Are we missing ‘previously treated’ smear-positive pulmonary tuberculosis under programme settings in India? A cross-sectional study [version 1; peer review: 1 approved with reservations]

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Abstract

Background: In 2007, a field observation from India reported 11% misclassification among ‘new’ patients registered under the revised national tuberculosis (TB) control programme. Ten years down the line, it is important to know what proportion of newly registered patients has a past history of TB treatment.

Methods: A study was conducted among new smear-positive pulmonary TB patients registered between March 2016 and February 2017 in 18 randomly selected districts to determine the effectiveness of an active case-finding strategy in marginalised and vulnerable populations. We included all patients detected through active case-finding. An equal number of randomly selected patients registered through passive case-finding from marginalised and vulnerable populations in the same districts were included. Before enrolment, we enquired about any history of previous TB treatment through interviews.

Results: Of 629 patients, we interviewed 521, of whom, 11% (n=56) had past history of TB treatment (public or private) for at least a month: 13% (34/268) among the active case-finding group and 9% (22/253) among the passive case-finding group (p=0.18). No factors were found to be significantly associated with misclassification.

Conclusion: Around one in every ten patients registered as ‘new’ had previous history of TB treatment. Corrective measures need to be implemented, followed by monitoring of any change in the proportion of ‘previously treated’ patients among all registered patients treated under the programme at national level.

Keywords
Tuberculosis/classification, Previously treated TB, New TB, Recurrent TB, Vulnerable populations

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Introduction
India has the highest tuberculosis (TB) burden in the world. The annual estimated TB incidence and deaths is 2.7 million and 0.4 million, respectively. Of the patients receiving treatment under its revised national tuberculosis control programme (RNTCP), the proportion of ‘previously treated’ patients (received anti-TB drugs in the past for one month or more) was 19% in 2016 and 15% in 2017. The national anti-tuberculosis drug resistance (2014–16) survey shows that ‘previously treated’ TB patients have four times higher prevalence of multidrug-resistant TB (MDR-TB) when compared to new patients (11.6% versus 2.8%).

In 2007, Atre et al. reported 11% misclassification among ‘new’ patients registered under the RNTCP. It is important to know how the programme is faring 10 years down the line. This study was carried out as a part of a larger study among new smear-positive pulmonary TB patients to determine the effectiveness of a community-based active case-finding (ACF) strategy when compared to passive case-finding (PCF) in 18 randomly selected districts of India. The ACF strategy was conducted as part of Project Axshya (meaning ‘free of TB’) whose focus was to increase detection of new smear-positive pulmonary TB patients among marginalised and vulnerable populations. Before enrolling the newly registered TB patients (both ACF and PCF patients) into our study, we enquired about their history of previous treatment. This provided us with a unique opportunity to document the proportion of newly registered smear-positive pulmonary TB patients that had previous history of TB treatment and were therefore misclassified.

Methods
Study design and participants
This was a cross-sectional study involving new smear-positive pulmonary TB patients from marginalised and vulnerable populations that were registered for treatment under the RNTCP in India between March 2016 and February 2017.

Setting
National TB programme (2016–17): India’s RNTCP infrastructure included national, state, district and sub-district level administrative units (one for 250 000 to 500 000 population) and designated microscopy centres for sputum smear microscopy. Before starting TB treatment, the medical officer in the health facility classified the patients as ‘new’ or ‘previously treated’.

During the study period (March 2016 to February 2017), new patients received two months of Isoniazid, Rifampicin, Pyrazinamide and Ethambutol followed by four months of Isoniazid, Rifampicin and Ethambutol. ‘Previously treated’ patients received two months of Isoniazid, Rifampicin, Pyrazinamide, Ethambutol and Streptomycin, one month of Isoniazid, Rifampicin, Pyrazinamide and Ethambutol and five months of Isoniazid, Rifampicin and Ethambutol. Among TB patients, a subset of patients who were at high risk to have MDR-TB (presumptive MDR-TB patients) underwent genotypic drug susceptibility testing (DST). These included patients previously treated for TB, patients with a TB-HIV co-infection, patients who upon follow up during TB treatment were smear-positive and contacts of a confirmed MDR-TB patient.

Project Axshya: Project Axshya is implemented in India by the South-East Asia office of the International Union against Tuberculosis and Lung Disease (The Union) to enhance the reach and visibility of RNTCP services among marginalised and vulnerable populations and to mitigate the impact of TB on the country (see Box for criteria for marginalised and vulnerable populations). Axshya SAMVAD (SAMVAD is an acronym for sensitization and advocacy in marginalised and vulnerable areas of the district) is the ACF strategy under the project. The word ‘SAMVAD’ in Sanskrit language means ‘conversation’. In 2016–17, the project covered 285 districts spread across 19 states.

Box. Criteria used for marginalised and vulnerable populations in districts under Project Axshya*, India (2016–17)

| 1. Slums |
| 2. Tribal areas |
| 3. Marginalised communities as per the constitution of India |
| 4. In pockets where occupational lung diseases are high |
| 5. In pockets where there is high risk of acquiring TB like; stone crushing/mining/weaving industry/unorganized labour (construction workers etc)/homeless people |
| 6. In pockets reported to have high HIV/AIDS burden |
| 7. In areas or communities where incidence of TB is high |
| 8. Among household contacts of smear-positive pulmonary TB patients |
| 9. Prisons |

Axshya SAMVAD study: This study was conducted among new smear-positive pulmonary TB patients to determine the effectiveness of Axshya SAMVAD on diagnosis and treatment initiation delays, costs due to TB diagnosis and treatment outcomes. We included all new smear-positive pulmonary TB patients from marginalised and vulnerable populations that were detected through ACF and registered under the programme in the 18 randomly sampled Axshya districts (simple random sampling) during March 2016 to February 2017. Every month in the same districts, we randomly sampled an equal number of new smear-positive pulmonary TB patients registered through PCF from marginalised and vulnerable populations (simple random sampling). Random numbers for simple random sampling were generated using Microsoft Excel.

Data collection
Under Axshya SAMVAD study, we collected data for each study participant through record review (age, gender, ACF/PCF status,
residence (urban/rural), distance of residence from microscopy centre, sputum smear grade, weight, diabetes status and HIV status) and patient interviews at their residence. Patient interviews were set up during the review of the participant’s record. Before starting the patient interviews, we enquired about their past history of TB treatment for at least one month either from the public or private sector. Those with a past history of treatment were excluded from the Axshya SAMVAD study and referred to the programme for appropriate management. These constitute ‘misclassification’ for the purpose of present analysis.

Data analysis
We double entered and validated the data using EpiData Entry software (version 3.1, EpiData Association, Odense Denmark). We analysed the data using STATA (version 12.1, copyright 1985–2011 StataCorp LP USA). We used frequency and proportions (95% confidence intervals (CI)) to summarise (infer) the extent of misclassification. Adjusted analysis was done using log binomial regression to determine the factors associated with misclassification. Variables collected during record review (age, gender, ACF/PCF status, residence (urban/rural), distance of residence from microscopy centre and sputum smear grade) were included in the adjusted analysis. Baseline weight was missing in two-fifths of patients; baseline diabetes status was missing for more than three-fifths and only one patient was living with HIV. Hence, we excluded them from the adjusted analysis. The association was summarized (inferred) using adjusted prevalence ratios (95% CIs).

Ethics
The Axshya SAMVAD study was approved by the Ethics Advisory Group of The Union, Paris, France (EAG number 15/15, dated 28 September 2015). We conducted the study after receiving approvals from the State Tuberculosis Officers in the respective states (18 randomly sampled Axshya districts belonged to seven states). We obtained written informed consent for participation from all the study participants.

Results
Figure 1 depicts the misclassification of ‘previously treated’ smear-positive pulmonary TB patients as ‘new’. A total of 629 newly registered smear-positive pulmonary TB patients were enrolled for the Axshya SAMVAD study. We couldn’t contact 108 (17%) for interview as patients were not available at their residence during the visit (a maximum of two visits were made).

Of the 521 interviewed, 56 [10.8% (95% CI: 8.4%, 13.7%)] had a past history of TB treatment (public or private) for at least a month: 12.7% (34/268) among the ACF group and 8.7% (22/253) among the PCF group (p=0.18). No factors were found to be significantly associated with misclassification (Table 1).

Discussion
Key findings
About one in ten ‘new’ TB patients had a past history of TB treatment. This misclassification meant that these patients received the wrong treatment regimen as per the national guidelines at the time. This is similar to the RNTCP report of 2018 and previous documentation in 2007. The misclassification among new smear-positive TB patients was two times higher than the 4.5% reported from Malawi in 2000.

One possible reason for this might be a lack of attention on the part of the medical officer to enquire for previous history of TB before starting treatment. Ambiguity in classification when
Table 1. Factors associated with the misclassification of ‘previously treated’ smear-positive pulmonary TB as ‘new’ among the new smear-positive pulmonary TB patients in the Axshya SAMVAD study across 18 randomly sampled Axshya districts in India, March 2016-February 2017.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total</th>
<th>Misclassification</th>
<th>PR (0.95 CI)</th>
<th>aPR* (0.95 CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>521**</td>
<td>56 (11)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Exposure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Axshya SAMVAD</td>
<td>268</td>
<td>34 (13)</td>
<td>1.5 (0.9, 2.4)</td>
<td>1.3 (0.7, 2.1)</td>
</tr>
<tr>
<td>Passive case finding</td>
<td>253</td>
<td>22 (9)</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Age categories in years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15–44</td>
<td>276</td>
<td>25 (9)</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>45–64</td>
<td>185</td>
<td>22 (12)</td>
<td>1.3 (0.8, 2.3)</td>
<td>1.1 (0.6, 1.9)</td>
</tr>
<tr>
<td>≥65</td>
<td>59</td>
<td>9 (15)</td>
<td>1.7 (0.8, 3.4)</td>
<td>1.5 (0.7, 3.1)</td>
</tr>
<tr>
<td>Missing</td>
<td>1</td>
<td>0 (0)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>346</td>
<td>39 (11)</td>
<td>1.2 (0.7, 2.0)</td>
<td>1.3 (0.7, 2.2)</td>
</tr>
<tr>
<td>Female</td>
<td>174</td>
<td>17 (10)</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Missing</td>
<td>1</td>
<td>0 (0)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Residence</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urban</td>
<td>59</td>
<td>1 (2)</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Rural</td>
<td>457</td>
<td>55 (12)</td>
<td>7.1 (1.0, 50.4)</td>
<td>6.4 (0.9, 48.2)</td>
</tr>
<tr>
<td>Missing</td>
<td>5</td>
<td>0 (0)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Distance from DMC in km</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤5</td>
<td>128</td>
<td>10 (8)</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>6–10</td>
<td>161</td>
<td>17 (11)</td>
<td>1.4 (0.6, 2.8)</td>
<td>1.0 (0.5, 2.0)</td>
</tr>
<tr>
<td>11–15</td>
<td>118</td>
<td>11 (9)</td>
<td>1.2 (0.5, 2.7)</td>
<td>0.8 (0.4, 1.9)</td>
</tr>
<tr>
<td>&gt;15</td>
<td>113</td>
<td>17 (15)</td>
<td>1.9 (0.9, 4.0)</td>
<td>1.4 (0.7, 2.9)</td>
</tr>
<tr>
<td>Missing</td>
<td>1</td>
<td>1 (100)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Sputum smear grading</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3+</td>
<td>90</td>
<td>7 (8)</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>1+/2+</td>
<td>413</td>
<td>48 (12)</td>
<td>1.5 (0.7, 3.2)</td>
<td>2.4 (0.3, 16.2)</td>
</tr>
<tr>
<td>Positive not quantified</td>
<td>18</td>
<td>1 (6)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

TB – tuberculosis; SAMVAD – sensitization and advocacy in marginalised and vulnerable areas of the district; Axshya SAMVAD – an active case-finding strategy under project Axshya implemented by The Union, South East Asia office, New Delhi, India, across 285 districts of India; aPR – adjusted prevalence ratio; CI – confidence interval.

*registered under programme between March 2016 and February 2017 for treatment after classification as ‘new’; **Total 661 were enrolled, 32 were later excluded as they did not fit the operational definition of study participant based on information obtained from record review. Among 629 eligible for patient interviews, 521 study participants could be contacted; @log binomial regression.

there was a large gap between previous and current treatment, absence of treatment records and patients’ reluctance to disclose previous treatment details due to possible stigma (fear of being seen as a ‘problem patient’) could be the other reasons.5

Limitations
This study has some limitations. First, this programmaticaly relevant finding was incidental and part of a larger study (Axshya SAMVAD study) and hence, we did not systematically record the details of past TB treatment (when, duration of treatment, whether under programme or in private sector) and the reasons for misclassification. Secondly, as patients with misclassification were excluded from the Axshya SAMVAD study, we do not know what happened to them, including their treatment outcomes. Thirdly, we did not include smear-negative pulmonary TB and extrapulmonary TB patients as they were
not part of the Axshya SAMVAD study. In Malawi (2000), they had a higher risk of misclassification when compared to smear-positive pulmonary TB patients. Finally, non-response was a limitation. However, in a best-case scenario (assuming all 108 non-responders did not have previous history of TB treatment), the proportion of misclassification would have been 8.9% (56/629) which is still programmatically significant.

Implications for the TB programme

Limitations notwithstanding, our study has programme implications. Of the new smear-positive pulmonary TB patients registered in India in 2016, 21% had an unfavourable outcome. Some of these unfavourable outcomes can be explained by wrong management – patients getting an inferior treatment regimen (previously treated patients being treated with a regimen meant for new cases) and missing an opportunity for drug susceptibility testing (as previously treated patients were eligible for DST at the time).

India has recently adopted the World Health Organization (WHO) recommendation that the category II regimen (for ‘previously treated’ patients) ‘should no longer be prescribed and drug susceptibility testing should be conducted to inform the choice of treatment regimen’. To make this a reality, India now recommends universal DST, meaning all diagnosed TB patients are eligible for testing via the Xpert MTB/RIF assay (Cepheid Sunnyvale USA) followed by first-line (if rifampicin susceptible) or second-line line probe assay (if rifampicin resistant). This further means that both new and previously treated patients are treated with the same regimen. Hence, in the present scenario, the impact of misclassification on individual patient management is minimal. This was not the case at the time of conduct of this study. Despite these developments, we think asking for previous treatment history is still relevant for two reasons. First, the information on the proportion of previously treated patients is epidemiologically an important piece of information and is regularly reported to the WHO for monitoring the global TB epidemic. Second, the universal DST is not a reality in every part of the country and in such instances, prioritizing previously treated patients for DST is a better strategy, given the higher prevalence of drug-resistant TB among them.

Future research

Our findings were based on patients from marginalised and vulnerable populations and this limits our generalisability to TB patients registered from the general population. The programme should consider replicating similar studies among patients from the general population.

Since 2017, the revised laboratory register at the level of designated microscopy centres under the RNTCP (one per 50,000 to 100,000 population) also captures this information of previous treatment. Hence, complete filling of the revised laboratory register at microscopy centres should be closely monitored by the programme and future operational research should focus on this.

Systematic qualitative enquiry is recommended to understand the ‘why’ (why does it happen) and ‘how’ (how can it be addressed) of misclassification.

Conclusions

This study demonstrated that ‘previously treated’ patients were being missed and were being registered as ‘new’ patients under the RNTCP in India. Corrective measures need to be implemented, followed by monitoring any change in the proportion of ‘previously treated’ patients among all registered patients treated under the programme at national level.

Data availability

Underlying data


Data are available under the terms of the Creative Commons Zero “No rights reserved” data waiver (CC0 1.0 Public domain dedication).

Extended data


This project contains the following extended data:

• S2 Annex.pdf (Part I of the questionnaire – record review)
• S3 Annex.pdf (Part II of the questionnaire – patient interview)

Data are available under the terms of the Creative Commons Zero “No rights reserved” data waiver (CC0 1.0 Public domain dedication).

Consent

Written informed consent for publication of the patients’ details was obtained from the patients.

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References

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The manuscript addresses one of the crucial problems with India’s Revised National TB Control Program. Interestingly, the study is based on our prior study (in which I was a lead author) in 2007, which was conducted in Mumbai and rural areas of Pune district. Given the research context and the data, I feel this manuscript should go as a brief communication or notes from the field rather than a full original research article. It does not make any novel contribution, but just confirms the earlier research finding. Even to make it a brief communication, I feel some points need to be provocatively addressed. My comments are as below.

1. Authors have provided details of their larger study, of which the current study is only a part. I feel that level of details is unnecessary here. On the other hand, unfortunately despite having a large team (as seen from the long list of authors), they did not do in-depth inquiry into the reasons for an erroneous categorization of cases, which is actually the main aim of the manuscript. They just mentioned the same reasons for erroneous categorization by providing a reference to our 2007 article without making any new contribution. Identifying the most prominent reasons would have been helpful to identify as a focus area for the policy makers to make some action plan for operational implementation of the program. In my opinion, there is not much substance to publish it as an original research article.

2. Authors nowhere discussed the major implication of their observation that even after 10 years, there remains a big disconnect between the operational research and the program implementation, which is really unfortunate. This finding has another major implication that because of erroneous categorization, previously treated cases are being treated with first-line regimen, which results in amplification of resistance in those cases who may have primary or acquired drug resistance (from prior treatment) and MDR-TB. This has been happening for over 10 years so one can see why India now faces the serious problem of drug resistant TB.

3. I am not convinced with the factor analysis in Table 1 because the detailed inquiry was not made into reasons for misclassification/erroneous categorization which should have been the main focus.

4. Authors state in discussion that as per the WHO recommendation, universal DST will be done for all TB cases. This is an ideal situation. The scale up of GeneXpert even remains questionable. The WHO global report 2018 showed that only 40% of TB cases in India were subjected to GeneXpert in 2017. There are problems of shortage of cartridges, falcon tubes, power outages etc. Given the glacial speed of translation of findings from operational research in the actual RNTCP implementation, India’s claim of TB elimination by 2025 looks really questionable.
Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Partly

Are sufficient details of methods and analysis provided to allow replication by others?
Partly

If applicable, is the statistical analysis and its interpretation appropriate?
Partly

Are all the source data underlying the results available to ensure full reproducibility?
Partly

Are the conclusions drawn adequately supported by the results?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Operational research on TB and MDR-TB in India

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

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