RESEARCH ARTICLE

REVISED Pathway to care for drug resistant tuberculosis cases identified during a retrospective study conducted in high TB burden wards in Mumbai [version 2; peer review: 2 approved]

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Abstract

Background: Mumbai is witnessing a rising incidence of all forms of drug resistant tuberculosis (DR-TB).
Methods: A population-based, retrospective study was conducted between April and July 2014, in 15 high TB burden wards in Mumbai, to capture the patient pathways to TB care. A total of 23 DR-TB patients were identified and their pathways to access DR-TB care were recorded using semi-structured interviews.
Results: The total DR-TB pathway time of new patients (who did not report any past episode of TB) (180 days; IQR 123,346) was found to be more than twice that of retreatment patients (who reported a past episode of TB) (69 days; IQR 42,128).
Conclusions: The unacceptable delay for diagnosis and treatment of DR-TB in Mumbai advocates for consistent implementation of early screening of patients using rapid gene-based technologies.

Keywords

Drug resistant Tuberculosis, Mumbai, delays, pathway to TB care

Open Peer Review

Approval Status ✓ ✓

	1	2
version 2 (revision) 10 May 2018	✓ view	✓ view
version 1 19 Feb 2018	? view	? view

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2. **Ramnath Subbaraman**, Tufts University School of Medicine, Boston, USA

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

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Author roles: Lobo E: Formal Analysis, Investigation, Supervision, Validation, Writing – Original Draft Preparation, Writing – Review & Editing; **Shah S**: Data Curation, Formal Analysis, Software, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Rangan S**: Writing – Review & Editing; **Dholakia Y**: Writing – Review & Editing; **Mistry N**: Conceptualization, Formal Analysis, Funding Acquisition, Project Administration, Supervision, Writing – Original Draft Preparation, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

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REVISED **Amendments from Version 1**

Additional details of the population-based sampling approach in the Methods section has been added as per suggestions made by both the referees. The Methods section now also includes a more detailed information on the inclusion and exclusion criteria. Figure 1 previously only had the reasons for why the cases were excluded but this has been modified to now include the number of patients that were excluded for various reasons. This will enable the readers to replicate the study design. Demographic details of the study population has been added. Another change in the revised version is the change in the test used to measure significant differences. We have now examined the median differences in the population using Mann Whitney U test as opposed to previously, wherein we examined the mean differences using t-test. This is keeping in mind that the delays did not follow a normal distribution. Limitations of findings due to a small sample size has been added in the Discussion. Based on suggestions by referee 2, we have modified our Discussion section to extrapolate the key findings of the results which now includes some additional references based on more current practices in TB diagnosis. The references are inserted as hyperlinks: 1) diagnostic algorithms for standards of care in paragraph 2 and 2) a new policy in paragraph 3.

See referee reports

Introduction

The rising threat of multidrug resistant-tuberculosis (MDR-TB), defined as *in vitro* resistance to at least isoniazid and rifampicin, necessitates early detection of drug resistance and appropriate treatment initiation. A total of 480,000 MDR-TB cases are identified annually worldwide, accounting for 3.3% of newly diagnosed TB patients and 20% of retreatment TB patients[1,2]. An estimated 71,000 MDR-TB cases are reported from India, making it not only a major public health threat, but a huge economic burden on patients and health-systems as well. Mumbai, a fast growing urban metropolis in India with about 60% population living in vulnerable settings, has become the epicenter of various forms of MDR-TB[3]. Whilst national estimates for MDR-TB are 2.5% among new and 16% among retreatment patients[1], reports from the city have recorded rates as high as 24% among new and 41% in retreatment patients[4].

A patient with TB continues to be infectious until initiated on effective treatment. It is therefore imperative to understand the amount of time taken to detect patients with DR-TB and initiate them on appropriate treatment. This study looks at the durations from the onset of symptoms until initiation of appropriate treatment and tries to understand the type of patients that show maximum delay in accessing care.

Methods

Study design and participants

Between April and July 2014, a population-based, two-stage, retrospective study was conducted in 15 high TB burden wards. BMGF consultants had provided the estimated sample size of around 100 TB cases based on TB prevalence surveys conducted in rural areas (N=D*Z2(p*q)/(e2)).

The first stage involved identification of patients treated for TB with a household (HH) survey, using a multistage cluster approach from the 2011 Census Enumerated Block (CEB) maps. Fifteen wards falling under MCGM consisting of both slum and non-slum areas were identified. Census Enumeration Blocks (CEB) maps were used as the reference point for the primary sampling unit (PSU) in the urban area. The CEB map consisted of 120–180 HHs in each block and helped demarcate the slum areas and the non-slum areas. The CEB in these selected 15 wards acted as the sampling frame for the survey. Assuming an average cluster size of 160 per CEB, 100 Urban Frame Survey (UFS) blocks were selected for the primary objective of conducting a survey of over 10,000 HHs. Going by the assumption that the CEB blocks have a clear demarcation of slum and non-slum areas, sampling frames consisting of the slum based CEBs were created. The blocks from each ward were selected proportionate to the total number of HHs in the slums of the 15 wards. The required number of PSUs (100 CEBs) was selected randomly from the list of all slum based CEBs for each of the wards. In a selected CEB, all HHs in the selected block unit were enumerated.

Cases of TB were identified by means of two questions. One that recorded details of all the cases of cough in the family and narrowed down to asking the family member if the doctor they had consulted had told them that they had TB on the basis of tests conducted. The other question that captured the TB cases pertained to those that had occurred in the past six months who due to some treatment being taken did not show any signs of coughing any more. Around 21,016 HHs were listed, of which 14,250 (68%) agreed for an interview. From these participating HHs, a total of 153 TB cases were drawn.

The second stage involved in-depth interviews of identified TB patients who were treated for pulmonary TB in Mumbai and had completed their anti-TB treatment in the past six months. A total of 82 patients consented to being interviewed using a pre-tested open-ended semi-structured interview schedule (Supplementary File 1). Pre-testing was conducted as per study protocol on six known TB cases from K/East ward who were excluded from the final study sample. Of the 82 patients that consented to be interviewed, 23 DR-TB patients were identified (28%), and only these interviews were included in the present analysis. The data from the remaining 59 patients has been previously published[5]. Patients were identified as DR-TB cases if they had completed their anti-DR-TB treatment in Mumbai within the past six months of the interview. Besides patient information, diagnosis and treatment records of patients were obtained and seen by the researchers. Photographs of these were taken and shown to our clinical consultant on the study (YD), on whose opinion, the cases were classified as DR-TB. Two were identified as extensively drug resistant (XDR) cases based on their line probe assay (LPA) (Hain Lifescience, Nehren-Germany) results. Monoresistance to Isoniazid (INH) could not be identified as drug sensitivity testing (DST) through the line probe assay LPA was not available for all cases at the time of the study.

Figure 1 shows the selection flowchart for the participants.

The 23 patients that were included in this study came from 10 of the 15 high burden TB wards namely: M/East (8 patients), H/East (2 patients), M/West (2 patients), F/North (2 patients), P/North (1 patient), G/North (2 patients), R/South (1 patient), L (1 patient), N (3 patients), S (1 patient).

All patient interviews were conducted at the participants' residence by trained health researchers.

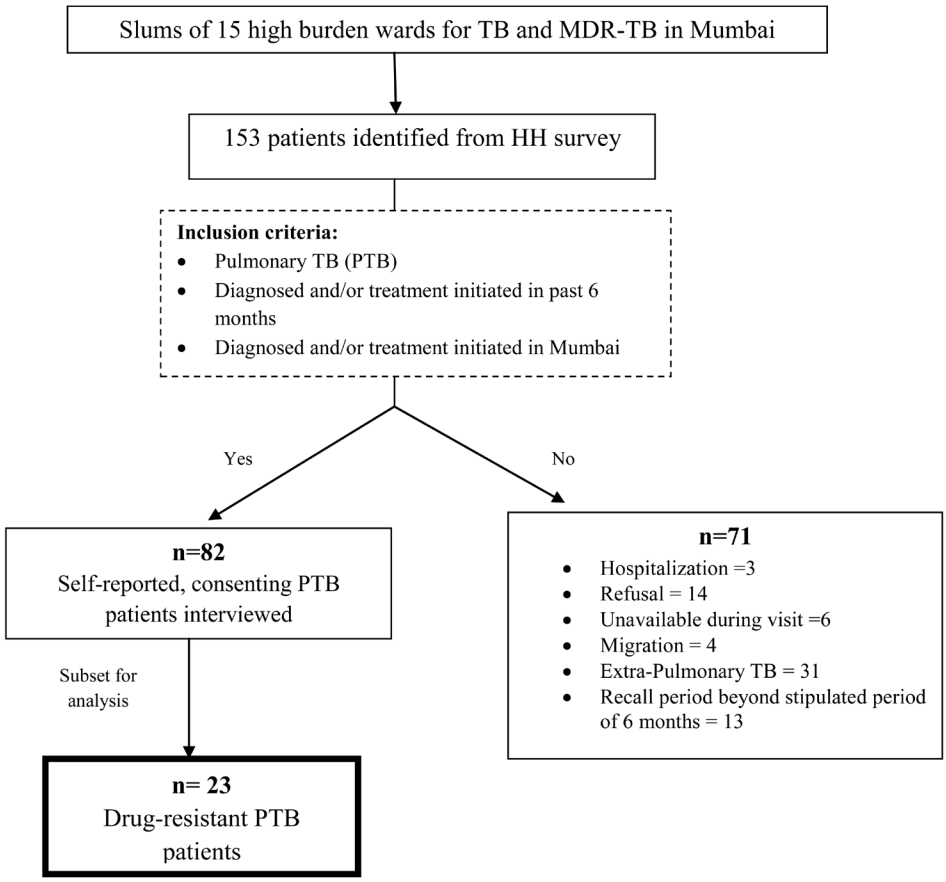

Figure 1. Patients selected for subset analysis of DR-TB pathway to care. The figure depicts the selection of patients for inclusion in the study and subset analysis presented.

Data collection

Patients were interviewed using a semi structured interview guide (Supplementary File 1) in their preferred local language (Hindi or Marathi) at a time and date convenient to them. Patient anonymity regarding name and address was maintained through a unique identification number. Interviews were audio recorded.

At the end of the interview, quantitative data were filled on physical formats by the researchers (Supplementary File 2). For the purpose of quality check, three levels of verification by listening to recorded interviews were conducted. First, each researcher team cross-checked the quantitative data forms of another research team. Further 25% interviews were cross-checked by senior researchers for errors, and finally a set of random 10% interviews were checked by consultants to the study.

Statistical analysis

The data was entered in CSPro v5, and exported into SPSS v19 (SPSS, Inc., Chicago, IL, USA) for analysis. Although other data was collected, it was not assessed herein as the purpose of this publication was to focus solely on the durations and testing practices followed. The total time taken from onset of TB symptoms to first care-seeking and until initiation of DR-TB treatment was estimated by dates collected for various events and presented as medians, means and interquartile range (in days). Median differences in pathways for new and re-treatment patients were compared using Mann Whitney U-test with significance established at P values ≤ 0.05.

Ethical statement

Ethical approval was obtained from the Institutional Ethics Committee (IEC) of the Foundation for Medical Research (vide IEC no. FMR/IEC/TB/01/2013).

Verbal informed consent for answering the survey was obtained from individuals who underwent the HH survey in stage 1 sampling. Following the verbal consent, field researchers then contacted the patients over the phone to schedule in-depth interviews. On meeting the patients, written informed consent was first obtained for the in depth interviews after which 82 patients who consented were included in the semi-structured interview. In the case of minors, written consent was obtained from their care-givers (parents/guardians). The consent obtained included participation in the interview, digital audio recording and note keeping, reviewing of patient's TB treatment-related documents

and permission to publish anonymised data in any report, journal, etc.

Results

The 23 DR-TB patients included 14 males and 9 females. Mean age group of the patients was 29 years with a majority of the patients (n=17) aged between 16–34 years, 4 patients between 35–54 years and 1 patient aged 14 years and 65 years each. Only 5 patients admitted to having addictions like tobacco, alcohol, recreational drugs and three reported having chronic co-morbid conditions with two being HIV positive and one asthmatic.

Thirteen of the 23 patients interviewed (56%) were retreatment patients, of whom only four (31%) were advised DST upon their initial presentation with TB symptoms. Nine (69%) of the retreatment patients were initiated on first line treatment before being diagnosed and treated as DR-TB. Of the 10 new patients with no past history of TB, only two were advised DST upon initial presentation with TB symptoms and the remaining eight (80%) were treated with first line anti TB medicines. Preference for Mumbai's strong and robust public sector for TB treatment was seen among the interviewed patients, with a significant shift from first seeking care from the private sector (n=19, 83%) for initial symptoms, to approaching the public sector (n=16, 70%) for diagnosis and treatment of DR-TB.

Only four patients (17%) were diagnosed with DR-TB using molecular tests like GeneXpert and LPA, facilities for which were available in both, the public and private sectors. Sixteen patients (70%) were diagnosed using only culture based / phenotypic tests. A combination of molecular and phenotypic tests were used for diagnosis in only two patients (9%) and the remaining three (13%) were presumptively diagnosed using only chest x-ray and sputum examination for acid fast bacilli. Due to lack of phenotypic testing facilities in the public sector, where a majority of the patients were diagnosed, it is most likely that the samples were sent to private labs for testing.

Figure 2 depicts the median (mean) durations and interquartile range in days for time taken from onset of symptom to first point of care, first point of care to DR-TB diagnosis and from DR-TB diagnosis to initiation of DR-TB treatment, for the entire cohort and for new and retreatment patients.

After the patients first sought care, the average time taken to diagnose and initiate DR-TB treatment was 87 days (IQR 17-202) for the entire cohort (data not shown in figure). Further analysis was undertaken to see the median difference in pathways of new and retreatment DR-TB patients (Figure 2). The time taken from first care seeking to DR-TB diagnosis (p value = 0.041) and the total pathway duration (p value = 0.016) were significantly shorter for retreatment patients. However the duration from onset of symptoms to first care seeking was almost similar for the two groups, indicating that patients with a past episode of TB were not seeking care earlier compared to new patients. Patients were further split into those diagnosed with DR-TB at presentation and those diagnosed after a course of first line treatment (Figure 3).

While no significant differences in pathway durations were observed after splitting the patients, (due to the small number

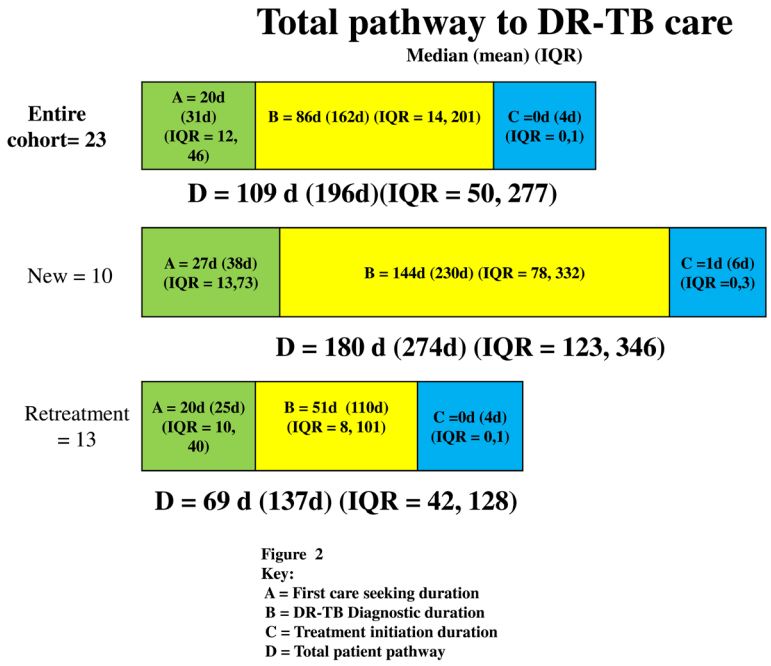

Figure 2. Total pathway to DR-TB care of the entire cohort. The figure depicts the pathway to DR-TB care for patients from the entire cohort, along with new patients and retreatment patients.

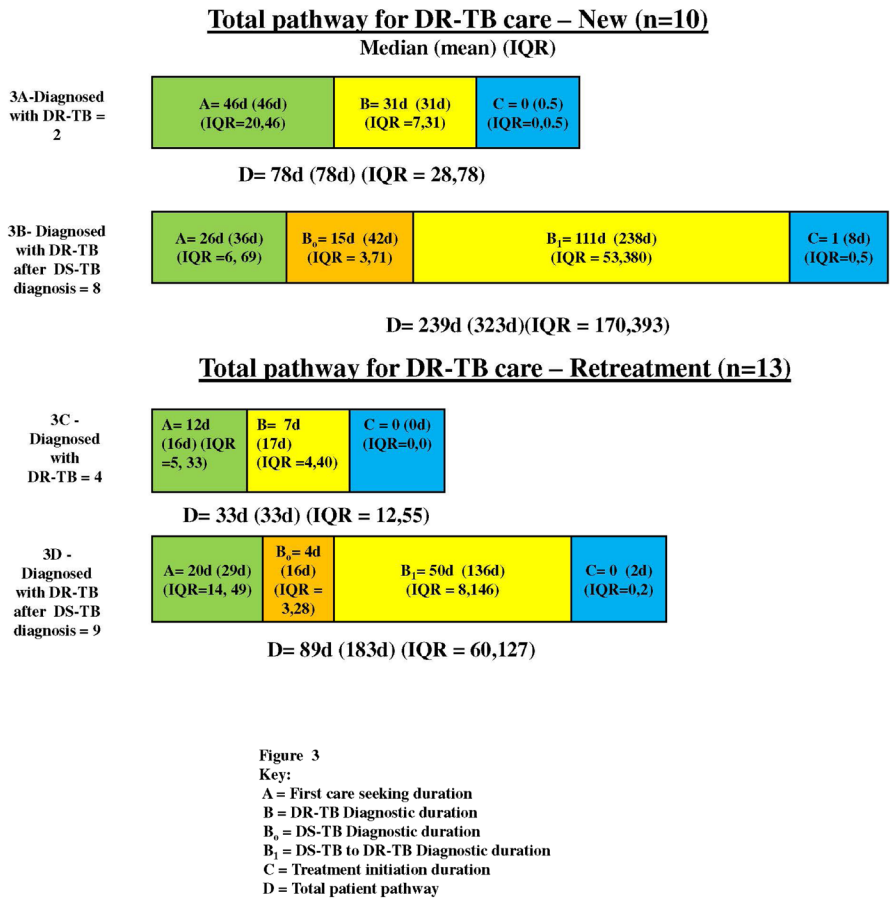

Figure 3. Total pathway to DR-TB care of new and retreatment patients. The figure depicts the pathway to DR-TB care for new and retreatment patients for patients diagnosed with DR-TB at presentation (A and C) and patients diagnosed after a course of first line treatment (B and D).

of patients in each group), new patients initially diagnosed and treated as drug susceptible patients showed the longest median pathway of eight months (Figure 3B). The study was not able to assess if the patients progressed from drug sensitive tuberculosis (DS-TB) to DR-TB or were incorrectly diagnosed with DS-TB. The shortest median pathway of one month was seen in retreatment patients who were diagnosed with DR-TB initially (Figure 3C).

Discussion

With respect to the entire cohort the median pathways after seeking first access to care was 86 days (IQR 14-202) which is relatively shorter than that reported in a multistate study (128 days, IQR 103-173)[6] but nevertheless long. Even though the study findings show certain significant differences in pathway durations of new and re-treatment DR-TB patients, we caution that in light of the small sample size, the observations currently be interpreted as indicative. The study throws light on patient related delay, seen specifically among retreatment patients who showed a similar time frame in accessing first care (20 days vs 27 days) on developing symptoms that were probably similar to their first disease episode. This could be due to patient denial of the disease and for lack of information/ counseling received from their TB care providers in the past[5].

Since it is more likely for a retreatment patient to be resistant at their second episode, DST testing is mandated at the time of diagnosis. However, the failure in undertaking this in over 70% of patients in the present study, exceeded the proportion (45%) reported in another study conducted in Andhra Pradesh, India[7]. This calls for a more stringent implementation of the diagnostic algorithms for standards of care in DR-TB at field level. This is particularly important for areas with high prevalence of DR-TB such as Mumbai.

The unacceptably long pathways for diagnosis and treatment of DR-TB in Mumbai advocates for stronger implementation of early screening of patients for DR-TB through use of rapid gene-based technologies. Patients with the least duration were the ones laboratory diagnosed with DR-TB prior to initiation of therapy. This advocates for the use of DR testing at the time of presentation of the patients to reduce their total pathway. This seems to be well on track with the number of GeneXpert machines available in the city increasing from eight when the study was initiated

in 2015, to 19 so far in 2017. There is also a new policy dated 1st Jan, 2018 which mandates all new cases to be tested with GeneXpert at time of presentation. Focus needs to be on people residing in vulnerable settings, contacts of DR-TB cases, immune-compromised patients and those living in compromised housing. Contemporary technologies need to be rapidly made available in the public sector and extended to patients seeking care from the private sector as well.

Data availability

Raw data in Excel format of the 23 drug resistant TB cases identified in Mumbai and the semi structured interview guide that was used to collect the data from the identified DR-TB patients are available on OSF: http://doi.org/10.17605/OSF.IO/8CTBV[8]

Competing interests

No competing interests were disclosed.

Grant information

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The funders had no role in study analysis, decision to publish, or preparation of manuscript.

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Supplementary material

Supplementary File 1: Semi structured interview schedule.

Click here to access the data.

Supplementary File 2: Quantitative data sheet.

Click here to access the data.

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Reference Source

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PubMed Abstract | Publisher Full Text | Free Full Text

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PubMed Abstract | Publisher Full Text | Free Full Text

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Data Source

Open Peer Review

Current Peer Review Status: ✔ ✔

Version 2

Reviewer Report 29 May 2018

https://doi.org/10.21956/gatesopenres.13891.r26435

✔ **Amrita Daftary**
McGill International TB Centre, McGill University, Montreal, QC, Canada

The authors have adequately responded to the reviewer comments.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Tuberculosis, health care seeking, mixed methods research

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.

Reviewer Report 11 May 2018

https://doi.org/10.21956/gatesopenres.13891.r26434

✔ **Ramnath Subbaraman**
Department of Public Health and Community Medicine, Tufts University School of Medicine, Boston, MA, USA

The authors have done an excellent job addressing all the concerns raised in my initial review.

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.

Version 1

Reviewer Report 26 March 2018

https://doi.org/10.21956/gatesopenres.13845.r26256

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Ramnath Subbaraman

Department of Public Health and Community Medicine, Tufts University School of Medicine, Boston, MA, USA

This is an important study that is a unique contribution for a few reasons. First, while numerous studies have evaluated delays in care-seeking for TB patients, fewer studies have looked at this issue in drug-resistant TB patients. Second, very few studies have used a population-based sampling approach to identify patients with TB and then to evaluate delays, since it is much easier to identify TB patients for these studies after they have been diagnosed at health facilities. While costly and time-intensive, using a population-based sampling approach may reduce biases that occur when recruiting patients who get diagnosed at particular health facilities. Third, the scale of this study is also unique—covering 15 city wards in Mumbai. While the sample size is relatively small for this study, this is understandable given the considerable challenges of identifying drug-resistant TB patients using a population-based approach.

The key finding of this paper - the considerable difference in delay between drug-resistant TB patients who were “new” versus “retreatment” cases is an important one. The figures, while a bit challenging to interpret initially, really bring home the authors’ points regarding differences in delays between groups of patients.

However, the following aspects of the manuscript could be improved:

1. **Details of the population-based sampling approach:** Very few details (<1 paragraph) are provided regarding the population-based sampling approach used to identify drug-resistant TB patients on treatment in the community. One of the criteria for evaluation for this journal is that the manuscript provides “sufficient details to allow replication.” For others to replicate this work, it would be helpful for the authors to provide more details on: (a) how randomized sampling of clusters within census blocks was conducted; (b) how many clusters the survey was conducted in and rough estimate of cluster sizes in number of households; and (c) how screening of household members was conducted to identify patients on TB therapy - including examples of the questions asked to identify patients and whether each individual in the household was asked questions directly or whether only the head of household was asked for all members.

2. **Reasons for low response rate and comparison of demographics:** If the authors have a sense of why the consent rate for the study was relatively low for identified TB patients (82 out of 153) it would be helpful to provide some information on this, even if not collected formally through a survey. Also, if any demographic details were collected on patients who

did not consent, a comparison of these details for patients who consented versus those who didn't would be helpful to see if those who participated were similar to the larger population of patients identified.

3. **Inclusion of a clear case definition:** It would be helpful to include a brief (2 to 3 sentence) case definition in the methods section clarifying exactly how you classified patients as being DR-TB patients. From the results section, it appears that 20 out of 23 patients had DR-TB based on laboratory confirmation (either culture, CB-NAAT, or LPA) but the remaining 3 were diagnosed with DR TB empirically. If so, how did the interviewers and researchers determine and confirm that these patients were being treated as DR-TB cases? Based on self-report? Or based on their medication regimen? It would be helpful to clarify this case definition and how you decided 23 out of 82 patients were DR-TB patients.

   Also, for patients with DR-TB based on culture results, did you only include MDR TB patients in this sample of 23 patients (i.e., resistant to INH and rifampicin at minimum) or did you also include patients with INH monoresistance? I am presuming that you are really only referring to MDR TB patients based on culture and rifampin-resistant TB patients based on CB-NAAT, but please clarify.

4. **Test for statistical significance:** The difference between the median and mean in most of the samples and sub-samples suggest that the values for delays might not follow a normal distribution. This is a relatively minor point, but I wonder whether it might be more appropriate to use a Wilcoxon-Mann-Whitney test rather than a t test as the test of significance for the various analyses.

5. **The first paragraph of the results section is confusing:** When you say that only 4 of 13 retreatment patients underwent drug susceptibility testing and only 2 of 10 new patients underwent drug susceptibility testing. But clearly 20 of 23 patients ultimately underwent drug susceptibility testing later in their clinical course to get diagnosed with DR TB based on what you say later. As such, I think what you mean to say in that first paragraph is that only 4 of 13 retreatment and 2 of 10 new patients underwent drug susceptibility testing upon their initial presentation with TB symptoms.

6. **The discussion section does not extrapolate on the key finding of the considerable difference in delays between new and retreatment patients:** This is the main finding highlighted in your abstract and in Figure 2; however, you do not provide more insight into this finding in the Discussion section. I think that this finding really highlights the terrible delays faced by DR TB patients without a prior TB history, and it may suggest that even new TB patients should be screened upfront with tests that include drug susceptibility testing, at least in the Mumbai setting.

7. Inclusion of a summary of the demographic details of the participants included in the study - that is, breakdown by age, gender, socioeconomic status in a small table or paragraph - would be helpful.

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?
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?
Partly

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

Are the conclusions drawn adequately supported by the results?
Yes

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.

Author Response 26 Apr 2018

Nerges Mistry, The Foundation for Medical Research, Mumbai, India

1. Response: Thank you for your comment. We have included further details on the HH cluster sampling and questions used to screen the patients. This has been added in the Methods section on page 3 in track change mode. It reads as, ***'Fifteen wards falling under MCGM consisting of both slum and non-slum areas were identified. Census Enumeration Blocks (CEB) maps were used as the reference point for the primary sampling unit (PSU) in the urban area. The CEB map consisted of 120-180 HHs in each block and helped demarcate the slum areas and the non-slum areas. The CEB in these selected 15 wards acted as the sampling frame for the survey. Assuming an average cluster size of 160 per CEB, 100 Urban Frame Survey (UFS) blocks were selected for the primary objective of conducting a survey of over 10,000 HHs. Going by the assumption that the CEB blocks have a clear demarcation of slum and non-slum areas, sampling frames consisting of the slum based CEBs were created. The blocks from each ward were selected proportionate to the total number of HHs in the slums of the 15 wards. The required number of PSUs (100 CEBs) was selected randomly from the list of all slum based CEBs for each of the wards. In a selected CEB, all HHs in the selected block unit were enumerated.***
TB cases were identified by means of two questions. One that recorded details of all the cases of cough in the family and narrowed down to asking the family member if the doctor they had consulted had told them that they had TB on the basis of tests conducted. The other question that captured the TB cases pertained to those that had occurred in the past six months who due to some treatment being taken and did not show any signs of coughing any more. Around 21,016 HHs were listed, of which 14,250 (68%) agreed for an interview. From these participating HHs, a total of 153 TB cases were drawn.'

2. Response: We have modified Figure 1. to give the number of cases excluded for various reasons. Only 14 did not consent to participate (refusals) whereas others either did not meet the inclusion criteria or were unable to be interviewed. The inclusion criteria for the second stage was more stringent as opposed to a more broader criteria used in selection at stage 1. Unfortunately demographic details for patients that did not consent or not included in the study were not collected as it did not fall in the purview of the study objective.

3. Response: Thank you for your comment. We have clarified this in the methods section, page 4 which reads as, ***'Patients were identified as DR-TB cases if they had completed their anti-DR-TB treatment in Mumbai within the past six months of the interview. Besides patient information, diagnosis and treatment records of patients were obtained and seen by the researchers. Photographs of these were taken and shown to our clinical consultant on the study (YD), on whose opinion, the cases were classified as DR-TB. Two cases were identified as XDR cases based on their LPA/DST results. Monoresistance to INH could not be identified as LPA was not available for all cases at the time of the study.'***

4 . Response: Thank you for bringing this to our notice. We had analyzed the median differences based on Mann-Whitney U test as mentioned in the results section. However, due to over-sight this was mis-represented in the methods section as t-test. Change in statistical test is reflected in the methods section under statistical analysis sub-section.

5. Response: Thank you for your comment. As you rightly mentioned, we do mean that the patients underwent DST upon their initial presentation with TB symptoms. We have modified the text in the results section, page 7 (paragraph 2) which now reads as, ***'Thirteen of the 23 patients interviewed (56%) were retreatment patients, of whom only four (31%) were advised drug sensitivity testing (DST) upon their initial presentation with TB symptoms.'*** And ***'Of the 10 new patients with no past history of TB, only two were advised DST upon initial presentation with TB symptoms.'***

6. Response: Thank you. Based on your suggestion, we have included additional details in the discussion which now reads as,
'With respect to the entire cohort the median pathways after seeking first access to care was 86 days (IQR 14-202) which is relatively shorter than that reported in a multistate study (128 days, IQR 103-173) [6] but nevertheless long. Even though the study findings show certain significant differences in pathway durations of new and re-treatment DR-TB patients, we caution that in light of the small sample size, the observations currently be interpreted as indicative. The study throws light on patient related delay, seen specifically among retreatment patients who showed a similar time frame in accessing first care (20 days vs 27 days) on developing symptoms that were probably similar to their first disease episode. This could be due to patient denial of the disease and for lack of information/counseling received from their TB care providers in the past [5] .
Since it is more likely for a retreatment patient to be resistant at their second episode, DST testing is mandated at the time of diagnosis. However, the failure in undertaking this in over 70% of patients in the present study, exceeded the proportion (45%) reported in another study conducted in Andhra Pradesh, India [7] . This calls for a more stringent

implementation of the diagnostic algorithms for standards of care in DR-TB at field level. This is particularly important for areas with high prevalence of DR-TB such as Mumbai. The unacceptably long pathways for diagnosis and treatment of DR-TB in Mumbai advocates for stronger implementation of early screening of patients for DR-TB through use of rapid gene-based technologies. Patients with the least duration were the ones laboratory diagnosed with DR-TB prior to initiation of therapy. This advocates for the use of DR testing at the time of presentation of the patients to reduce their total pathway. This seems to be well on track with the number of GeneXpert machines available in the city increasing from eight when the study was initiated in 2015, to 19 so far in 2017. There is also a new policy dated 1 st Jan, 2018 which mandates all new cases to be tested with GeneXpert at time of presentation. Focus needs to be on people residing in vulnerable settings, contacts of DR-TB cases, immune-compromised patients and those living in compromised housing. Contemporary technologies need to be rapidly made available in the public sector and extended to patients seeking care from the private sector as well.'
The hyperlink to the diagnostic algorithms in standards of TB care has been inserted and not been mentioned under references as per journal norms.

7. Response: Thank you for your suggestion. We have added a paragraph on demographic profile of the patients as paragraph 1. It reads as, ***'The 23 DR-TB patients included 14 males and 9 females. Mean age group of the patients was 29 years with a majority of the patients (n=17) aged between 16-34 years, 4 patients between 35-54 years and 1 patient aged 14 years and 65 years each. Only 5 patients admitted to having addictions like tobacco, alcohol, recreational drugs and three reported having chronic co-morbid conditions with two being HIV and one asthmatic.'***

Thank you once again for your valuable feedback. We hope to have addressed all your concerns.

Sincerely,
Nerges Mistry and Team

Competing Interests: No competing interests were disclosed.

Reviewer Report 02 March 2018

https://doi.org/10.21956/gatesopenres.13845.r26258

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Amrita Daftary
McGill International TB Centre, McGill University, Montreal, QC, Canada

This is a well-written, timely and relevant article that suggests there is a significant the difference in TB diagnostic delay between primary DRTB cases and retreatment cases. This is a novel findings and the TB scientific community in India would benefit from this knowledge, as well as a a fuller understanding of the reasons underlying these differential delays. I would request a few points of clarification from the authors.

1. It looks like interviews were conducted with a qualitative stance but analyzed quantitatively (open ended responses appear to have been quantified). Some transparency around this would be appreciated because the methods section suggests the interviews were much richer than the data presented.

2. Far more qualitative and categorical data appear to have been collected (as suggested by both supplemental files) but only a few aspects appear to be presented in this article. Similarly, there is no qualitative (or for that matter, objective) data around reasons for delay, or triangulation b/w the quant and qual findings - one would expect this in a typical mixed methods analysis. Perhaps these will be published later. If so, the authors may want to reconsider how to describe the methods and findings so it is clear at the outset what this paper specifically seeks to address. For example, the may want to highlight that although other data were collected, these data will not be assessed herein.

3. This foundational paper[1] should be cited and compared against when discussing the current study findings.

4. Were there any significant associations or trends in the data with regards to patients' sociodemographic (especially, gender and income) or other characteristics collected as part of the standardized survey? While time delay is the primary focus of this paper, it appears, it would be helpful to comment if other factors played a role.

5. The abstract suggests a 180 day delay in DRTB diagnosis (1st episode) whereas the results indicate a median 87 day delay (data not shown). Later in the discussion, the number 86 appears. I would advise maintaining some consistency in the ways in which these findings are reported.

6. With a sample size of 23, the authors may want to acknowledge and address the implications of conveying statistically significant results from their small sample.

Thank you.

References

1. Sreeramareddy CT, Qin ZZ, Satyanarayana S, Subbaraman R, et al.: Delays in diagnosis and treatment of pulmonary tuberculosis in India: a systematic review.*Int J Tuberc Lung Dis*. 2014; **18** (3): 255-266 PubMed Abstract | Publisher Full Text

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?

Yes

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

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?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Tuberculosis, health care seeking, mixed methods research

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 19 Mar 2018

Nerges Mistry, The Foundation for Medical Research, Mumbai, India

Referee Report 02 Mar 2018
Amrita Daftary, McGill International TB Centre, McGill University, Montreal, QC, Canada
Approved with Reservations

This is a well-written, timely and relevant article that suggests there is a significant the difference in TB diagnostic delay between primary DRTB cases and retreatment cases. This is a novel findings and the TB scientific community in India would benefit from this knowledge, as well as a a fuller understanding of the reasons underlying these differential delays. I would request a few points of clarification from the authors.

- It looks like interviews were conducted with a qualitative stance but analyzed quantitatively (open ended responses appear to have been quantified). Some transparency around this would be appreciated because the methods section suggests the interviews were much richer than the data presented.

Response: Thank you for your comment. As mentioned in the methods section and rightly pointed out, all 23 in-depth interviews were conducted qualitatively but were however, analyzed in a more quantitative manner. This was keeping in mind the funders requirement for quantifying the care seeking pathway of TB patients pre and post intervention of an interface agency. However, an in depth thematic qualitative analysis is being undertaken which will be sent on for publication shortly.

- Far more qualitative and categorical data appear to have been collected (as suggested by both supplemental files) but only a few aspects appear to be presented in this article. Similarly, there is no qualitative (or for that matter, objective) data around reasons for delay, or triangulation b/w the quant and qual findings - one

would expect this in a typical mixed methods analysis. Perhaps these will be published later. If so, the authors may want to reconsider how to describe the methods and findings so it is clear at the outset what this paper specifically seeks to address. For example, they may want to highlight that although other data were collected, these data will not be assessed herein.

Response: As suggested, we will add the disclaimer to our Methods section which will read as, ***"Although other data was collected, it will not be assessed herein as the purpose of this publication was to focus solely on the durations and testing practices followed."*** As you have rightly mentioned, we are currently in the process of writing a qualitative paper that highlights reasons for delays: socio demographic reasons, health seeking behavior, role of health systems, etc for DR-TB patient pathways.

- This foundational paper[1] should be cited and compared against when discussing the current study findings.

Response: Thank you for your suggestion. The foundational paper has been cited in our previous publication; (Mistry N, Rangan S, Dholakia Y, et al.: Durations and delays in care seeking, diagnosis and treatment initiation in uncomplicated Pulmonary Tuberculosis patients in Mumbai, India. PLoS One. 2016; 11(3): e0152287) wherein we have compared the pathway delays of DS-TB patients. Since pathways for DR-TB patients are much longer, our paper is focused on highlighting the increased pathways they have in terms of being diagnosed with the correct type of TB and being initiated on the appropriate treatment.

- Were there any significant associations or trends in the data with regards to patients' sociodemographic (especially, gender and income) or other characteristics collected as part of the standardized survey? While time delay is the primary focus of this paper, it appears, it would be helpful to comment if other factors played a role.

Response: There was no difference noted based on socio demographic factors. However, keeping the sample size in mind, we kept the focus only on durations and resisted from attempting to highlight the lack of associations in this paper.

- The abstract suggests a 180 day delay in DRTB diagnosis (1st episode) whereas the results indicate a median 87 day delay (data not shown). Later in the discussion, the . I would advise maintaining some consistency in the ways in which these findings are reported.

Response: The figure mentioned in the abstract (median 180 days) is the total pathway duration for **only new patients (1st episode)** whereas median of 87 days mentioned in the results is from first point of care to treatment initiation for **the entire cohort**. Median of 86 days is from first point of care to diagnosis for the entire cohort (this does not come up in the discussion but is reflected in Figure 2).

- With a sample size of 23, the authors may want to acknowledge and address the implications of conveying statistically significant results from their small sample.

Response: Thank you for pointing this out. We will reflect this in our discussion section as, ***"Even though the study findings show certain significant differences in pathway durations of new and re-treatment DR-TB patients, we caution that in light of the small sample size, the observations currently be interpreted as indicative."***

This and other clarifications will be made in the manuscript at the appropriate locations once the comments from additional referees have been received as recommended by the journal.

Thank you once again for your valuable feedback. We hope to have addressed all your concerns.

Sincerely,
Nerges Mistry

Competing Interests: No competing interests were disclosed.

Author Response 26 Apr 2018

Nerges Mistry, The Foundation for Medical Research, Mumbai, India

1. Response: Thank you for your comment. As mentioned in the methods section and rightly pointed out, all 23 in-depth interviews were conducted qualitatively but were however, analyzed in a more quantitative manner. This was keeping in mind the funders requirement for quantifying the care seeking pathway of TB patients pre and post intervention of an interface agency. However, an in depth thematic qualitative analysis is being undertaken which will be sent on for publication shortly.

2. Response: As suggested, we have added the disclaimer to our Statistical analysis section, page 5 which read as, ***"Although other data was collected, it will not be assessed herein as the purpose of this publication was to focus solely on the durations and testing practices followed."*** As you have rightly mentioned, we are currently in the process of writing a qualitative paper that highlights reasons for delays: socio demographic reasons, health seeking behavior, role of health systems, etc for DR-TB patient pathways.

3. Response: Thank you for your suggestion. The foundational paper has been cited in our previous publication; (Mistry N, Rangan S, Dholakia Y, et al.: Durations and delays in care seeking, diagnosis and treatment initiation in uncomplicated Pulmonary Tuberculosis patients in Mumbai, India. PLoS One. 2016; 11(3): e0152287) wherein we have compared the pathway delays of DS-TB patients. Since pathways for DR-TB patients are much longer, our paper is focused on highlighting the increased pathways they have in terms of being diagnosed with the correct type of TB and being initiated on the appropriate treatment.

4. Response: There was no difference noted based on socio-demographic factors. However, keeping the sample size in mind, we kept the focus only on durations and resisted from attempting to highlight the lack of associations in this paper.

5. Response: The figure mentioned in the abstract (median 180 days) is the total pathway duration for **only new patients (1st episode)** whereas median of 87 days mentioned in the results is from first point of care to treatment initiation for **the entire cohort**. Median of 86 days is from first point of care to diagnosis for the entire cohort (this does not come up in the discussion but is reflected in Figure 2).

6. Response: Thank you for pointing this out. We have reflected this in our discussion section, paragraph1 as, ***"Even though the study findings show certain significant***

differences in pathway durations of new and re-treatment DR-TB patients, we caution that in light of the small sample size, the observations currently be interpreted as indicative."

Thank you once again for your valuable feedback. We hope to have addressed all your concerns.

Sincerely,
Nerges Mistry and team

Competing Interests: No competing interests were disclosed.