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

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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. 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, which include as a target within the health-related SDGs is to end the tuberculosis epidemic, as measured by TB incidence, by 2030. The World Health Organization’s (WHO) 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. 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, measured through population cohort studies and periodic prevalence surveys, respectively. There is general agreement that it would be too expensive and impractical to conduct TB incidence surveys on a national scale, while many countries do not meet the recommended criteria to conduct national TB notification surveillance registers, e.g. the National TB Programme (NTP) register. Ideally, data on TB incidence should be obtained from routine national TB notification surveillance systems, 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 the number of new TB cases that are diagnosed and registered, 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...
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. The total case detection gap is the sum of the accessibility, diagnosis, treatment and notification gaps. Population cohort and periodic prevalence surveys can (partly) address accessibility, diagnosis and treatment gaps. An 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 conditions can subsequently estimate TB incidence, i.e. including the number of TB patients not present in the registers used for linkage. 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...
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 under-
reporting of cases from the private and, in some cases, public sectors, and the under-diagnosis of
cases missed due to lack of access to diagnosis, misdiagnosis of patients who do seek care, or
laboratory errors. TB inventory studies offer a customized 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 (CR) analysis.

**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 establishedTB surveillance system, as well as other national,
health-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
creation most often possible in resource-limited settings, which involves the creation of study
registers, e.g., 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, as well as prospective data collection for TB cases diagnosed during the study
period. 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). 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
support study objectives, one involving the measurement of TB under-reporting and the other the estimation of TB incidence through capture-recapture analysis. In principle, all countries with an unknown level of underreporting are eligible for inventory studies. However, these types of studies may be most relevant for countries where there is substantial underreporting 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 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 with a strong surveillance system are also eligible for inventory studies will may could produce clear and quantifiable evidence, if required, that notified TB 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,9,10.

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 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.

Results

There has been considerable momentum during the last 10 years in the implementation of national inventory studies to measure TB under-reporting, and in many cases in
Combination of capture-recapture analysis, in countries including the Netherlands, the UK, French Guiana, Egypt, Yemen, Iraq, Pakistan and Kenya. Hypothesis-generating investigations to assess the level of TB under-reporting various TB case detection gaps were also completed in India (cross-sectional survey of households) and, Indonesia and Viet Nam (nested within a national prevalence surveys among adults). The level of TB under-reporting found was 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.

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. 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.

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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 and Europe. 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, 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, these studies support the establishment or expansion of public-private and public-public mix recording and reporting by building links with sectors that are not normally under the purview of the NTP, such as paediatric specialists. Both retrospective and prospective inventory studies 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 they improve data linkages between the NTP and non-NTP (including laboratories) sectors. Where the prospective design is implemented, the studies

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 also be used to improve the detection of cases of TB and to 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 of the different types of facilities that diagnose and treat TB. This type of study may 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 under the purview of the NTP, such as paediatric specialists. Both retrospective and prospective inventory studies 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 they improve data linkages between the NTP and non-NTP (including laboratories) sectors. Where the prospective design is implemented, the studies
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 and 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.

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; most importantly the independence of case source registers. 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 urgently required.
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**Conflicts of interest:** None to declare.
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