed with TB, as a proportion of the much larger pool of missing cases which are not detected by the health system at all.

## Conclusion

Strengthening national TB surveillance systems and the data they produce is the only credible way to ensure the robust and routine monitoring of progress towards international targets for TB. Inventory studies are an important tool, one of the few available to us today, to achieving that goal for TB surveillance. As countries begin working towards the new TB incidence targets set within the SDGs and WHO post-2015 global TB strategies, increased commitment from NTPs and funding agencies to conducting and funding TB inventory studies is studies is urgently required.

**Commented [MvdW19]:** Suggest to add this and then remove reference 22. Maybe you can do the same for reference 21.

BABIS: Done

**Commented [IA20]:** Reference?

EB: Added.

**Commented [IA21]:** I would suggest doing a text box with a list of these limitations

BABID: Disagree, an only box in the viewpoint highlighting limitations of these studies will send the wrong message.

**Commented [IA22]:** I will link this back to the monitoring of SDG goals

EB: See suggestion below.

BABIS: Looks great thanks.



**Disclaimers:** The views expressed in this publication are those of the authors alone and do not necessarily represent the views of their institutional affiliations. Charalambos Sismanidis, Philippe Glaziou and Katherine Floyd are staff member of the World Health Organization. The authors alone are responsible for the views expressed in this publication and they do not necessarily represent the decisions or policies of the World Health Organization. The findings and conclusions in this paper are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention [or the United States Agency for International Development](#).

**Author contributions:** CS provided the initial concept and wrote the first draft of the manuscript. All authors contributed substantially to the final manuscript.

**Conflicts of interest:** None to declare.

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