RESEARCH ARTICLE

Patient treatment pathways of multidrug-resistant tuberculosis cases in coastal South India: Road to a drug resistant tuberculosis center [version 1; peer review: 2 approved with reservations]

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Abstract

Background: Delays in initiating multidrug-resistant tuberculosis (MDR TB) treatment adds risk to individual patients and the community due to disease progression, and on-going transmission. The Government of India offers free TB diagnosis and treatment, however many presumptive MDR TB patients wander within the Indian healthcare system and delay accessing the programme. To better improve access to care, it is imperative to understand the treatment pathways taken by MDR TB patients. We aimed to describe the diagnostic and treatment pathway taken by presumptive MDR TB patients registered in the Programmatic Management Drug-resistant TB Program (PMDT).

Methods: We conducted a cross-sectional study of all patients registered during August 2016 – April 2017 at one PMDT center of a district in Karnataka, India. A semi-standardized questionnaire collected the number, type (private vs public sector), and dates of healthcare facilities (HCFs) visits prior to the initiation of MDR TB treatment. Delays were the number of days, expressed in medians and interquartile range (IQR), from the date of onset of illness until the date of initiation of MDR TB treatment.

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Results: We found that patients preferred private HCFs; however, due to lack of treatment and unaffordability they shifted to public HCFs. Median delay to register under the program was more in private HCFs (180days) in comparison with public HCFs (120 days). We also found that the diagnosis of MDR among presumptive MDR cases (detection rates) were much higher (80%) in public HCFs.

Conclusion: Awareness regarding the availability of free standard diagnosis and appropriate treatment under the TB program should be increased in the general population and private practitioners. The government should involve private HCFs to provide standard diagnostics and treatment to the patients seeking a private facility.

Keywords

Diagnostic delay, Treatment delay, Patient delay, Health care system delay Programmatic management of Drug resistant TB, detection rate, Private health care facility, Public health care facility.

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Introduction

Multidrug-resistant tuberculosis (MDR TB), is defined as tuberculosis (TB) bacilli resistant to at least two first-line drugs — rifampicin and isoniazid. According to the Global TB Report 2017 published by the World Health Organization (WHO), India ranks first globally in the burden of TB and MDR TB with an incidence rate of 27% and 24% of global burden^{1,2}. Nearly 3% of new TB cases and 12% of previously treated patients in India are MDR TB^{1,2}.

To reduce transmission of MDR TB, the Government of India developed and implemented a national policy for the programmatic management of drug-resistant TB (PMDT) in 2007³. The strategies and objectives of PMDT complement the National Strategic Plan for TB Elimination (2017–2025), and include treatment of MDR TB, enhancing laboratory systems for faster diagnosis, and offering social protection and supportive systems to ensure uninterrupted treatment with shorter, less toxic regimens^{3–5}.

Delays in MDR diagnosis and appropriate treatment initiation impacts individual patients, through advance disease progression, additional costs, and poor quality of life; but also in the community through increased risk of ongoing transmission to other individuals⁶. The time taken to seek care, type of health care facility being sought and reasons for shifting from one health care facility to other are important factors for understanding delays in diagnosis, PMDT treatment initiation, poor outcomes. Describing health seeking behaviors and pathways taken by persons presumed to be MDR TB case is a vital step in developing and implementing interventions that bridge the gap between timely diagnosis and treatment, and policies that improve the overall health system.

In India, approximately 20% of the persons needing MDR TB treatment actually receive it, and among those who do receive treatment, less than half (48%) who start treatment finish successfully^{1,2}. These poor outcomes are largely due to persons who are lost to follow-up and premature death. In 2017, the proportion of deaths during MDR TB treatment in India was higher than the global average (21% vs. 14%)¹.

Therefore, in this study we aimed to determine the health-seeking pathway of presumptive MDR TB patients prior to treatment at the PMDT center. We also assessed the median time taken, and reasons for shifting from one health care facility (HCF) to another.

Methods

Study setting

We conducted a cross-sectional study of all patients registered during August 2016 – April 2017 at one PMDT center of a district in Karnataka, India. The PMDT center is on the campus of a 150-year-old district hospital, which has recently been awarded as one of the best government run hospitals in India, by Kayakalp⁶. This PMDT center caters to three nearby districts. It has ten inpatient beds, facilities for diagnosis, pre-treatment evaluation and treatment of MDR TB, monitoring complications associated with second-line antituberculosis treatment. After

inpatient care to initiate treatment (approximately 2 weeks), the patient is released to outpatient care for continuation of care at Directly Observed Treatment (DOT-Plus) centers throughout the community.

After obtaining approval from the Institutional Ethics Committee (IEC) of Medical College Mangalore (IEC KMC MLR 11-16/328) and permission from DR-TB center, all patients registered under PMDT program were asked to enroll in the study. A line list was taken from DR-TB center, every day, and patients present in DR-TB center were approached by the Principal investigator (PI) at the DR-TB center. The purpose of the study was explained to the patients in their vernacular language and written informed consent was obtained from patients. PI collected data using a questionnaire by interviewing the patients.

Data collection

Face to face interviews were guided by a semi-structured questionnaire, which had been developed based on a literature review and the content was validated by experts in epidemiology (CDC Atlanta), a PMDT medical officer, and a layperson (local ground staff member working in the tertiary care hospital). The interview enquired about the various healthcare facilities (HCFs) visited by the patient from the time they experienced TB symptoms, designated as a presumptive MDR patient, until they registered for treatment at the PMDT center. We noted the time interval and reason for shifting from one facility to another. All information was penned down on the questionnaire at the time of the interview without any audio or video recording.

Data analysis

Data collected was entered and analyzed using Statistical Package for Social Science (SPSS) version 11.5. Kolmogorov-Smirnov test was done to find the normality of data. Results were expressed in median and inter-quartile range (IQR). Chi-square test was performed to find out the association between type of HCF visited by patients and reasons for shifting from one HCF to the other. The patient treatment pathway has been used to express health seeking behavior of the patients and was created using Adobe Illustrator trial version. The pathway was created using vector images with the visits being represented with different colors and different kinds of lines used for the diagnostic status of the patient. The meaning of both the lines as well the colors have been explained in the legends accompanying the pathways. Moreover, the number of patients shifting between HCF has been represented using the numbers accompanying the respective lines.

Operational definitions. *Multidrug resistant TB (MDR-TB):* Patients with sputum-smear positive pulmonary TB, and at least one *M. tuberculosis* isolate with demonstrated resistance to at least isoniazid and rifampicin.

Pathway: The various type of HCF visited by a presumptive MDR patient before registering for PMDT treatment in a chronological sequence. The various HCF were merged into two broad types: private and public health care sectors. Public

HCFs include Primary Health Centers (PHCs) and Public Referral Hospitals (PRHs), including secondary and tertiary referral centers. Private HCF include secondary and tertiary referral center participating in Revised National Tuberculosis Control Program, non-participating allopathic clinics and practitioners (registered and unregistered) and Ayurveda Yoga Unani Sidda Homeopathy (AYUSH) practitioners⁷

*Time delays in the health care pathways*⁸: The total delay is the time interval from the onset of illness until the initiation of anti MDR-TB drugs. It is the sum of two-time intervals: 1) diagnostic delay (time interval between the onset of symptoms and labelling of the patient as a MDR-TB patient); 2) treatment delay (time interval between MDR-TB diagnosis and initiation of anti MDR-TB drugs).

The total delay is also the sum of patient delay (time interval between onset of symptoms and presentation to first health care provider) and healthcare system delay (time interval between the date of health-seeking behavior at a health care provider and the initiation of anti MDR-TB treatment), since it can be attributed to these types of delay,

Reasons for shifting from one HCF to another: treatment not available, the appropriate treatment for the symptoms was unavailable in that HCF; treatment not affordable, cost of treatment was beyond the paying capacity of patient and its family; referred, patient was asked to visit another HCF for review/consultation or appropriate treatment; not satisfied, symptoms did not alleviate or the patient perceived that the services being provided were inadequate.

Results

During the study period, a total of 55 patients were initiated on treatment at the PMDT center; however only 40 patients consented to participate in the study. The mean age in our study was 40 years (SD: 13.9). There were 28 (70%) male patients and 12 (30%) female patients. In total, 35 patients were educated at least until primary level, while only 12.5% of patients were illiterate. A total of 65% of the study participants belonged to rural areas while only 14 patients lived in an urban area.

Details of first visit and shift from one HCF to other HCF

Out of 40 patients interviewed, 15 went to a public HCF and 25 went to a private HCF as their first clinic encounter (Figure 1 and Figure 2). In total, 23 (57.5%) were diagnosed with MDR TB during this encounter.

Amongst the 15 patients who went to the public HCF at the first encounter, 12 (80%) were diagnosed with MDR and were transferred directly to the PMDT center., whilst the remaining three patients required additional visits before MDR diagnosis (two went to public HCF and one went to private HCF).

Among the 25 patients who went to the private sector at the first clinical encounter, 11 (44%) were diagnosed with MDR, and

were transferred directly to the PMDT center. The remaining 14 required additional visits before MDR diagnosis (9 went to public HCF and 5 went to private HCF).

Details of second visit and shift from one HCF to other HCF

All 40 patients underwent a second visit: 18 went to DRTB center, 15 opted for public HCF, while 7 went to private HCF. Out of the 17 undiagnosed patients, 14 (82.3%) were diagnosed.

Out of the 15 who went to public HCF for second visit, four were already diagnosed (two from public HCF and two from private HCF) and 11 were undiagnosed. Of the 11 undiagnosed, 10 were diagnosed on this visit and were referred to the DR TB center. One undiagnosed patient went to another public sector. Out of four previously diagnosed patients, two were referred to DR TB center and two again shifted to another public sector HCF. Hence a total of 12 patients out of 15 shifted to DRTB center and three visited other public HCF.

Seven patients went to private HCF for a second visit. Out of these seven, one was previously diagnosed in other private institution and six were undiagnosed (five came from private HCF and one from public HCF). In this visit, of the six patients who were undiagnosed, four were diagnosed. Five patients (one previously diagnosed and four newly diagnosed) visited DR TB center from a private HCF. Two still remained undiagnosed. One went to the DR TB center. The other undiagnosed patient visited another private sector HCF.

Overall, 18 patients (12 from public HCF and six from private HCF) visited DRTB center in their third visit.

Details of third and fourth visit and third shift from one HCF to other HCF

Of the 40 patients, 22 patients underwent a third visit to HCF. Among them, 18 came to DR TB Center, three went to public HCF while one went to the private sector. Out of the three who went to public HCF, one was undiagnosed and two were previously diagnosed (1st visit). The undiagnosed case received a diagnosis and went to the DR TB center. The two previously diagnosed patients also went to DR TB center in their fourth visit.

One undiagnosed patient from the private HCF was diagnosed and referred to DR TB center in the fourth visit.

Time delay in treatment pathway of MDR patients

The median (IQR) patient delay was found to be 25 (10, 60) days. For patients contacting public HCF as their first point of health care contact, the median patient delay was 30 days, while for those contacting private HCF, it was found to be 20 days.

In the first visit among the 23 patients who were diagnosed to have MDR TB, the median delay in reaching the DR TB center after contacting the first HCF was 120 (30, 240) days. Median (IQR) delay in a public health care facility was 105 (60, 382) days with the highest being 1825 days, while in a private health care facility the median delay was 180 (10, 240) days with the highest being 300 days.

Figure 1. Patient diagnostic and treatment pathway.

Among the patients diagnosed in second visit, the median delay in reaching DRTB center was 210 (82,270) days from the day of first HCF contact. In public HCF, this delay was found to be 195 (82,247) days with the highest being 365 days while it was 255 (105, 341) days in private HCF with the highest being 365 days.

One patient who remained in the public sector was diagnosed at his third visit with a delay of 210 days. Similarly, a patient who remained in the private sector was diagnosed after a delay 120 days on his third visit.

Furthermore, median delay among female patients (30 days) was more than male patients (20 days). Also patients aged more than 45 years had more median delay of 30 days as compared to those below 45 years.

The most common reason for shifting from first to second HCF was referral (both public and private) followed by

non-affordability (only seen in private HCFs) and non-satisfaction (seen more in private HCFs). Similarly, the reasons for shifting from 2nd to 3rd HCF were referral (mostly in public), non-satisfaction and non-affordability in private. In the third shift, only reason given was referral to DR TB center (Table 1).

Discussion

MDR TB is an emerging disease in India. The disease is difficult to treat and treatment outcomes are poor, making it a potential public health threat in the future. Our study sheds light on patients' treatment pathway and reasons for shifting between health care providers for diagnosis and treatment for MDR TB.

In our study, 63% of patients went to private health care facilities (HCF) as first point of health care contact, which was slightly more than the average 48% as seen in a systematic review from India^{9,10}. This pattern is also seen in other studies done in India and in other developing countries¹⁰⁻¹⁶. The health seeking behavior of a patient depends on the knowledge about the

Figure 2. Median time delay in treatment pathway of MDR Patients.

Table 1. Reasons for shifting from one HCF to other.

Reasons for shifting	Public, n (%)	Private, n (%)	P value
First to second visit			
Treatment not available	1 (50)	1 (50)	0.31
Treatment not affordable	0 (0)	8 (100)	
Referred	13 (54.2)	11 (45.8)	
Not satisfied	1 (16.7)	5 (83.3)	
Second to third visit			
Not affordable	0 (0)	2 (100)	0.23
Referred	14 (82.4)	3 (17.6)	
Not satisfied	1 (33.5)	2 (66.7)	

disease, severity of symptoms and social support available, especially in a communicable and stigmatized disease like TB¹⁷. Studies conducted in India showed that most people had poor awareness about TB-related symptoms, transmission, and the services offered by the national TB control programs^{18,19}. Moreover, patients in India have reported treatment barriers, such as, long distance between the TB centers and their homes, lack of confidence in the efficacy of government supplied medication, and the lack of privacy during directly observed treatment sessions^{12,18,20}. All these reasons suggest a preference for private HCF as their preferred health provider for TB diagnosis and treatment.

A study done by Arinaminpathy *et al.*²¹ shows that the quality of care meted out to TB patients is sub-optimal²². This negligence in treatment of TB cases later gives rise to DR TB as

the bacterial strains achieve antimicrobial resistance. Further, the private sector poses many hurdles in TB control. Studies show that the sectors' disorganization produces gaps in TB surveillance due to irregular notification of cases and absence of guidelines²².

However, there was a delay on the part of patients to report to their first point of health care contact after appearance of symptoms. The median delay was found to be 20 days which is slightly more than two weeks of the cough criterion issued by RNTCP for TB screening. This was in line with studies done by Dhanvij *et al.* (20 days), Nimbarte *et al.* (19 days) and Ananthkrishnan *et al.* (18.3 days), while at the same time was quite less than shown in studies done by Goel *et al.* (30 days), Kulkarni *et al.* (8 weeks), Selvam *et al.* (28 days) and Shamim *et al.* (>30 days)^{12,22–27}. This shows the diversity in patient delay across India. Also, the median delay was found to be more among female patients as compared to male patients. This has been shown in various studies done in India as well as in some developing countries^{8,14,28}. However study done by Nimbarte *et al.* in Central India shows that the delay is less among females than in males²³. Further, we also found that patients above the age of 45 years postponed seeking health care as compared to younger patients. This is in line with the study done by Charles *et al.*²⁸. The median delay was found to be greater among those who had public HCF as their first point of contact which has also been seen in the study done by Nimbarte *et al.*²³.

In our study, 57.5% of the patients were diagnosed at their first point of contact, while 82.3% were diagnosed at their second point of contact. The results are similar to those seen in the study done by Ananthkrishnan *et al.*²⁶. Among the 55% of patients who made a second visit to a different HCF other than DR TB center, 68% of the patients went to a public HCF. This is also seen in the study done by Charles *et al.*²⁸. Also we find that in all the visits, the yield of diagnosis at public HCF was always more than that at private HCF. This could be due to improper tests done for detection or lack of technologies for doing the same, as seen in a review by Satyanarayana *et al.*²⁹.

The most common reason for shifting between HCF other than referrals was unaffordability followed by dissatisfaction. This is in contrast to the study done by Charles *et al.* where the major reason was found to be dissatisfaction with the available HCF followed by unaffordability²⁸. In public HCF, the most common reason was referral which was in accordance to the PMDT guidelines. This was followed by patient reasons such as dissatisfaction.

Conclusion

The present study found that there was substantial patient delay and total delay in diagnosis and treatment of DR TB patients.

Since the patient delay was more in females and elderly people, they can be prioritized for screening and diagnosis by active and enhanced case finding methods.

The study also projects the importance of a public-private collaboration in treating DR TB cases. As stated by many patients that their reason for shifting from one private HCF to other was non-affordability of the treatment, hence provisions of standard diagnostic services and treatment at low to no costs can reduce the delay in treatment. This can be achieved by incentivizing treatment and providing standard diagnostic modalities to private sector under RNTCP.

Actions should be taken from the government side to improve the quality of services provided in a public HCF, better infrastructure and human resources. Hence stigma and dissatisfaction related to public health services can be tackled and better awareness about government disease control programs can be created.

Data availability

Underlying data

According to the IEC of Medical College Mangalore, we are not permitted to share data with any external agency for protection of data as it contains information which is personal and can be identified. However, if required by anyone, the data can be requested from the corresponding author after full justification of usage of the information. Conditions of access: researchers must use the data for similar research or sufficiently anonymize and give due credit to the authors of this study.

Extended data

Open Science Framework: Patient treatment pathways of multidrug-resistant tuberculosis cases in coastal South India: Road to a drug resistant tuberculosis center: Structured questionnaire, <https://doi.org/10.17605/OSF.IO/TQNUE>³⁰

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

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Douglas Fraser Wares

KNCV Tuberculosis Foundation, The Hague, The Netherlands

Review of "Patient treatment pathways of multidrug-resistant tuberculosis cases in coastal South India: Road to a drug resistant tuberculosis center" paper for F1000Research.

The authors have written about an important topic related to the treatment pathways of drug-resistant TB patients in India. The manuscript reads well, however I have a number of major comments which need to be addressed to ensure the scientific level of the manuscript is raised. My major and minor comments follow, namely:

Major comments:

1. In the flowchart and text, the authors talk about "Presumptive MDR-TB patients". However the patients enrolled in the study are diagnosed and registered MDR-TB cases. These are not the same thing. How is "Presumptive MDR-TB patients" defined and is the same definition being used in both the private and public sector facilities in the study? This needs to be stated by the authors and how the "Presumptive MDR-TB patients" are being identified in the facilities of the 2 sectors and whether similar levels of identification of "Presumptive MDR-TB patients" was being done in the different sector facilities?
2. Time to diagnosis will be determined to a degree by what diagnostic capacity is available in the respective health facility. Hence if a facility has the capacity for rapid molecular diagnosis of TB and rifampicin resistance (RR-TB) e.g. if it has a GeneXpert machine on site, then diagnosis of RR-TB can be done within the day. If not and the patient or sample has to be sent to another facility which then does only culture and phenotypic drug susceptibility testing (DST) and not rapid molecular DST, there will be an inherent time difference between the patients seen at the initial health facility. So did all the health facilities involved in the study have the same access to diagnostic capacity?
3. Even if the diagnostic capacity available to all health facilities involved in the study, where any RR-/MDR-TB cases diagnosed but not registered? If yes, were the proportions the same in the different sectors analysed?

4. Were the 15 DR-TB patients who did not consent to be participate in the study similar to the 40 patients who did participate in the study? Was there any difference in these 15 patients between those who initially visited a public sector facility versus those who visited a private facility initially?

Minor comments:

1. Reference 1 and related text could be updated as the WHO 2019 Global TB Report is available.
2. Introduction, 2nd paragraph. It should be stated that PMDT is part of the Revised National TB Control Programme (now renamed as the National TB Elimination Programme) and is not a separate programme as implied by the current text.
3. Introduction, 2nd paragraph. Reference 5 should be updated as it refers currently to a 2011 WHO document which has been updated since then.
4. Introduction, 3rd paragraph. Reference 6 is from a paper dealing with Argentina. Is there no relevant reference paper from India that could be used instead? Also does the current reference paper talk about DS-TB and/or DR-TB?
5. Methods, Study settings, 1st paragraph. The district name and hospital name where the PMDT centre is located should be given. As should the names of the 3 districts that the centre caters for.
6. Methods, Study settings, 1st paragraph. For non-Indian readers, the meaning of "... by Kayakalp." needs to be explained. Also the reference given is no. 6 which refers to a paper dealing with Argentina and hence seems incorrect.
7. Methods, Study settings, 1st paragraph. The authors mention "... DOTS-Plus centres" and only mention about initial in-patient care. DOTS-Plus is outdated terminology and initial in-patient care practice alone is outdated practice under RNTCP. The text should be amended so the reader understand what is current RNTCP terminology and practice. Especially as in Figure 1, the term of DR-TB Centre is used.
8. Methods, Study settings, 2nd paragraph. 12.5% of patients in the study were illiterate, hence how was "written consent" given?
9. Methods, Data collection, 1st paragraph. Is it correct then that there was no actual field testing of the questionnaire prior to the study being conducted? What training did the PI have on the questionnaire prior to conducting the patient interviews?
10. Methods, Operational definitions, reasons for shifting from one HCF to another, 1st paragraph. As pointed out by the previous reviewer, what is listed here are options or answers expected to be provided by the patients. Hence this part of the methods section needs revising.
11. Results, 1st paragraph. Need to be consistent in the use of both numbers and % in the last sentence.

12. Results, Details of first visit and shift from one HCF to other HCF, 2nd paragraph. Although 12 of the 15 who initially visited a public HCF were diagnosed with MDR, only 10 were immediately referred to the DR-TB centre. Why did the 2 other patients have to attend a HCF for a 2nd time before referral to the DR-TB Centre?
13. Discussion. As stated by the previous reviewer, the authors spend a lot of the discussion section comparing with other studies. Many of the times this is just in relation to confirming previous observations. Such text could be reduced (e.g. 2nd and 4th paragraphs).
14. Discussion, 2nd paragraph. Should ease of access to service be more prominent amongst important issues surrounding health seeking behavior of patients? Is this not a major reason why patients initially seek care in the private sector rather than the public sector?
15. Discussion, 3rd paragraph. DR-TB is now more of a “transmitted” disease rather than the “acquired resistance” as discussed in the first few sentences of the paragraph. This needs to be noted. Also the meaning of the sentence “Further, the private sector poses many hurdles in TB control.” is unclear?
16. Discussion, 5th paragraph. For clarity of reading, the authors should to include the actual numbers involved when they state “57.5%” (=23/40) and “82.3” (=14/17).
17. Discussion, 6th paragraph. Did the study by Charles *et al.* (ref 28) include DR-TB cases as well as DS-TB? If not, how relevant is the reference to the current study?
18. Limitations. The authors need to include a paragraph or two on “Limitations” of the study.
19. Conclusions. Some of the statements made are pretty sweeping with little data or evidence from the study to support them. For example the statements in the 1st paragraph made about female and the elderly – these are based on very small patients numbers and hence how valid and generalizable are they? In the 2nd paragraph, an alternative view is that there may be better awareness in the community of the disease and availability of services. Hence a higher proportion of those who actually have the disease present to the public sector facilities for their 1st visit. And surely better linkages between the HCFs of the two sectors needs to be established, in addition to the option of providing everything in all private HCFs?
20. Consistency of language. DOTS-Plus centers / DR-TB Centre / PMDT center are all used in the manuscript. Firstly I would suggest the authors use “centre” and “programme”, and also are consistent in the term they use for the centre where the DR-TB patients were registered.

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?

Yes

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

Yes

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: Programmatic care and control of tuberculosis; drug-resistant 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.

Author Response 02 May 2020

Priya Rathi, Kasturba Medical College Hospital, Manipal, India

We have answered all query/comments point to point and have indicated its current location in modified manuscript.

In the flowchart and text, the authors talk about "Presumptive MDR-TB patients". However, the patients enrolled in the study are diagnosed and registered MDR-TB cases. These are not the same thing. How is "Presumptive MDR-TB patients" defined and is the same definition being used in both the private and public sector facilities in the study? This needs to be stated by the authors and how the "Presumptive MDR-TB patients" are being identified in the facilities of the 2 sectors and whether similar levels of identification of "Presumptive MDR-TB patients" was being done in the different sector facilities?

This study was a retrospective inquiry on pathway taken to reach Drug Resistance TB Center. The starting point of this inquiry was taken from the time these patients were presumptive DR case which by definition as per Programmatic Management of Drug Resistant Tuberculosis Guidelines is: Presumptive MDR case are Any of the following: It refers to the following patients in order of their risk: TB patients found positive on any follow-up sputum smear examination during treatment with first-line drugs including treatment failures; - TB patients who are contacts of DR-TB; - previously treated TB patients; - new TB patients with HIV co-infection. These definitions were used in the study.

Method –Data collection, Operational definition.

Time to diagnosis will be determined to a degree by what diagnostic capacity is available in the respective health facility. Hence if a facility has the capacity for rapid molecular diagnosis of TB and rifampicin resistance (RR-TB) e.g. if it has a GeneXpert machine on site, then diagnosis of RR-TB can be done within the day. If not and the patient or sample has to be sent to another facility which then does only culture and phenotypic drug susceptibility testing (DST) and not rapid molecular DST, there will be an inherent time difference between the patients seen at the initial health facility. So did all the health facilities involved in the study have the same access to diagnostic capacity?

Not all the health facilities involved in the study have the same diagnostic capacity. This is what we are trying to bring out from our study, that those patients who visited such health care facility which lacked Standard Diagnostic facilities were diagnosed late as compare to those who visited Government Health facility which has better diagnostic facility with Standard Operating Procedures (SOPs) and standard of care with respect to DR-TB. Under PMDT programme, DDR- TB centers are developed which complies with Standard Diagnostic and Treatment guidelines.

Even if the diagnostic capacity available to all health facilities involved in the study, where any RR-/MDR-TB cases diagnosed but not registered? If yes, were the proportions the same in the different sectors analyzed?

We have only considered those patients who were registered at DDR- TB Center and enquired which health care facilities they visited prior to DRTB Center and their sequence to what happened there with respect to diagnosis and treatment and referral. For the patients in the Government Sector, registration is done under the National TB Program. For patients who are initiated with treatment in the private sector, the private sector notifies to the government. In this study, our objective was to find out the pathway and the source of information was the patient themselves and not the health care providers. Hence, we did not enquire on the notification of the cases if diagnosed at private sector.

Were the 15 DR-TB patients who did not consent to participate in the study similar to the 40 patients who did participate in the study? Was there any difference in these 15 patients between those who initially visited a public sector facility versus those who visited a private facility initially?

Since the direction of inquiry was retrospective and the unit of inquiry was the patient or close relative, in the 15 patients who did not consent for the study, we were unable to find their first point of contact to Health care facility. However, with respect to the current diagnosis of TB and treatment regimen, they were the same as both were done at DRTB center with standard protocol and SOP.

Reference 1 and related text could be updated as the WHO 2019 Global TB Report is available. We have changed the reference to the latest report.

Reference 1

Introduction, 2 paragraph. It should be stated that PMDT is part of the Revised National TB

Control Programme (now renamed as the National TB Elimination Programme) and is not a separate programme as implied by the current text.

We have mentioned it now and have highlighted it as well.

Introduction, 2nd paragraph.

Introduction, 2 paragraph. Reference 5 should be updated as it refers currently to a 2011 WHO document which has been updated since then.

We have updated the same.

Introduction, 2nd paragraph
Reference 5.

Introduction, 3 paragraph. Reference 6 is from a paper dealing with Argentina. Is there no relevant reference paper from India that could be used instead? Also, does the current reference paper talk about DS-TB and/or DR-TB?

We have not taken any data from the Argentina study, we have just cited the conceptual knowledge of delay in diagnosis, hence the same reference can be used, the study included DS and Previously treated TB patients. We have also added one Indian study as well, however it covers only a few points as compared to Argentina study

Introduction, 3rd paragraph. Reference 6 and 7

Methods, Study settings, 1 paragraph. The district name and hospital name where the PMDT Centre is located should be given. As should the names of the 3 districts that the Centre caters for.

The DRTB center is situated in district hospital of Dakshina Kannada District, Karnataka State, India which also caters to two neighboring districts of Chikmagalur and Shimoga. This has been included now in the first paragraph.

Methods, Study settings, paragraph 2

Methods, Study settings, 1 paragraph. For non-Indian readers, the meaning of "... by Kayakalp." needs to be explained. Also, the reference given is no. 6 which refers to a paper dealing with Argentina and hence seems incorrect.

This has been removed and the above statement has been mentioned instead.

Methods, Study settings, 2nd paragraph

Methods, Study settings, 1 paragraph. The authors mention "... DOTS-Plus centers" and only mention about initial in-patient care. DOTS-Plus is outdated terminology and initial in-patient care practice alone is outdated practice under RNTCP. The text should be amended so the reader understands what is current RNTCP terminology and practice. Especially as in Figure 1, the term of DR-TB Centre is used.

We have changed the terms to District Drug resistance TB center (DDR-TBC) and Peripheral Health Institution (PHI) as per PMDT guidelines.

Methods, Study settings, paragraph 3

Study settings, 2nd paragraph. 12.5% of patients in the study were illiterate, hence how was "written consent" given

Those who were illiterate, the informed consent process was conducted in front of literate impartial witness as per ICMR ethics guidelines.(https://www.icmr.nic.in/sites/default/files/guidelines/ICMR_Ethical_Guidelines_2017.pdf)

Reference 8

Methods, Data collection, 1st paragraph. Is it correct then that there was no actual field testing of the questionnaire prior to the study being conducted? What training did the PI have on the questionnaire prior to conducting the patient interviews?

The tool was pilot tested in two patients. PI holds an MD degree in Community Medicine, where there is training in epidemiology and has conducted multiple projects in the past. The questionnaire was content to validate independently by two experts and discussed for feasibility along with the pilot testing.
Not applicable

Methods, Operational definitions, reasons for shifting from one HCF to another, 1st paragraph. As pointed out by the previous reviewer, what is listed here are options or answers expected to be provided by the patients. Hence this part of the methods section needs revising.

We have modified the section as Follows-These were the options provided to the patients-1. treatment not available, the appropriate treatment for the symptoms was unavailable in that HCF; 2. treatment not affordable, cost of treatment was beyond the paying capacity of the patient and its family; 3. referred, the patient was asked to visit another HCF for review/consultation or appropriate treatment; 4. not satisfied, symptoms did not alleviate or the patient perceived that the services being provided were inadequate. Also, along with this, they were also asked if any other reasons not included in the list.

Methods- Operational definition

Result-1st paragraph. Need to be consistent in the use of both numbers and % in the last sentence.

We have improvised the result with consistency.

Result-1st paragraph

Results, Details of first visit and shift from one HCF to other HCF, 2nd paragraph. Although 12 of the 15 who initially visited a public HCF were diagnosed with MDR, only 10 were immediately

referred to the DR-TB center. Why did the 2 other patients have to attend a HCF for a 2nd time before referral to the DR-TB Centre?

These two patients were from the other districts, they were referred from PHC to District hospital of the concerned district and from there to the DDR-TBC.

Discussion. As stated by the previous reviewer, the authors spend a lot of the discussion section comparing with other studies. Many of the times this is just in relation to confirming previous observations. Such text could be reduced (e.g. 2nd and 4th paragraphs).

We have modified the discussion as suggested, we have removed the comparing figures and have only mentioned relevant texts, we have reduced 2nd and 4th paragraph
Discussion

Discussion, 2nd paragraph. Should ease of access to service be more prominent amongst important issues surrounding health seeking behavior of patients? Is this not a major reason why patients initially seek care in the private sector rather than the public sector?

Yes, we have incorporated the point in the discussion

Discussion Paragraph 2

Discussion, 3rd paragraph. DR-TB is now more of a "transmitted" disease rather than the "acquired resistance" as discussed in the first few sentences of the paragraph. This needs to be noted. Also the meaning of the sentence "Further, the private sector poses many hurdles in TB control." is unclear?

There are both kind of cases, acquired as well as transmitted, we have now included your point in our discussion, also we have explained how the private sector can hinder the outcome of DRTB

Discussion paragraph 2

Discussion, 5th paragraph. For clarity of reading, the authors should to include the actual numbers involved when they state "57.5%" (=23/40) and "82.3" (=14/17).

Changes have been incorporated

Discussion paragraph 4

Discussion, 6th paragraph. Did the study by Charles et al. (ref 28) include DR-TB cases as well as DS-TB? If not, how relevant is the reference to the current study?

We have removed this part of the discussion.

Not applicable

Limitations. The authors need to include a paragraph or two on "Limitations" of the study.

Thank you for the insight. We have incorporated the paragraph for limitation.

Limitation reads as:

This study was conducted among the 40 patients from one DDR-TBC of Karnataka therefore the findings can be generalized to the population seeking health care from the same DDR-TBC. Second limitation would be the subject variability of the definition, however we have made full effort to validate the findings with medical reports of the patients from DDR-TBC to ensure the starting and end point of the pathway. Since the study was based on recall of the patients, there are chances of inherent recall bias.

Limitation

Conclusions. Some of the statements made are pretty sweeping with little data or evidence from the study to support them. For example, the statements in the 1st paragraph made about female and the elderly – these are based on very small patients numbers and hence how valid and generalizable are they? In the 2nd paragraph, an alternative view is that there may be better awareness in the community of the disease and availability of services. Hence a higher proportion of those who actually have the disease present to the public sector facilities for their 1st visit. And surely better linkages between the HCFs of the two sectors needs to be established, in addition to the option of providing everything in all private HCFs?

We have modified the conclusion based on your suggestion.

Conclusion read as-

The present study found that there was substantial patient delay and total delay in diagnosis and treatment of DR TB patients. The study projects the need of a public-private collaboration in treating DR TB cases; in terms of linkages between public and private sector for diagnosis and treatment of drug resistance TB, provisions of standard diagnostic services and treatment at low to no costs. This may be achieved by incentivizing treatment and providing standard diagnostic modalities to private sector under NTEP.

Conclusion

Consistency of language. DOTS-Plus centers / DR-TB Centre / PMDT center are all used in the manuscript. Firstly I would suggest the authors use “centre” and “programme”, and also are consistent in the term they use for the centre where the DR-TB patients were registered.

We have changed it to District drug resistance TB center (DDR-TBC), We have also clarified and changed center and programme.

All throughout the manuscript

Competing Interests: Nil

Reviewer Report 16 September 2019

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Sharath Burugina Nagaraja

Department of Community Medicine, Employees State Insurance Corporation Medical College and Post Graduate Institute of Medical Sciences and Research, Bengaluru, Karnataka, India

I congratulate your efforts on working on treatment pathways of drug resistant TB patients. Overall, the manuscript reads well. However, I have few comments for your consideration which will help in betterment of the manuscript. The comments are mentioned separately below.

Comments:

1. The authors in the introduction state that “we aimed to determine the health- seeking pathway of presumptive MDR TB patients prior to treatment at the PMDT center”. The manuscript lacks clarity on identifying the presumptive MDR-TB patient under the programmatic settings. Probably, the authors should specifically say that the presumptive MDR-TB is based on laboratory diagnosis rather than a clinical presumption.
2. Study settings: The authors have to specify the name of the hospital, location of the PMDT centre with the names and population of the districts it is catering to. They should also briefly describe about the types/numbers of public and private health facilities in the districts.
3. The statement “the patient is released to outpatient care for continuation of care at Directly Observed Treatment (DOT-Plus) centers throughout the community” needs to be modified because under programmatic conditions the patients are referred for domiciliary care in the community.
4. The name of the institution which has accrued ethics approval needs to be mentioned.
5. Data collection: It is found that the details were collected from the time the patients experience TB symptoms. These details are not analysed and was beyond the scope of the study. For a patient, there is a thin line of difference from being a presumptive TB case and a presumptive DR-TB case. There could be a lot of subjective variability in remembering the things which have occurred in the past. It is better if the authors explain the measures taken to negate such variability during the process of interview and increased their accuracy of findings.
6. Data analysis: Please mention the reference for adobe illustrator trail version.
7. Time delays in health care pathways: I feel the definitions needs further clarity. The starting point for delay calculations is the point of onset of illness. We presume that the authors are taking into account that it is from the point when the patient has a laboratory diagnosis of DR-TB. The authors should explicitly mention in their definitions.
8. Reasons for shifting from one HCF to others: These are the options or answers expected

from the patients. They have to be presented in the results as the findings of patients' interviews. Hence, should be removed from the method section.

9. Results: For better understanding the authors have to describe their findings as numbers (percentages). The 'p' values mentioned in table 1 should be removed, it has no relevance.
10. Among the 25 patients who went to private sector, 11 were diagnosed as MDR TB. What type of diagnosis did the private sector facilities made? Clinical or laboratory diagnosis? It is also mentioned that the patients are transferred to PMDT centres. Under programmatic settings, the transfer happens from one RNTCP administrative unit to the other.
11. There is a scope for authors to present the findings of proportions of patients who underwent 1,2,3 and 4 HCF visits as a bar diagram/table stratified by public and private facilities.
12. Discussions: The authors should remain focused on the study context. There has been much comparison with other studies. This tends to lose the focus of the readers. The recommendations have to be relevant to the study findings.
13. Limitations: The authors can add a paragraph on limitations of the study (response rate, sample size, generalizability, definitions-subjective variability).
14. Conclusion: The conclusion should be specific and should be described in a paragraph.

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?

Yes

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.

Reviewer Expertise: Tuberculosis, HIV, Diabetes - Operational 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 02 May 2020

Priya Rathi, Kasturba Medical College Hospital, Manipal, India

I congratulate your efforts on working on treatment pathways of drug resistant TB patients. Overall, the manuscript reads well. However, I have few comments for your consideration which will help in the betterment of the manuscript. The comments are mentioned separately below.

We thank the reviewer for the kind words of appreciation and recognising the work behind the manuscript. We have answered all query/comments point to point and have indicated its current location in the modified manuscript.

The authors in the introduction state that “we aimed to determine the health- seeking pathway of presumptive MDR TB patients prior to treatment at the PMDT centre”. The manuscript lacks clarity on identifying the presumptive MDR-TB patient under the programmatic settings. Probably, the authors should specifically say that the presumptive MDR-TB is based on laboratory diagnosis rather than a clinical presumption.

We have now included the exact definition of a presumptive diagnosis of DRTB based on PMDT guidelines

Methods data collection paragraph 2 and operational definition

Study settings: The authors have to specify the name of the hospital, location of the PMDT centre with the names and population of the districts it is catering to. They should also briefly describe about the types/numbers of public and private health facilities in the districts.

We have now specified the facility name, location and other details as suggested by the reviewer

Methods. Study setting paragraph 1

The statement “the patient is released to outpatient care for continuation of care at Directly Observed Treatment (DOT-Plus) centers throughout the community” needs to be modified because under programmatic conditions the patients are referred for domiciliary care in the community.

We have now changed this based on the PMDT guidelines

Methods. Study setting paragraph 2

The name of the institution which has accrued ethics approval needs to be mentioned.

Name of the IEC has been added

Methods. Study setting paragraph 3

Data collection: It is found that the details were collected from the time the patients experience TB symptoms. These details are not analysed and was beyond the scope of the study. For a patient, there is a thin line of difference from being a presumptive TB case and a presumptive DR-TB case. There could be a lot of subjective variability in remembering the things which have occurred in the past. It is better if the authors explain the measures taken to negate such variability during the process of interview and increased their accuracy of findings.

We have mentioned the measures taken for alleviating subjectivity as follows
We validated the starting point with the reports and patient file from the DDR-TBC to look for HIV co infection, previous lab reports, history of contact, previous treatment history, if available.

Data collection

Data analysis: Please mention the reference for adobe illustrator trail version.

We have incorporated the reference and link

Data analysis

Time delays in health care pathways: I feel the definitions needs further clarity. The starting point for delay calculations is the point of onset of illness. We presume that the authors are taking into account that it is from the point when the patient has a laboratory diagnosis of DR-TB. The authors should explicitly mention in their definitions.

We have changed the definition to make it clearer to understand.

Operational Definitions

Reasons for shifting from one HCF to others: These are the options or answers expected from the patients. They have to be presented in the results as the findings of patients' interviews. Hence, should be removed from the method section.

These were the options given to the patients hence we have mentioned in both the sections

Results:

For better understanding, the authors have to describe their findings as numbers (percentages). The 'p' values mentioned in table 1 should be removed, it has no relevance.

We have included the numbers and also removed p-value from table 1

Among the 25 patients who went to private sector, 11 were diagnosed as MDR TB. What type of diagnosis did the private sector facilities made? Clinical or laboratory diagnosis? It is also mentioned that the patients are transferred to PMDT centres. Under programmatic settings, the transfer happens from one RNTCP administrative unit to the other.

There are private sectors with diagnostic facilities, hence the diagnosis refers to laboratory diagnosis. We meant, that the patient was referred to the public sector from the private sector

Details of first visit and shift from one HCF to other HCF

Paragraph 3

There is a scope for authors to present the findings of proportions of patients who underwent 1,2,3 and 4 HCF visits as a bar diagram/table stratified by public and private facilities.

Since our objective was to map the pathway, we have incorporated the different color lines for different number of visit (1,2,3,4)

This has been explained in the data analysis section as follows

The meanings of both the lines as well the colours have been explained in the legends accompanying the pathways. Moreover, the number of patients shifting between HCF has been represented using the numbers accompanying the respective lines.

Data-analysis

Figure 2 legends

Discussions: The authors should remain focused on the study context. There has been much comparison with other studies. This tends to lose the focus of the readers. The recommendations have to be relevant to the study findings.

We have now removed the comparing figures and have kept only relevant text

Discussion

Limitations: The authors can add a paragraph on limitations of the study (response rate, sample size, generalisability, definitions-subjective variability).

Thank you for your insight. We have incorporated the paragraph for limitation.

Limitation reads as

This study was conducted among the 40 patients from one DDR-TBC of Karnataka therefore the findings can be generalized to the population seeking health care from the same DDR-TBC. Second limitation would be the subject variability of the definition, however we have made full effort to validate the findings with medical reports of the patients from DDR-TBC to ensure the starting and end point of the pathway. Since the study was based on recall of the patients, there are chances of inherent recall bias.

Limitation

Conclusion: The conclusion should be specific and should be described in a paragraph.

We have made it specific and conveyed it in a single paragraph.

Conclusion read as-

The present study found that there was substantial patient delay and total delay in diagnosis and treatment of DR TB patients. The study projects the need of a public-private

collaboration in treating DR TB cases; in terms of linkages between public and private sector for diagnosis and treatment of drug resistance TB, provisions of standard diagnostic services and treatment at low to no costs. This may be achieved by incentivising treatment and providing standard diagnostic modalities to private sector under NTEP.

Competing Interests: Nil

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