



RESEARCH ARTICLE

REVISED **Are we missing ‘previously treated’ smear-positive pulmonary tuberculosis under programme settings in India? A cross-sectional study [version 2; peer review: 1 approved, 2 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 for at least one month (henceforth called ‘misclassification’).

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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Any reports and responses or comments on the article can be found at the end of the article.

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REVISED Amendments from Version 1

Based on the reviewer comments, the following key edits were made to the manuscript:

1. Definition of 'Misclassification' was introduced early in the manuscript (both in Abstract as well as in the main text)
2. In the Discussion section, under implications for the TB programme, we added point regarding how misclassification over the last 10 years might have contributed to the amplification of resistance in those who may have primary or acquired drug resistance (from prior treatment) and MDR-TB.
3. In the Discussion section, the sub-section heading "Future research" was replaced by "Recommendations". Under this sub-section, we added possible solutions to address the issue of misclassification based on our programme experience.
4. Affiliation 2 has been corrected to: The Union South East Asia, New Delhi, 110016, India

See referee reports

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, respectively¹. 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^{2,3}. 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%)⁴.

In 2007, Atre *et al.*⁵ 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^{6,7}. 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 (henceforth called 'misclassification').

Methods

Study design and participants

This was a cross-sectional study involving new smear-positive pulmonary TB patients (≥ 15 y) 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 microscopy⁸. 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

TB – tuberculosis; *HIV* – human immunodeficiency virus; *AIDS* – acquired immunodeficiency syndrome; *Project *Axshya* –implemented by The Union, South East Asia office, New Delhi, India, across 285 districts of India, to enhance the reach and visibility of national TB programme services among marginalised and vulnerable populations and to mitigate the impact of TB on the country. *Axshya* in Sanskrit means 'free of TB'.

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^{6,7}. 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)^{6,7}. 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, sex, 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 software⁹ (version 3.1, EpiData Association, Odense Denmark). We analysed the data using STATA (version 12.1, copyright 1985–2011 StataCorp LP USA)¹⁰. We used frequency and proportions (0.95 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, sex, 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 HIV status was missing for two-fifths. 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

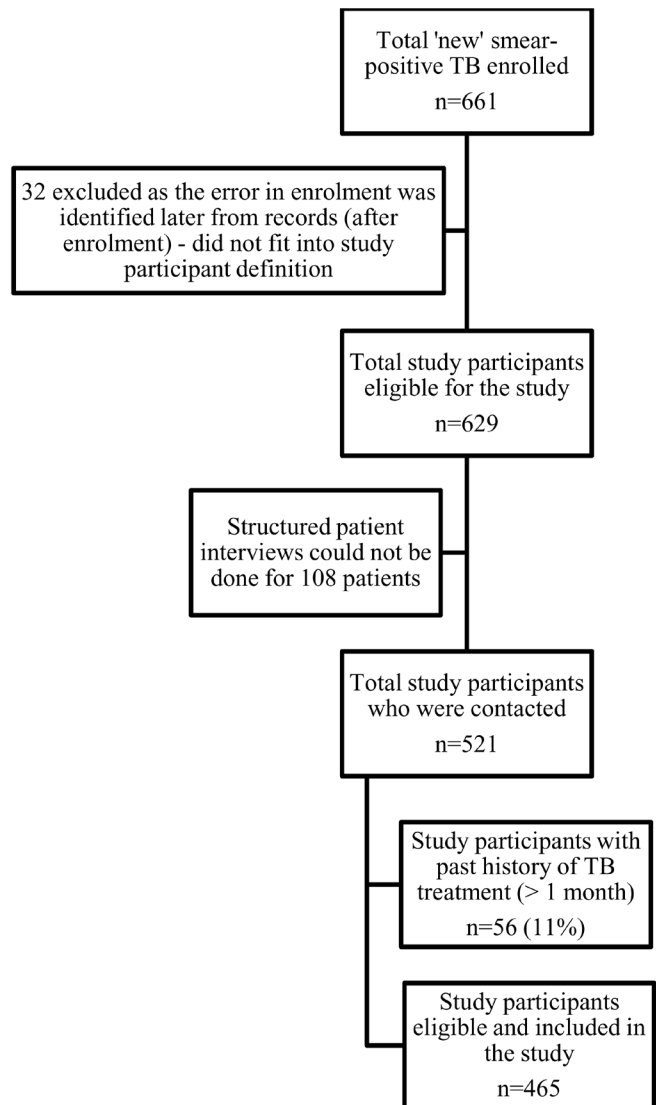


Figure 1. Flow chart depicting the misclassification of people (≥ 15 y) with 'previously treated' smear-positive pulmonary TB as 'new' among the study participants enrolled in the *Axshya SAMVAD* study across 18 randomly sampled *Axshya* districts in India, March 2016-February 2017*. TB – tuberculosis; 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. *registered under programme between March 2016 and February 2017 for treatment after classification as 'new'.

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). Patients belonging to rural areas had higher prevalence of misclassification when compared to urban areas (12% vs 2%), but this difference was not statistically significant probably due to small sample size.

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 2018³ and previous documentation in 2007⁵. The misclassification among new smear-positive TB patients was two times higher than the 4.5% reported from Malawi in 2000¹¹.

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 there was a large gap between previous and current treatment, absence of treatment records and patients' reluctance to disclose

Table 1. Factors associated with the misclassification of 'previously treated' smear-positive pulmonary TB as 'new' among the new smear-positive pulmonary TB patients (≥ 15 y) in the Axshya SAMVAD study across 18 randomly sampled Axshya districts in India, March 2016-February 2017*.

Variable	Total	Misclassification	PR (95% CI)	aPR [®] (95% CI)
	N	n (%)		
Total	521**	56 (11)	-	-
Exposure				
Axshya SAMVAD	268	34 (13)	1.5 (0.9, 2.4)	1.3 (0.7, 2.1)
Passive case finding	253	22 (9)	Ref	Ref
Age categories in years				
15–44	276	25 (9)	Ref	Ref
45–64	185	22 (12)	1.3 (0.8, 2.3)	1.1 (0.6, 1.9)
≥ 65	59	9 (15)	1.7 (0.8, 3.4)	1.5 (0.7, 3.1)
Missing	1	0 (0)	-	-
Sex				
Male	346	39 (11)	1.2 (0.7, 2.0)	1.3 (0.7, 2.2)
Female	174	17 (10)	Ref	Ref
Missing	1	0 (0)	-	-
Residence				
Urban	59	1 (2)	Ref	Ref
Rural	457	55 (12)	7.1 (1.0, 50.4)	6.4 (0.9, 48.2)
Missing	5	0 (0)	-	-
Distance from DMC in km				
≤ 5	128	10 (8)	Ref	Ref
6–10	161	17 (11)	1.4 (0.6, 2.8)	1.0 (0.5, 2.0)
11–15	118	11 (9)	1.2 (0.5, 2.7)	0.8 (0.4, 1.9)
> 15	113	17 (15)	1.9 (0.9, 4.0)	1.4 (0.7, 2.9)
Missing	1	1 (100)	-	-
Sputum smear grading				
3+	90	7 (8)	Ref	Ref
1+/2+	413	48 (12)	1.5 (0.7, 3.2)	2.4 (0.3, 16.2)
Positive not quantified	18	1 (6)	-	-

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.

previous treatment details due to possible stigma (fear of being seen as a ‘problem patient’) could be the other reasons⁵.

Limitations

This study has some limitations. First, this programmatically 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)¹¹, 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 outcome³. 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). Inferior regimen might have also contributed to amplification of resistance in those 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.

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*’¹². 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)^{4,13}. This further means that both new and previously treated patients are treated with the same regimen^{4,8,14}. 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.

Recommendations

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 with a possible sub-group to look for rural-urban differences.

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 treatment⁸. RNTCP staff needs to be re-sensitized to “ask” for previous history of TB 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. In the national case-based TB notification software (*NIKSHAY*), record linkage and deduplication using key attributes may be considered to identify repeat notification of the same person separated by a time period.

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

figshare: Underlying data. <https://dx.doi.org/10.6084/m9.figshare.7756688>¹⁵

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

Extended data

figshare: Questionnaire *Axshya SAMVAD* study. <https://dx.doi.org/10.6084/m9.figshare.7768589>¹⁶

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.

Grant information

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Open Peer Review

Current Peer Review Status: ? ✓ ?

Version 2

Reviewer Report 27 June 2019

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Banurekha Velayutham

ICMR–National Institute for Research in Tuberculosis (ICMR-NIRT), Chennai, Tamil Nadu, India

The authors have attempted to quantify the magnitude of misclassification among new smear positive pulmonary TB patients. In the current scenario of universal DST and removal of Category II regimen, this information may not of much value. Nevertheless, the 11% misclassification emphasizes the importance of appropriate history taking which could benefit patient management. Though new and previously treated patients are treated with the same 6-month daily regimen if found to be drug sensitive the distinction based on previous treatment would be important to analyse the response to treatment in future. The major limitation of this study is that it was not planned but rather incidental as mentioned by the authors. Hence, the reasons for such misclassification from patient and provider perspective which could have added more value to the study is lacking. The findings are worth communicating as a Brief communication article. Some clarifications are requested on the following:

1. What was the time interval between registration for treatment and the patient interview
2. The rationale for considering distance from DMC as a factor for misclassification

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: Epidemiology, Tuberculosis


I confirm that I have read this submission and 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.

Reviewer Report 20 May 2019

<https://doi.org/10.5256/f1000research.21019.r48633>

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Sachin R. Atre 

Center for Clinical Global Health Education (CCGHE), Johns Hopkins University, Baltimore, MD, USA

I feel many of my points are not addressed by the authors except a few minor changes.

Is the work clearly and accurately presented and does it cite the current literature?

Partly

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.

I confirm that I have read this submission and 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.

Reviewer Report 16 May 2019

<https://doi.org/10.5256/f1000research.21019.r48632>

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Otavio T. Ranzani 

Pulmonary Division, Heart Institute (InCor), Hospital das Clinicas (HCFMUSP), Faculdade de Medicina, University of São Paulo, São Paulo, Brazil

The authors addressed all my comments.

Is the work clearly and accurately presented and does it cite the current literature?

Partly

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: Epidemiology, Infection, Tuberculosis, Pneumonia, Air Pollution

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 12 April 2019

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Otavio T. Ranzani

Pulmonary Division, Heart Institute (InCor), Hospital das Clinicas (HCFMUSP), Faculdade de Medicina, University of São Paulo, São Paulo, Brazil

The authors conducted a secondary analysis on the data originated from the *Axshya SAMVAD* study aiming to describe the proportion of patients with smear-positive pulmonary tuberculosis labelled as "new" (regarding antibiotic treatment), but that actually have had tuberculosis before. The research question is of public health importance, it is not widely reported in the literature, and makes this short article interesting to the literature. The authors should be commended. I have some comments below aiming to improve the manuscript.

1. The authors should clarify to the reader on abstract that "new" refers to previous TB treatment for at least 30 consecutive days.
2. The authors should revise the entire manuscript, particularly Abstract and Introduction, to clarify about what "misclassification" refers to. Misclassification is an epidemiological term, but it can refer to different variables depending on the context. And during the read, it became clear only after going to the results section. Example: (abstract) "reported 11% misclassification among 'new' patients". Maybe the authors could rephrase as: "reported that 11% of patients with tuberculosis were misclassified as new patients regarding previous treatment history" or "reported that 11% of patients with tuberculosis were misclassified as new patients despite their previous TB treatment" or "reported that 11% of patients with tuberculosis were misclassified as new patients despite previously treated"
3. Regarding the inclusion criteria, did it only include adults?
4. Regarding Table 1: Why did you categorize age? And why in only 3 categories merging different age profile? For instance, the range 15-44 covers different population. You might have loose power and contrast. You should use age as continuous and/or open the category 15-44. Do the authors have converge problems with the log-binomial model? The authors should re-phrase their statements on the prevalence ratio associated factors on Table 1. For instance, it is clear that Residence (rural/urban) is an important factor, with a big point estimate, but wide confidence interval (6.4 (0.9, 48.2)). Likely with a bigger sample size and/or higher number of events, you would have better precision and would achieve "significance" or "no include 1".
5. How is it possible to have such low prevalence of positive HIV status in a vulnerable population? How was the HIV testing coverage?
6. The discussion section must be improved: Although recommended and ideal, DST will not be available for all. Even if available, the previous history treatment is fundamental. The authors should propose solutions for the problem, such as linkage deduplication, linked records from the national system, etc. Please, better discuss the potential selection bias and representative of the included population regarding India population.

Minor:

1. Maybe better to use the notation of 95% CI rather than 0.95
2. Figure 1. I think the first box at left has a wrong "the" : as AN error
3. Change gender to sex

Is the work clearly and accurately presented and does it cite the current literature?

Partly

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

Yes

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

Partly

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

No

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

Yes

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Epidemiology, Infection, Tuberculosis, Pneumonia, Air Pollution

I confirm that I have read this submission and 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.

Author Response 07 May 2019

Hemant Deepak Shewade, International Union Against Tuberculosis and Lung Disease (The Union), South-East Asia Office, New Delhi, India

REVIEWER #2

Otavio T. Ranzani, University of São Paulo, Brazil; Barcelona Institute for Global Health (ISGlobal), Spain

REVIEWER COMMENT

The authors conducted a secondary analysis on the data originated from the Axshya SAMVAD study aiming to describe the proportion of patients with smear-positive pulmonary tuberculosis labelled as "new" (regarding antibiotic treatment), but that actually have had tuberculosis before. The research question is of public health importance, it is not widely reported in the literature, and makes this short article interesting to the literature. The authors should be commended. I have some comments below aiming to improve the manuscript.

AUTHOR RESPONSE

Thank you very much for the constructive comments.

REVIEWER COMMENT

The authors should clarify to the reader on abstract that "new" refers to previous TB treatment for at least 30 consecutive days.

AUTHOR RESPONSE

We are not clear here what the reviewer intends to mean. 'New' refers patients who have not been previously treated for TB (at least for one month).

REVIEWER COMMENT

The authors should revise the entire manuscript, particularly Abstract and Introduction, to clarify about what "misclassification" refers to. Misclassification is an epidemiological term, but it can refer to different variables depending on the context. And during the read, it became clear only after going to the results section. Example: (abstract) "reported 11% misclassification among 'new' patients". Maybe the authors could rephrase as: "reported that 11% of patients with tuberculosis were misclassified as new patients regarding previous treatment history" or "reported that 11% of patients with tuberculosis were misclassified as new patients despite their previous TB treatment" or "reported that 11% of patients with tuberculosis were misclassified as new patients despite previously treated"

AUTHOR RESPONSE

Thank you for the comment. In the revised manuscript, both at beginning of abstract and main text introduction, we have clarified as to what we mean by 'misclassification' (reproduced below)

Abstract

"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 for at least one month (henceforth called as 'misclassification')."

Introduction (main text)

"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 (henceforth called as 'misclassification')."

REVIEWER COMMENT

Regarding the inclusion criteria, did it only include adults?

AUTHOR RESPONSE

Thank you for pointing this out. Yes it included only adults (≥ 15 y). We have clarified this under study population and titles of tables and figures.

REVIEWER COMMENT

Regarding Table 1: Why did you categorize age? And why in only 3 categories merging different age profile? For instance, the range 15-44 covers different population. You might have loose power and contrast. You should use age as continuous and/or open the category 15-44. Do the authors have converge problems with the log-binomial model? The authors should re-phrase their statements on the prevalence ratio associated factors on Table 1. For instance, it is clear that Residence (rural/urban) is an important factor, with a big point estimate, but wide confidence interval (6.4 (0.9, 48.2)). Likely with a bigger sample size and/or higher number of events, you would have better precision and would achieve "significance" or "no include 1".

AUTHOR RESPONSE

Thank you for the comment. We categorized aged, because we wanted to explore whether misclassification was significantly higher among certain meaningful sub-groups. Regarding opening up the category 15-44 y, we decided not to do this as there are only 25 events of interest (=misclassification) in this sub-group. If we further divide this sub-group, the event of interest could get reduced and this would have further widened the 95% CI for the adjusted prevalence ratios. As per reviewer comments, we have added a line under results narrative in the revised manuscript to discuss at adjusted prevalence ratio for the variable 'residence' (reproduced below).

“Patients belonging to rural areas had higher prevalence of misclassification when compared to urban areas (12% vs 2%), but this difference was not statistically significant probably due to small sample size.”

REVIEWER COMMENT

How is it possible to have such low prevalence of positive HIV status in a vulnerable population?
How was the HIV testing coverage?

AUTHOR RESPONSE

The HIV percentage among all TB patients in India is around 3%. In our study, HIV status was missing in records for two-fifth patients and among those whose test results were recorded (n=288), one was positive.

REVIEWER COMMENT

The discussion section must be improved: Although recommended and ideal, DST will not be available for all. Even if available, the previous history treatment is fundamental. The authors should propose solutions for the problem, such as linkage deduplication, linked records form the national system, etc. Please, better discuss the potential selection bias and representative of the included population regarding India population.

AUTHOR RESPONSE

Thank you very much. We have reviewed and revised the discussion section as per the comments. We agree that DST may not be available for all. Hence, in the “Implications for the TB programme” sub-section under discussion section we have included this this. We are reproducing it below:
“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.”

Regarding DST availability, we are reproducing the relevant discussion lines below

“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” (second paragraph under ‘implications for TB programme’ sub-section of discussion)

Regarding potential selection bias and representativeness, we are reproducing the relevant discussion lines below:

“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 with a possible sub-group to look for rural-urban differences.” (First paragraph under ‘recommendations’ sub-section of discussion)

Regarding proposing solutions, we have revised it as per reviewer suggestions under recommendations subsection of discussion (reproducing below)

“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 treatment⁸. RNTCP staff needs to be re-sensitized to “ask” for previous history of TB 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. In the national case-based TB notification software (*NIKSHAY*), record linkage and deduplication using key attributes may be considered to identify repeat notification of the same person separated by a time period."

REVIEWER COMMENT

Minor:

Maybe better to use the notation of 95% CI rather than 0.95

AUTHOR RESPONSE

We have revised throughout the manuscript as per reviewer suggestion

REVIEWER COMMENT

Figure 1. I think the first box at left has a wrong "the" : as AN error

AUTHOR RESPONSE

We are not clear as to what the reviewer means here. We did not find this error in the first left box of figure 1. However, we re-checked figure 1 and found it no grammatical errors.

REVIEWER COMMENT

Change gender to sex

AUTHOR RESPONSE

We have revised throughout the manuscript as per reviewer suggestion


Competing Interests: There are no competing interest to declare

Reviewer Report 09 April 2019

<https://doi.org/10.5256/f1000research.20077.r46256>

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Sachin R. Atre 

Center for Clinical Global Health Education (CCGHE), Johns Hopkins University, Baltimore, MD, USA

The manuscript addresses one of the crucial problems with in 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 GeneXert 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 confirm that I have read this submission and 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.

Author Response 07 May 2019

Hemant Deepak Shewade, International Union Against Tuberculosis and Lung Disease (The Union), South-East Asia Office, New Delhi, India

REVIEWER #1

Sachin R. Atre, Johns Hopkins University, USA; Dr. D.Y. Patil Medical College, Hospital and Research Centre Pune, India

REVIEWER COMMENT

The manuscript addresses one of the crucial problems with in 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.

AUTHOR RESPONSE

Thank you for the comment. F1000Research does not have the article types as suggested: brief communication or notes from the field. 'Research notes' is the closest option, but here too there is no specific word count mentioned. Considering our manuscript is around 1800 words only, we are fine if F1000Research agrees to consider this as a research note.

We agree the findings are not novel, but are timely considering 10 years down the line, the issue remains as it is and this is important to highlight.

We have addressed your comments, details below.

REVIEWER COMMENT

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.

AUTHOR RESPONSE

The actual study was done across 18 randomly spread districts of the country (Axshya SAMVAD study – Axshya SAMVAD is an ACF strategy for detecting TB and is implemented by The Union South East Asia). As mentioned, the findings were accidental (not intended) and we thought it is important to report this and look for differences in rates of misclassification across various patient sub-groups.

The Axshya SAMVAD study was conducted by project Axshya staff in operational setting without any additional funding for the study itself. The research team in the field (project Axshya staff) were not trained and did not have the required capacity to conduct qualitative research. Hence, we could not go in-depth into the reasons. But, one key point is that our study was conducted in randomly selected 18 districts of the country and hence, the findings are representative.

We agree the findings are not novel, but are timely considering 10 years down the line, the issue remains as it is and this is important to highlight.

Considering our manuscript is around 1800 words only, we are fine if F1000Research agrees to consider this as a research note.

REVIEWER COMMENT

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.

AUTHOR RESPONSE

Thank you very much for your comment. We agree with the reviewer. We have included the above point in the revised manuscript as suggested by the reviewer. We have discussed the implications in the first paragraph of 'Implications for the TB programme' in the revised manuscript (reproduced below):

"Limitations notwithstanding, our study has programme implications. Of the new smear-positive pulmonary TB patients registered in India in 2016, 21% had an unfavourable outcome³. 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). Inferior regimen might have also contributed to amplification of resistance in those 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."

REVIEWER COMMENT

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.

AUTHOR RESPONSE

Thank you for the comment. In Table 1, we are quantitatively looking for patient sub-groups who have higher prevalence of misclassification. Though not statistically significant, programmatically significant differences were observed in misclassification in urban and rural areas (12% in rural and 2% in urban areas). We agree that we have not looked into the 'why' and 'how' of misclassification (limitations). But, based on our programme experiences made some useful recommendations in the revised manuscript (reproduced below)

"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 with a possible sub-group to look for rural-urban differences.

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 treatment⁸. RNTCP staff needs to be re-sensitized to "ask" for previous history of TB 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. In the national case-based TB notification software (*NIKSHAY*), record linkage and deduplication using key attributes may be considered to identify repeat notification of the same person separated by a time period."

REVIEWER COMMENT

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 GeneXert 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.

AUTHOR RESPONSE

Thank you for the comment. We agree with the reviewer. We agree that DST for all TB patients is an ideal situation. Therefore, we have also stated that in a non-ideal situation (DST not possible for all TB patients), DST may be focussed on those with previous history of TB treatment. Therefore, correct classification as new or previously treated is still relevant. We have mentioned this in the last three lines of the section 'implications for the TB programme' (reproduced below):

"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."

Competing Interests: There are no competing interests to declare

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