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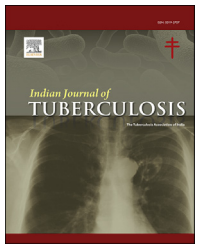

Editorial

Changing climate and respiratory diseases

There are lot of evidences that suggest that major changes in atmosphere and climate have an impact on the biosphere and human environment. Increased concentration of green house gases especially carbon dioxide in the earth's atmosphere have already substantially warned the planet, causing severe and prolonged heat waves, temperature variability, increased length and severity of pollen season, air pollution, forest fires, draughts and the floods, all of which put respiratory health at risk. The main diseases of concern are asthma, rhinosinusitis, chronic obstructive airway diseases and respiratory tract infections including tuberculosis. But the extent to which these spreads will vary according to the proportion of susceptible individuals in a given population. Individuals with pre-existing cardio pulmonary disease are at higher risk of suffering from climate changes. Areas of greater poverty with limited access to medical care will suffer more. The other groups at risk are migratory population and slum dwellers.

Climate change cannot be regarded in isolation as it is a process which affects to our health and as well as our surroundings. The Marrakesh Declaration acknowledges that almost one quarter of the global burden of disease and approximately 12.6 million deaths each year are attributable to modifiable environmental factors. It outlines how global, environmental and social changes, including climate change, are driving many of these risks and impacting directly on human health. Making the point directly, it notes that despite the strengthening evidence of the effects that environmental and climate risk factors have on health, the political action and investment currently underway is not yet at a sufficient scale to address these challenges globally.[1]

Changes in climate are reality going to worsen in the coming years. Climate change causes a massive threat to respiratory health by directly aggravating the existing respiratory diseases and by increasing exposure to risk factors for respiratory diseases. Climate change leads to increases in pollens and allergens produced by each plant, mould proliferation and the concentrations of outdoor ozone and particulate matter at ground level.

Climate change in form of rising temperatures and heat waves alone can cause an increase in respiratory deaths, hospital admissions and the need for management. Extreme heat and high humidity trigger asthma symptoms. Studies suggest chronic obstructive pulmonary disease (COPD) patients are at increased risk of exacerbation and hospitalisation during periods of high temperature and with an increased frequency of thunderstorm, asthma epidemics can be expected.

In addition to direct effect of rising temperatures, climate change triggers an increased exposure to other risk factors for respiratory disease like more frequent flooding will lead to greater dampness, moisture and mould in indoor spaces causing asthma, allergic rhinitis and some respiratory infections. Similarly, amplification of air pollution, in terms of higher levels of ozone, which reduces lung function is responsible for several respiratory effects.[2]

Climate change also leads to extended periods of different seasons. Adverse health effects are less well understood and require further research, in particular the effects of extreme natural phenomena. Of particular importance are: 1) The lengthening of the pollen season resulting in exacerbations of allergic respiratory diseases.[3] 2) The increasing impact of natural particulate matter from wildfires, desertification and sandstorms, which is less monitored or not considered at all to date and not taken into account in evaluating whether particulate matter concentrations are exceeding standards or not. This will also be responsible for various health effects beyond the respiratory system, including cardiovascular, metabolic and neurodegenerative conditions, as well as premature birth and cancer. 3) The association between dust storms and the risk of hospitalisation due to COPD[4] and asthma.[5] Recent studies have also shown the same association with pneumonia.[6] 4) The insufficient knowledge base available on the implications of respiratory infections for respiratory health, despite vector-borne diseases and infections being amongst the most well studied of the diseases associated with climate change.

Greenhouse gas emissions are mainly caused by increasing population, economic activity, lifestyle and energy use patterns. Combating climate change requires a combination of mitigation to address the causes and adaptation to address the impact. Both types of action are necessary and achievable but are of course not without their challenges and indeed their challengers.

We must make certain policy decisions to reduce the production of greenhouse gases and decrease air pollution (including short-life pollutants and pollen) as recognised by the World Health Organization (WHO). Some 10 years ago, an Intergovernmental Panel on Climate Change (IPCC) report outlined technologies and policy measures which, if pursued, would reduce greenhouse gas levels. In the energy field, the reduction of fossil fuel subsidies and taxes or carbon charges on fossil fuels were suggested, while in transport the use of cleaner diesel, more fuel-efficient vehicle fleets and investment in public transport and non-motorised transport options were touted as solutions.

Today, while not widespread, the prioritisation of clean energy finds and the phasing out fossil fuels is need of the hour. For example, Canada, France, Germany, The Netherlands, Austria, Finland and Portugal have already committed to phasing out coal-fired power plants. Furthermore, Paris, Madrid, Athens and Mexico City have all pledged to ban diesel cars by 2025. Such kind of efforts, though episodic or spouse, are also being undertaken in our country and need to be strengthened by strong political backup.

Adaptation options require dealing with the impact of climate change. From local heat-health action plans, emergency medical services and improved climate-sensitive disease surveillance and control to safe water and improved sanitation, there are numerous ways to improve our response[7]. Actions need to be taken to reduce pollution, inhibiting fassil fuels, popularising clean fuels, providing clean water and sensitization. These need not only to be done voluntarily but also legislations should be made to tackle these issue so as to provide clear environment and climate to our next generations and avoiding respiratory diseases.

REFERENCES

1. DAnato Gennaro, Cacchi Lorenzo, Amate Mariella D, et al. Climate change and respiratory diseases. *Eur Respir Rev*. 2014;23:161–169.
2. Ayres JG, Forsberg B, Annesi-Maesano I, et al. Climate change and respiratory disease: European Respiratory Society position statement. *Eur Respir J*. 2009;34:295–302.
3. D'Amato G, Cecchi L. Effects of climate change on environmental factors in respiratory allergic diseases. *Clin Exp Allergy*. 2008;38:1264–1274.
4. Vodonos A, Friger M, Katra I, et al. The impact of desert dust exposures on hospitalizations due to exacerbation of obstructive pulmonary disease. *Air Qual Atmos Health*. 2014;7:433–439.
5. Yitshak-Sade M, Novack V, Katra I, et al. Non-anthropogenic dust exposure and asthma medication purchase in children. *Eur Respir J*. 2015;45:652–660.
6. Vodonos A, Kloog I, Boehm L, et al. The impact of exposure to particulate air pollution from non-anthropogenic sources on hospital admissions due to pneumonia. *Eur Respir J*. 2016;48:1791–1794.

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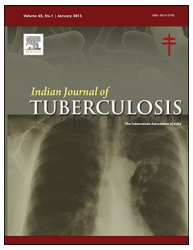

Original article

Performance of Xpert MTB/RIF for detection of *Mycobacterium tuberculosis* and rifampicin resistance in pus aspirates

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ABSTRACT

Introduction: WHO endorsed Xpert MTB/RIF assay has proven to be rapid with results obtained within 2 h. The evidence base regarding the use of Xpert MTB/RIF in pulmonary TB is strong. Relatively few performance data have been published to date on detection of *Mycobacterium tuberculosis* in aspirated pus specimens from abscesses.

Objectives: The aim of the study was to determine the sensitivity and specificity of Xpert MTB/RIF assay for the detection of *M. tuberculosis* and rifampicin resistance in aspirated pus specimens using culture on Lowenstein Jensen (LJ) medium and economic variant of proportion method (PM) for drug susceptibility testing (DST) as the reference standard.

Results: Xpert MTB/RIF assay in comparison to conventional reference method showed sensitivity and specificity of 76.19% and 68.75% for detection of *M. tuberculosis* and 71.4% and 100% for detection of rifampicin resistance respectively.

Conclusion: The simplicity, sensitivity, speed and automation makes this assay a very promising diagnostic test for detection of *M. tuberculosis* and rifampicin resistance in aspirated pus specimens.

Tuberculosis (TB) manifests as both pulmonary and extrapulmonary tuberculosis. Extrapulmonary tuberculosis (EPTB) accounts for 10% and 42% of cases of TB.[1] In India 10–15% of TB cases are estimated to have extrapulmonary disease and due to lack of diagnostic means, they remain untreated with a 25–50% mortality rate within months. Hence detection of extrapulmonary tuberculosis (EPTB) becomes extremely important. In contrast to pulmonary tuberculosis, the diagnosis of EPTB is still a serious problem and it remains undetected for a long time in a number of cases. The paucibacillary nature and difficulty in sample collection from deep seated abscesses makes it a diagnostic challenge. The low bacterial load affects the sensitivity of acid fast bacilli (AFB) microscopy.[2] Prolonged turnaround time and limited infrastructure in resource restricted laboratories undermine the utility of culture based diagnosis.

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Table 1 – Sensitivity and specificity of diagnosis of *M. tuberculosis* by ZN smear and Xpert MTB/RIF in comparison to culture (*n* = 101).

Test	Sensitivity	95% CI	Specificity	95% CI
ZN smear	47.6	25.7–70.2%	91.2	82.8–96.4%
M. tuberculosis detection by GeneXpert	76.1	52.8–91.7%	68.7	57.4–78.6%

WHO endorsed Xpert MTB/RIF assay based on automated real time PCR and molecular beacon technology has shown to have great potential in being rapid with results in 2 h and requires minimal biosafety facilities.[3] A large number of studies have evaluated the performance of Xpert MTB/RIF in pulmonary specimens. Recent papers have investigated the capacity of Xpert MTB/RIF assay to diagnose EPTB of which some have included aspirated pus specimens but very few have included significant numbers of pus and some do not have a separate analysis for pus specimens. Moreover, there is a paucity of data on evaluation of accuracy of Xpert MTB/RIF in detecting rifampicin resistance in pus aspirates.

In this study we evaluated the performance of Xpert MTB/RIF for detection of *M. tuberculosis* and rifampicin resistance in aspirated pus specimens. The objectives were to determine the sensitivity and specificity of Xpert MTB/RIF assay for the detection of *Mycobacterium tuberculosis* and rifampicin resistance in pus specimens using culture on Lowenstein Jensen (LJ) medium and economic variant of proportion method (PM) for drug susceptibility testing (DST) as reference.

1. Materials and method

This was a retrospective study conducted from February to December 2016 on aspirated pus samples of 106 consecutive patients in a tertiary care hospital in Mumbai. Most of the pus aspirates were from breast, liver, paravertebral and psoas abscesses. A minimum two ml of aspirated pus sample were collected in sterile falcon tubes, which was divided into two parts. One part was used for smear and culture, and the other for performing Xpert MTB RIF assay.

Smears were processed by Ziehl Neelsen (ZN) staining and examined under the light microscope. For inoculation on Lowenstein Jenson medium (LJ), 0.1 ml sample was used and incubated at 37 °C. Any growth on LJ was confirmed to be AFB by ZN stain and was speciated by growth rate, LJ with paranitro benzoic acid (PNB), niacin and nitrate tests. Drug Susceptibility Test (DST) of only the isolates identified as *M. tuberculosis* was performed by economic variant of proportion method on LJ medium.[4]

The Xpert MTB/RIF assay was performed according to the manufacturer's instructions (Cepheid, Sunnyvale, CA, USA). Briefly, sample reagent was added in a 2:1 ratio to 0.5 ml of the pus specimen. The closed tube was manually agitated two times during the 15 min incubation period at room temperature before two ml of the sample reagent mixture was transferred to Xpert MTB/RIF cartridge. Catridges were inserted into the Xpert MTB/RIF device and the system automatically interpreted all results from measured fluorescent signals into the following categories: *M. tuberculosis* (MTB) detected, MTB not detected or invalid if PCR inhibitors were detected with amplification failure. Positive results were measured as low, very low, medium or high depending on the bacterial load and defined as susceptible or resistant depending on the detection of mutations in rpoB gene. The tests were performed by different laboratory staff, thus blinding the result of the other test.

Statistical analysis included determination of sensitivity, specificity, positive and negative predictive values. Comparison between categorical variables was made by the Fisher's test, a p value of <0.05 was considered statistically significant.

As this was a retrospective study, Ethics approval was not required.

2. Results

A total of 106 pus specimens were processed by the method mentioned in the study. Of these five were excluded from the study, as three were culture contaminated and two gave invalid result on Xpert MTB/RIF. Thus the final sample size for analysis was 101 pus specimens. Of these, 21 (20.7%) were culture positive for *M. tuberculosis*.

The sensitivity and specificity of smear were 47.6% and 91.2% respectively and the same of Xpert MTB/RIF for detection of *M. tuberculosis* were 76.1% and 68.7% respectively as seen in Table 1. The sensitivity of Xpert MTB/RIF in smear negative samples was 72% which was lower than in smear positive samples (80%) (Table 2).

Phenotypic DST by economic variant of PM was performed in 21 isolates. Five of the isolates gave invalid results by PM method and *M. tuberculosis* was not detected by Xpert MTB/RIF in two isolates though valid results were obtained by PM. Therefore, 14 isolates were analysed for rifampicin resistance detection as seen in Table 3. Xpert MTB/RIF detected rifampicin resistance in seven cases of which five were in agreement with the PM method. The sensitivity and specificity of rifampicin detection by Xpert MTB/RIF were 71.4% and 100% respectively as depicted in Table 3.

M. tuberculosis was isolated on LJ medium from 20.79% of the pus specimens. Out of 21 culture positive pus specimens, 16 gave valid DST results. Multidrug resistant tuberculosis (MDR-TB) was found in three (18.75%) and four (25%) were resistant to rifampicin but were sensitive to isoniazid.

Table 2 – Sensitivity and specificity of diagnosis of *M. tuberculosis* by Xpert MTB/RIF in comparison to culture.

GeneXpert sensitivity	
Overall	76.1%
Smear positive and culture positive	80
Smear negative and culture positive	72
GeneXpert specificity	68.7%

Table 3 – Sensitivity and specificity of rifampicin resistance detection by Xpert MTB/RIF in comparison to economic variant of Proportion method (*n* = 14).

Test	Sensitivity	95% CI	Specificity	95% CI
Rifampicin resistance detection by GeneXpert	71.4	29–96.3%	100	59–100%

3. Discussion

There are enough published literature available on Xpert MTB/RIF performance in diagnosing TB with an improvement of the diagnostic process.[5] We evaluated the performance of Xpert MTB/RIF for detection of *M. tuberculosis* and rifampicin resistance in aspirated pus specimens.

The overall sensitivity of Xpert MTB/RIF for detection of *M. tuberculosis* in pus was 76.1%. This was similar to findings of Tortolli et al.,[2] and Moure et al.,[6] who had analysed pus samples in their studies and found sensitivities of 85% and 76.5% respectively. In culture positive cases the sensitivity of Xpert MTB/RIF was 80% in smear positive and 72% in smear negative cases, which is comparable with Vadwai et al. who found sensitivities of 95% and 89% in smear positive and negative respectively. The specificity of *M. tuberculosis* detection by Xpert MTB/RIF was 68.7%. Vadwai et al.[7] found specificity of 46% in pus specimens when compared to culture. They had also examined the sensitivity and specificity against composite reference standard and specificity was found to be higher. This was the limitation of our study as we had compared with only conventional solid culture. Sharma et al. studied 153 cold abscess pus specimens and found the specificity to be 71% respectively.[8] A study by Singh et al.[9] showed specificity of 78% for pus specimens. Thus specificity of MTB detection in pus specimens in our study was comparable to the Indian studies.[7–9]

In our study the sensitivity of *M. tuberculosis* detection by Xpert MTB/RIF was 76.1% which scored higher than smear microscopy which was 47.6% when compared to culture on LJ. Tortolli et al. also found a sensitivity of 48% in smear when compared to culture.[2] Out of 21 culture positive pus samples, 11 (52.31%) were smear negative. Xpert MTB/RIF had detected *M. tuberculosis* in 8 (72%) of the smear negative samples. Hence Xpert MTB/RIF increased detection of *M. tuberculosis* in smear negative samples. These 8 cases would have received treatment only when culture results would have become available. Xpert MTB/RIF overcame this delay leading to prompt treatment of the patient, thus reducing poor outcome and the risk of spread to others. Therefore, Xpert MTB/RIF can be an invaluable aid to diagnose of EPTB in pus in which smears are negative. Moreover, for both smear positive and negative samples providing a rapid screening for rifampicin resistance mutations whenever *M. tuberculosis* is detected, will help in making appropriate treatment decisions leading to better clinical outcomes.

In our study, sensitivity and specificity of rifampicin resistance detection was 71.4% and 100% respectively. The overall sensitivity and specificity of detection of rifampicin resistance were 81.8% and 100% when compared to phenotypic method in a study by Singh et al.[9] It was not possible to adequately compare the diagnostic accuracy of rifampicin resistance exclusively in pus as most studies have given the overall sensitivity and specificity in EPTB specimens and not for pus separately. In the present study, 2 of the isolates which were rifampicin resistant by PM were sensitive by Xpert MTB RIF. The detection of only rifampicin resistance determining region RRDR mutations by Xpert MTB/RIF misses the resistance determining mutations outside this hotspot. Such mutations are responsible for 5% of all rifampicin mutations and that might explain the discordance in the two isolates in our study. Heteroresistance which is the existence of both resistant and sensitive *M. tuberculosis* populations can also lead to false negative and positive results in Xpert MTB/RIF assay. For detection of drug resistance in such a mixed population, the rpoB allele responsible for rifampicin resistance should be present in at least 65% of DNA present in the sample. This also could explain why rifampicin resistance was detected by PM and not by Xpert MTB/RIF.

Of the 101 pus specimens included in the study, 20.7% were culture positive. In an Indian study by Ravindran et al. the culture positivity was 23.7% in pus aspirates.[10] Tortolli et al. found 23.9% of pus specimens to be positive for *M. tuberculosis*. In the present study, Multi Drug resistance (MDR) was found to be 21.4% and 4 (25%) were resistant to rifampicin but were sensitive to isoniazid. As mentioned earlier, 2 of these isolates which were rifampicin resistant by PM were sensitive by Xpert MTB/RIF. The other 2 isolates had been reported as resistant by Xpert MTB\RIF and sensitivity to isoniazid was known only when the DST results were obtained. Though we had not come across rifampicin sensitive but monoresistance to isoniazid in the pus aspirates, there has been a study from India where the authors reported isoniazid monoresistance in rifampicin susceptible cases.

PCR inhibition leading to invalid test is a major concern while testing non-respiratory specimens. There were 2 invalid results by Xpert MTB/RIF and hence were not taken in the final analysis. Hence it shows that this issue is of lesser concern in Xpert MTB/RIF due to the fact that this is a self contained automated test which requires minimal hands on manipulation leading to lower PCR inhibition rates. As rapid and accurate case detection is critical for effective treatment, prevention of transmission of infection choice of the right test plays a significant role.

4. Conclusion

Xpert MTB/RIF's sensitivity scored higher in comparison with microscopy, thus increasing the proportion of rapid diagnosis. In settings with a limited laboratory capacity it may be an additional tool in detecting tuberculosis in pus aspirates not detected by microscopy. The Xpert MTB/RIF assay has shown a substantial capacity for diagnosis of EPTB from pus aspirates. This assay with its modest sensitivity and specificity along with simplicity and rapidity is an useful technology for early

diagnosis of *M. tuberculosis* and detection of rifampicin resistant extrapulmonary tuberculosis in pus aspirates.

Conflicts of interest

The authors have none to declare.

REFERENCES

1. World Health Organisation. *Global Tuberculosis Report 2013*. Geneva: World Health Organisation; 2013.
2. Tortolli E, Russo C, Ciersimoni C, et al. Clinical validation of Xpert MTB/RIF for the diagnosis of extrapulmonary tuberculosis. *Eur Respir J*. 2012;40:442–447.
3. World Health Organisation. *Policy Statement: Automated Real Time Nucleic Acid Amplification Technology for Rapid and Simultaneous Detection of Tuberculosis and Rifampicin Resistance: Xpert MTB/RIF System*. Geneva: WHO; 2011.
4. *Revised National Tuberculosis Control Programme Training Manual for Mycobacterium tuberculosis Culture and Drug Susceptibility Testing*. New Delhi: Central Tuberculosis Division; April 2009.
5. Maynard-smith L, Larke N, Peters JA, Lawn SD. Diagnostic accuracy of the Xpert MTB/RIF assay for extrapulmonary and pulmonary tuberculosis when testing non-respiratory samples: a systematic review. *BMC Infect Dis*. 2014;14:709.
6. Moure R, Martin R, Alcaide F. Effectiveness of an integrated real time PCR method for detection of the *Mycobacterium tuberculosis* complex in smear negative extrapulmonary samples in an area of low tuberculosis prevalence. *J Clin Microbiol*. 2012;50(2):513–515.
7. Vadwai V, Shetty A, Rodrigues C. Xpert MTB/RIF: a new pillar in diagnosis of extrapulmonary tuberculosis. *J Clin Microbiol*. 2011;49:2540–2545.
8. Sharma S, Kohli M, Chaubey J, et al. Evaluation of MTB/RIF assay performance in diagnosing extrapulmonary tuberculosis among adults in a tertiary care centre in India. *Eur Respir J*. 2014;44:1090–1093.
9. Singh UV, Pandey P, Mehta G. Genotypic, phenotyping and clinical validation of GeneXpert in extra pulmonary and pulmonary tuberculosis in India. *PLOS ONE*. 2016;11(2):01–16.
10. Ravindran R, Oberoi JK, Wattal C. MDR pulmonary and extrapulmonary tuberculosis: a 13 years retrospective hospital based analysis. *Indian J Med Res*. 2015;142:575–582.

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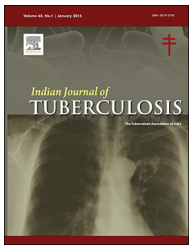

Original article

Pulmonary tuberculosis: An analysis of isolation practices and clinical risk factors in a tertiary hospital

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ABSTRACT

Background: Inadequate isolation of patients with active pulmonary tuberculosis causes exposure whereas over-cautious isolation generates time and cost inefficiencies. This study aims to ascertain the delays involved in isolating subjects and the importance of risk factors.
Methods and material: Between December 2010 and January 2013, a retrospective analysis of 271 subjects was performed. Information was obtained from discharge letters, radiological and microbiological results.
Results: The median time taken to isolate subjects was 0 days, and 71.7% were isolated within 1 day. Most subjects (75.3%) had sputum samples obtained after isolation, of which 14.7% were positive. The median time from admission to first sputum sample was 1 day. Smear was negative in 174 subjects (85.3%). Country of birth (high or low risk) did not significantly affect sputum positivity (25.5% vs 19.4%, $p = 0.52$). Suspicious radiological findings were noted in 38.6% subjects, and 32.8% had a suspicious clinical history. Subjects with both clinical and radiological probability had more sputum positivity (46.2%), compared to subjects who had neither (2.7%).
Conclusion: There are delays with isolation and diagnosis of subjects with a high probability of tuberculosis. Clinical and radiological probability were more significant in predicting sputum positivity than country of birth.

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Abbreviations: AFB, acid fast bacilli; CXR, chest X-ray; CT, computed tomography; RPH, Royal Perth Hospital; MRN, medical record number; LTBI, latent tuberculosis infection; TB, *Mycobacterium tuberculosis*; PTB, pulmonary tuberculosis; SD, standard deviation.

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1. Introduction

Tuberculosis is an important disease in Australia in the context of increasing immigration rates.[1,2] In 2014 there were 142 notifications of tuberculosis in Western Australia alone, corresponding to a rate of 5.5 cases per 100,000 population.[3] Numerous studies have detailed that hospital staff are at a higher risk of acquiring the infection compared to the general population.[4–6]

Current guidelines for reducing transmission of TB in hospitals advise that inpatients with a high probability of having pulmonary TB should be isolated in negative-pressure single rooms.[7–10] Recommended contact precautions include high-filter respirators to reduce transmission.[7–10] The number of single rooms suitable for isolating patients varies considerably between hospitals and can pose significant operational challenges if utilized ineffectively.

Delays in identification and isolation of patients with TB places staff and patients at risk of infection. The few studies that have investigated this issue were performed in the 1990s. Bennet et al. examined delays in consideration of TB and isolation in 1277 subjects in a multi-centre retrospective cohort study and found that a hospital with one of the lowest rates of TB isolation had an outbreak of nosocomial multi-drug resistant TB. This led the authors to recommend further educational efforts on the benefits of early TB identification/isolation.[11] A retrospective study by Rao et al. from 1988 to 1996 found that delays in the recognition of tuberculosis resulted in an average of 23.9 health care workers being exposed per subject with confirmed tuberculosis. Substantial additional expenditure would have been incurred to evaluate these workers.[12]

2. Objectives

The primary objective of this study was to establish the appropriateness of admission, isolation and de-isolation of subjects with possible pulmonary tuberculosis. Secondary objectives were to determine delays in collecting sputum samples, correlating country of birth, clinical probability and radiological probability to subsequent sputum positivity.

3. Materials and methods

3.1. Data collection

This study was conducted at an adult tertiary hospital in Western Australia. Subjects isolated were provided single rooms with negative-pressure ventilation. Nursing staff wrote information including the subject's medical record number (MRN) and period of isolation on cards, which were displayed on the door of the subject's room. After discharge or de-isolation, these cards were retained by the Microbiology Department. Demographic data, admission and discharge dates and results of sputum smears and cultures were obtained from the hospital's clinical management software.

The total number of sputum samples, dates on which samples were collected, and AFB smear result were obtained from the medical records. The records were checked at least eight weeks after the samples to ensure TB cultures were included. All positive samples were analyzed with Gene-Xpert, but these results were not relevant to the objectives of study. Chest X-Ray reports were reviewed for changes consistent with active PTB.

Sputum samples during a patient's admission were considered. As there is no consensus on ideal duration between collection of samples, an arbitrary time of 6 h was used.

The subjects included in the study were further classified as possessing one or more of the following risk factors:

- Symptoms at presentation suspicious for TB (e.g. prolonged cough, night sweats, weight loss, haemoptysis).
- WHO risk profile supportive of diagnosis of TB (according to country of birth and incidence of TB, defined as "high risk" for countries with incidence of TB cases ≥ 40/100,000 population).[13]
- Radiological (CXR) findings suggestive of TB.[14]

3.2. Population selection

Inpatients at RPH between December 2010 and January 2013 who were suspected to have a high enough probability of pulmonary tuberculosis to be placed in an isolation room with airborne precautions were included in this study. Patients who were in isolation rooms for other conditions were not included.

3.3. Ethics approval

This study was approved by the Human Research Ethics Committee of Royal Perth Hospital, with a waiver for consent as there was no subject contact required, no intervention was performed and outcomes for the subjects concerned remained unchanged.

3.4. Statistical analyses

Statistical analyses were done using SPSS (Version 22) and Microsoft Excel 2013 (Version 15.0.4535.1507).

4. Results

4.1. Population demographics

The total study population comprised of 271 subjects with 175 males (65%) and 96 females (35%). The median and mean age was 50 years (range 18–94 years). Two hundred and fifty-two subjects (93.0%) had a clinical history recorded in the discharge letter with 219 (86.9%) needing admission based on the clinical presentation.

4.2. Time to isolation (exposure)

There were 258 subjects with a recorded isolation date and an admission date. Thirteen subjects were excluded due to either

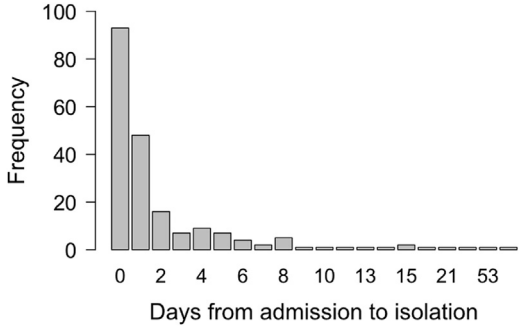

Fig. 1 – Frequency distribution of the number of days from admission to isolation.

a lack of admission data (12) or an unknown isolation date (1). Although the median time taken to isolate subjects was 0 days, the average was 2.45 days (range of 0–65 days). A few patients had a prolonged time to isolation, possibly due to delays in obtaining sputum and not considering pulmonary tuberculosis as the primary diagnosis. The majority (71.7%) of subjects were isolated within one day (Fig. 1).

Of the 30 subjects (11.1%) who had sputum microscopy that was positive for AFBs, there was a median delay in isolation of 0 days, with a mean of 1.7 days and a range between 0 and 15 days.

4.3. *Sputum analysis*

Sputum samples were obtained in 204 subjects (75.2%), of which 30 (14.7%) were positive for AFB. At least 3 sputum samples were collected in 141 subjects (69.1%). Twenty-four (17.0%) of those had at least one positive sputum sample and 16 (11.3%) had 3 positive sputum samples.

The median time from admission to first sputum sample was 1 day, with a mean of 3.63 days and a range between 0 and 114 days (Fig. 2).

Without considering delay between samples, 141 subjects had at least 3 sputum samples collected. A hundred and thirty-two (93.6%) had 3 sputum samples collected at least 6 h apart, allowing potential exclusion of TB. The median time taken to obtain three samples was 4 days, with an average of 6.11 days and range of 1–25 days.

Of the 30 patients who had positive sputum smears, 28 had a recorded de-isolation date. The median duration of isolation for these patients was 6.5 days (mean 12, range 1–46).

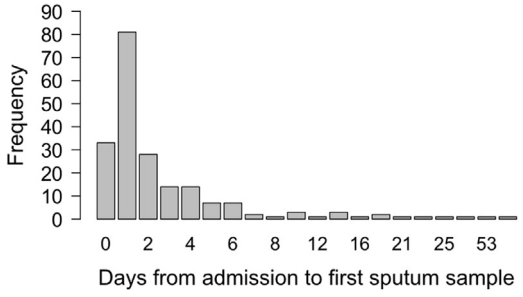

Fig. 2 – Frequency distribution of the number of days from admission to first sputum sample.

4.4. *De-isolation*

A de-isolation date was recorded in 253 subjects (93.4%). The median time a subject spent in isolation was 5 days, with an average of 5.77 days and range of 1–30 days. One hundred and twenty-seven subjects (50.2%) were de-isolated with less than three (126) or no (1) sputum samples taken during the admission.

Of the 97 subjects with 3 negative sputum samples taken at least 6 hours apart, 5 were de-isolated before the third sputum was sent. The 92 subjects remained isolated after the third negative sputum for a median of 2 days, with an average of 2.71 days (range 0–11).

4.5. *Country of birth*

Country of birth was recorded in 108 subjects (39.9%), with 72 (66.7%) originating from high-risk and 36 (33.3%) from low-risk countries. High-risk countries were defined by an incidence of pulmonary tuberculosis of more than 40 per 100,000 of the population.[13] The sputum samples of 14 subjects from the high-risk country subgroup (25.5% of the subgroup) were positive.

Six of the 31 subjects (19.4%) from low-risk countries had positive sputum samples. Being born in a high-risk country did not significantly increase the percentage of sputum positivity (19.4% vs 25.5%, $p = 0.52$ on Chi-squared test).

4.6. *Radiological findings*

A CXR was done during admission for 246 (90.8%) subjects and 95 (38.6%) had findings suspicious for pulmonary TB. Two hundred and four subjects had both a CXR and at least one sputum sample obtained. Sputum positivity was found in 5 of the 120 subjects with normal CXRs and 23 of the 84 subjects with abnormal CXRs ($p = 0.000002$).

4.7. *Clinical probability*

Discharge letters were complete for 242 subjects, of which 83 (34.3%) had clinical findings that were consistent with a diagnosis of pulmonary TB.

Two hundred and two subjects had sputum samples sent. Sputum positivity was found in 15 of the 133 (11.3%) with no clinical probability and 14 of the 55 (25.5%) with clinical probability. There was no significant correlation between clinical probability and sputum positivity ($p = 0.08$).

Two hundred and thirty-seven had clinical history recorded and a CXR done. Positive CXR findings were found in 62 of the 156 subjects (39.7%) with no clinical probability and 32 of the 81 subjects (39.5%) with clinical probability. There was therefore no significant correlation between clinical probability and radiological findings ($p = 0.97$).

4.8. *Risk factor analysis*

Clinical history and CXR was recorded on admission in 237 subjects (87.5%). Two hundred subjects (84.4%) had sputum samples collected during the admission, with a total of 27 sputum samples being positive for AFBs. The percentage of

Table 1 – Number of subjects born in WHO classified high risk and low risk countries, number of subjects with sputum samples available and percentage of subjects with positive sputum.

Country of birth	Number of subjects	Sputum available	Sputum positive (%)
Low risk	72	55	14 (25.5%)
High risk	36	31	6 (19.4%)
Total	108	86	20 (23.3%)

Table 2 – Subjects classified according to radiological and clinical probability with the number and percentage of positive sputum samples.

Radiological probability	Clinical probability	No. of subjects	Sputum available	Positive sputum (%)
N	N	94	75	2 (2.7%)
N	Y	49	42	2 (4.8%)
Y	N	62	57	11 (19.3%)
Y	Y	32	26	12 (46.2%)
Total		237	200	27 (13.5%)

sputum positivity was low without clinical or radiological probability (2.7%) and high with both clinical and radiological probability (46.2%) (Tables 1 and 2).

Ninety-nine (36.5%) subjects had data recorded for country of origin, clinical findings and CXR results. Eighty-five (85.9%) of these subjects had at least one sputum sample taken during their admission. Nineteen (22.4%) had at least one positive sputum. Further analysis was performed on the 85 subjects, sub-grouped into having some or all of the risk factors (Table 3). A multivariate logistic regression was performed with odds ratios revealing an increased risk of a positive sputum with a positive CXR (OR 5.3), and with clinical suspicion (OR 3.1), but not with a higher risk of country of birth (OR 1.1) (Table 4). The time to isolation from admission was no different when taking into account these other factors (OR 0.95).

5. Discussion

5.1. *Isolation delays*

Of the 252 patients with a documented history of presenting complaint on the discharge letter, 219 (86.9%) had clinical features that necessitated admission and isolation. These included fever lasting more than 2 weeks, persistent productive cough, haemoptysis, loss of weight and loss of appetite. The remaining 33 subjects were admitted for reasons such as viral symptoms, abnormal CXR on routine screening and investigation of chronic cough. This suggests that a small proportion of subjects need not have been admitted, saving cost and exposure to staff. Furthermore, clinically stable subjects could have been treated as outpatients at the nearby TB clinic instead of being admitted. Our study shows that only 32 out of 237 subjects (13.5%) had both clinical and radiological findings suggestive of pulmonary TB.

The median time taken to isolate a patient was 0 days (range 0–65 days), suggesting that most subjects, including 30 with positive sputum smears, were isolated almost immediately. However, delays were present up to 65 days and up to 15 days in a few patients with positive smears, causing significant risk of exposure. This delay is notable given that 6 subjects out of the 30 who ultimately tested positive were only isolated after a positive sputum sample, with an average isolation time of 2.2 days resulting in significant exposure to staff and the wider public. Practitioners who request sputum AFB based on a sufficiently high index of clinical probability of tuberculosis should initiate isolation precautions concurrently.

Table 3 – Probability of tuberculosis on admission based on clinical probability, radiological probability and country of birth (WHO risk status), with the number and percentage of positive sputum samples in each group. Low risk is defined by countries with an incidence of pulmonary tuberculosis of less than 40/100,000 population.

Radiological probability	Clinical probability	Subjects per group (% of total)	Number of subjects and WHO risk		Subjects with AFB positive sputum and WHO risk		Total subjects with AFB positive sputum (% of group)
			Low risk	High risk	Low risk	High risk	
N	N	27 (31.8%)	9	18	2 (22.2%)	0 (0%)	2 (7.4%)
N	Y	14 (16.5%)	6	8	0 (0%)	2 (25%)	2 (14.3%)
Y	N	27 (31.8%)	13	14	2 (15.4%)	4 (28.6%)	6 (22.2%)
Y	Y	17 (20.0%)	3	14	2 (66.7%)	7 (50.0%)	9 (52.9%)

Table 4 – Multivariate logistic regression model, demonstrating the odds of having a positive sputum sample with a positive CXR, higher risk WHO country of birth, clinical suspicion, and delay in isolation.

	Estimate	Standard error	Odds ratio	z	*p*	95% Confidence interval (odds ratio scale)	
						Lower bound	Upper bound
(Intercept)	−2.76	0.709	0.063	−3.893	<0.001	0.016	0.254
CXR	1.661	0.638	5.264	2.605	1.509	1.509	18.364
WHO risk category	0.054	0.608	1.055	0.088	0.32	0.32	3.474
Clinical suspicion	1.128	0.58	3.091	1.946	0.992	0.992	9.631
Delay from admission to isolation	−0.047	0.11	0.954	−0.43	0.769	0.769	1.183

Of the 204 subjects (75.3%) had sputum samples, 30 (14.7%) were positive for AFBs. Of the quarter (24.7%) that did not have sputum samples taken, subject difficulties or extra-pulmonary TB (in which case the subject need not have been isolated) may have been contributing factors. Only half of the subjects (52.0%) had at least 3 sputum samples analyzed, of which 24 (17%) were positive for AFBs. This is in contrast to guidelines which require three negative sputum samples in order to remove isolation precautions.[15] With the 253 subjects for whom both isolation and de-isolation date was available, we found that most subjects spent 5 days in isolation.

It took a median of 2 days after a third negative sample to remove isolation precautions. This represents a significant delay given the median total isolation period of 5 days. Exposure and cost can be further reduced by encouraging more urgent collection of a complete set of sputum samples, which would allow timelier de-isolation. We suggest that a single entity (e.g. infection control nurses) oversee isolation of subjects during an admission and follow-up the same subjects to ensure accurate record keeping and appropriate follow-up.

5.2. *Risk factor analysis*

In contrast to common expectations, the results do not suggest that subjects born in high-risk countries have significantly higher rates of sputum positivity.

Radiological findings on admission resulted in a significant difference in sputum positivity. This confirms that radiological evaluation should play a significant role in the decision to isolate subjects. Clinical probability from history also increased the percentage of subjects with positive sputum samples (11.3% vs 25.5%), though not significantly.

Although clinical probability or radiological changes alone cannot form a guideline, a combination of the two correlates with an increased rate of sputum positivity in study subjects (2.7% if neither positive, 46.2% if both positive). As illustrated in Table 3, WHO risk status did not independently correlate with radiological probability ($p = 0.98$), clinical probability ($p = 0.28$) or sputum positivity ($p = 0.52$).

The presence of a suspicious CXR and suspicious clinical history increased the odds risk of positive sputum, by approximately 5 and 3 times respectively. These findings are consistent with previous studies that have demonstrated the correlation between clinical findings, radiological changes (such as cavitating upper lobe lesions) and the confirmation of pulmonary tuberculosis.[15–17] However, the risk of having a positive sputum was no different between patients from low-risk countries and high-risk countries, which was an unexpected finding. This goes against common conception and protocol suggesting that patients be isolated for possible pulmonary tuberculosis partly based on country of origin.

Interestingly, the time to isolation from admission was the same regardless of the risk factors, suggesting the decision to isolate was largely protocol-driven rather than by the risk factors mentioned earlier.

5.3. *Limitations*

The retrospective analysis used had limitations. The use of discharge summaries for clinical information may have resulted in misclassification bias if the full clinical impression had not been recorded. The presence of outpatient investigations (CXR, sputum samples) that were recorded in the hospital records may have altered the results.

Furthermore, due to the observational nature of this study, as well as the limited cohort assessed in a span of 2 years, it is poorly powered to establish causality between the variables being studied.

The time difference between admission, isolation and sputum collection was calculated in number of days rather than number of hours due to limitations in the software used. Given lack of data for specific variables in the study, statistical analyses had to be performed within sub-groups. This resulted in the exclusion of a number of subjects for each sub-analysis.

6. Conclusion

Most admissions were appropriate with the majority of subjects being isolated promptly. However, the study reveals areas of significant concern, including the finding of TB-positive patients being isolated after a positive sputum sample, delays in obtaining sputa, de-isolation without sufficient sputa samples and unnecessary prolonged isolation of sputum-negative subjects. There is a need for clear and complete documentation as well as effective and appropriate isolation and de-isolation procedures. This requires improved staff education regarding the isolation and management of patients with a high probability of pulmonary tuberculosis.

The results suggest a significant association exists between clinical and radiological risk and sputum positivity. WHO risk status classification based on country of birth did not significantly increase the prevalence of sputum positivity. However, there is still a significant lack of data in the literature on this subject. With further multi-centre analyses, a combination of clinical and radiological risk patterns could be used to establish standard emergency department guidelines for isolating subjects on admission as well as guidelines for their management thereafter.

Authors' contribution

Dr. Srivathsan Thiruvengadam involved in the conception and design of the work, the acquisition, analysis and interpretation of data and principal investigator.

Dr. Lauren Giudicatti and Dr. Siaavash Maghami involved in analysis and interpretation of data and contribution to article authorship.

Dr. Kumaraweerage Ruad Herman Perera involved in analysis and interpretation of data, supervisor to conception and design, and reviewing and suggesting important intellectual content.

Dr. Hussein Farah involved in analysis and interpretation of data, including complex statistical analyses and reviewing and suggesting important intellectual content.

Dr. Justin Waring and Professor Grant Waterer involved in revision of paper for important intellectual content.

Conflicts of interest

The authors have none to declare.

REFERENCES

1. Toms C, Stapledon R, Waring J, Douglas P. Tuberculosis notifications in Australia, 2012 and 2013. *Commun Dis Intell Q Rep.* 2015;39(June (2)):E217–E235.
2. Horner J, Wood JG, Kelly A. Public health in/as 'national security': tuberculosis and the contemporary regime of border control in Australia. *Crit Publ Health.* 2013;23 (December (4)):418–431.
3. *Tuberculosis notifications in Western Australia*. Perth: Western Australian Department of Health; 2015. Available from: http://www.public.health.wa.gov.au/3/1532/3/tuberculosis.pm [cited 27.08.15].
4. Baussano I, Nunn P, Williams B, Pivetta E, Bugiani M, Scano F. Tuberculosis among Health Care Workers. *Emerg Infect Dis.* 2011;17(March (3)):488–494.
5. Lien LT, Hang NTL, Kobayashi N, et al. Prevalence and risk factors for tuberculosis infection among hospital workers in Hanoi, Viet Nam. *PLoS ONE.* 2009;4(August (8)):e6798.
6. Christopher DJ, Daley P, Armstrong L, et al. Tuberculosis infection among young nursing trainees in South India. *PLoS ONE.* 2010;5(April (4)):e10408.
7. Granich R, Binkin NJ, Jarvis WR, Simone P, Rieder H, Espinal M. Guidelines for the prevention of tuberculosis in health care facilities in resource-limited settings. World Health Organisation. Available from: http://www.who.int/tb/publications/who_tb_99_269.pdf?ua=1 [cited 29.01.15].
8. Maloney SA, Pearson ML, Gordon MT, Del Castillo R, Boyle JF, Jarvis WR. Efficacy of control measures in preventing nosocomial transmission of multidrug-resistant tuberculosis to patients and health care workers. *Ann Intern Med.* 1995;122(January (2)):90–95.
9. *Tuberculosis: Clinical Diagnosis and Management of Tuberculosis, and Measures for its Prevention and Control*. Manchester: National Institute for Health and Clinical Excellence; 2011. Report No.: CG117. Available from: https://www.nice.org.uk/guidance/cg117 [cited 02.01.15].
10. *Active Surveillance for Tuberculosis in Health Care Workers*. Perth: Western Australian TB Control Program; 2011. Available from: http://www.health.wa.gov.au/acc/docs/Policy%206.3_TB%20and%20HealthCareWorkers.pdf [cited 02.02.15].
11. Bennett CL, Schwartz DN, Parada JP, et al. Delays in tuberculosis isolation and suspicion among persons hospitalized with HIV-related pneumonia. *Chest.* 2000;117 (January (1)):110–116.
12. Rao VK, Iademarco EP, Fraser VJ, Kollef MH. Delays in the suspicion and treatment of tuberculosis among hospitalized patients. *Ann Intern Med.* 1999;130(March (5)):404–411.
13. *WHO Global Tuberculosis Report 2014*. World Health Organisation; 2014. Available from: http://www.who.int/tb/publications/factsheet_global.pdf [cited 02.06.15].
14. Woodring JH, Vandiviere HM, Fried AM, Dillon ML, Williams TD, Melvin IG. Update: the radiographic features of pulmonary tuberculosis. *AJR Am J Roentgenol.* 1986;146(March (3)):497–506.
15. Sokolove PE, Lee BS, Krawczyk JA, et al. Implementation of an emergency department triage procedure for the detection and isolation of patients with active pulmonary tuberculosis. *Ann Emerg Med.* 2000;35(April (4)):327–336.
16. Barnes PF, Verdegem TD, Vachon LA, Leedom JM, Overturf GD. Chest roentgenogram in pulmonary tuberculosis. New data on an old test. *Chest.* 1988;94(August (2)):316–320.
17. Solari L, Acuna-Villaorduna C, Soto A, et al. A clinical prediction rule for pulmonary tuberculosis in emergency departments. *Int J Tuberc Lung Dis.* 2008;12(June (6)):619–624.

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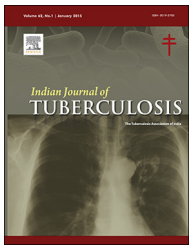

Original article

Why are people dying due to tuberculosis? A study from Alappuzha District, Kerala, India

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ABSTRACT

Background: Tuberculosis (TB)is a major killer disease worldwide. It is the ninth leading cause of death worldwide and the leading cause from a single infectious agent. In India also, TB kills about 480,000 persons every year and more than 1400 every day. Vision of the National TB Control Programme is TB-Free India with zero deaths, disease and poverty due to TB. Specific targets set in the End TB strategy include a 90% reduction in TB deaths and an 80% reduction in TB incidence by 2030, compared with 2015. Understanding about real cause of death is important to plan strategies to further prevent TB deaths. In the above circumstances we conducted a study, the objective of which was to find out the cause of deaths among patients registered in RNTCP unit of Alappuzha district of Kerala, India.

Methods: In RNTCP a patient who died during the course of treatment regardless of cause is declared as 'Died' due to TB. During the year 2015, 1618 cases were registered in RNTCP of Alappuzha district of which 90 patients died, showing a case fatality rate of 5.56%. Verbal autopsy can be considered as an essential public health tool for studying reasonable estimate of the cause of death at a community level even though not an accurate method at individual level. As part of the study, we visited the 4 RNTCP units of the district and collected the address of the TB patients who died in the area. With the help of the field staff we visited their houses and filled the death audit form of RNTCP along with the additional details. Verbal autopsy was conducted using WHO verbal autopsy format 2012 with immediate house hold contacts.

Results: Out of 90 deaths which occurred, three addresses could not be traced and another 15 patient relatives could not be contacted as they migrated out or were not available at their homes on two visits. Among them, mean age was found to be 62.6 years (SD + 12.9). Males were 67 (77%) and rest 20 (23%)were females. Cause of death was analysed after Verbal autopsy for 72 deaths. Among 72 deaths, it was found that 29 (40.3%) had nothing other than TB, where as cause of death for 13 (18.1%) patients was myocardial infarction, 11 (15.3%) had cancer, 2 (2.8%) stroke and 17 (23.7%) other causes which include bronchiectasis, COPD, chicken pox, hepatitis, renal failure, and suicide. Only in 35 cases nothing other than TB

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could be suggested as a cause of death. Thus in 52 out of 87 (60%) cases, the causes of death were diseases other than TB.

Conclusion: Among the TB deaths in Alappuzha district, 60% of deaths were due to diseases other than TB. Along with early diagnosis of all TB cases, screening for co-morbidity, appropriate management of co-morbidity and periodic clinical review of TB patients should also be part of the major strategies to prevent TB related deaths.

1. Background

Tuberculosis (TB) is a major killer disease worldwide. TB is the ninth leading cause of death worldwide and the leading cause from a single infectious agent, ranking above HIV/AIDS. Worldwide in 2016 there were 10.4 million new cases and 1.67 million deaths.[1] TB kills an estimated 480,000 Indians every year and more than 1400 every day. Mortality due to TB is the third leading cause of years of life lost (YLLs), in the country. For the cohort of treatment experienced patients registered under the programme in the entire country during 2015, 8% died during the course of treatment.[2]

Vision of the National TB Control Programme is TB-Free India with zero deaths, disease and poverty due to TB. For the period 2016–2035, the national strategies for TB control has been aligned with WHO's End TB Strategy and the United Nations' (UN) Sustainable Development Goals (SDGs), which share a common aim to end the global TB epidemic. Specific targets set in the End TB strategy include a 90% reduction in TB deaths and an 80% reduction in TB incidence by 2030, compared with 2015. National Strategic Plan proposed for 2017–2025 for TB control in India aims to bring down the mortality due to TB from the current rate of 32/100,000 to less than 3 per 100,000 by 2025.[3]

Kerala is a rated as a well performing state as far as RNTCP is concerned with evidences for a lower level of TB transmission and drug resistant TB. RNTCP has registered 20969 cases in Kerala in 2016 with a notification rate of 69/100,000 population. Proportion of HIV cases among TB cases is less than 1% in the state. The state reported 5% deaths among the microbiologically confirmed TB cases in 2016. Even though Standards for Tuberculosis Care in India (STCI) emphasised the need to audit for all TB deaths, it is not being practised as a routine measure. Auditing is important to get an idea about cause of death in TB patients. Understanding about real cause of death is important to plan strategies to further prevent TB deaths. In the above circumstances we conducted a study, the objective of which was to find out the cause of deaths among patients registered in RNTCP unit of Alappuzha district of Kerala, India.

2. Methodology

Alappuzha is a coastal district of Kerala with a population of 2.12 million. RNTCP is in place since 2003 and the District TB control programme comprises of District TB Centre (DTC), Sub-district-TB Unit (TU), and Peripheral Health Institutions (PHIs). There are four TUs in the district, each comprising of 18–23 PHIs. The private sector comprises of private clinics run by single practitioners and polyclinics or hospitals with multi-specialty services.

In RNTCP a patient who died during the course of treatment regardless of cause is declared as 'Died' due to TB. During the year 2015, 1618 cases were registered in RNTCP of Alappuzha district of which 90 patients died, showing a case fatality rate of 5.56%. Proportion of deaths among TB patients who were registered for treatment under RNTCP in Alappuzha district in 2015 were as follows. New sputum positive – 5.8% (42/729, new sputum negative – 4.7% (17/360), new extra pulmonary – 4.6% (16/344), Category II – 8.3% (11/132) and others – 7.5% (4/53) – those who have previously been treated for TB but whose outcome is unknown or undocumented.

Verbal autopsy is a systematic approach for determining cause of death in population without routine medical certification.[4] It can be considered as an essential public health tool for studying reasonable estimate of the cause of death at a community level even though not an accurate method at individual level. Verbal autopsy ascertain the cause of a death based on an interview with next of kin or other caregivers. This is done using a standardised questionnaire that elicits information on signs, symptoms, medical history and circumstances preceding death. The cause of death, or the sequence of events that led to death, are assigned based on the data collected by a questionnaire and any other available information.[4]

As part of the study, we visited the 4 RNTCP units of the district and collected the address of the TB patients who died in the area. With the help of the field staff we visited their houses and filled the death audit form of RNTCP along with the additional details. Records including treatment details and death certificates were verified. Verbal autopsy was conducted with immediate household contacts. WHO verbal autopsy format 2012 was used.[4] The questionnaire had three versions, one for neonates, one for children and one for adults. In our study, as all the deaths were in adults, we used only the adult version. It has different sections to assess the socio-demographic characteristics of the deceased, symptoms and signs experienced before death, history of accidents, place of death and available health records. There is also open-ended question on the circumstances of death. Other factors like regularity of treatment, history of any default, personal history like smoking, alcoholism, history of co-morbidities like diabetes, HIV, lung cancer, etc. were also asked for using a pretested questionnaire. The details were discussed among the investigators on a case-to-case basis before assigning the

final cause of death. Data was entered in Microsoft Excel and analysed using SPSS version 16 software. Qualitative variables were analysed using percentages and proportions and quantitative variables using mean and SD.

3. Results

Total TB deaths reported among patients registered under RNTCP in Alappuzha district during the year 2015 were 90. Among them, three addresses could not be traced and another 15 patient relatives could not be contacted as they migrated out or were not available at their homes on two visits.

Socio-demographic characteristics are given in Table 1. Of the total 87 patients who died, 5 (5.7%) were less than 40 years of age, 30 (34.5%) between 41 and 60 years and 52 (59.8%) were above 60 years of age. Mean age was found to be 62.6 years (SD ± 12.9). Males were 67 (77%) and rest 20 (23%) were females. Mean age in males was 62.5 years (SD ± 12.1) and mean age in females was 63 years (SD ± 15.6). When education status was taken, only 2.8% were degree holders and the remaining had education below that. Majority (52.8%) were manual labourers. In this study 53 (60.9%) were smokers, 45 (51.7%) were alcoholics and 2 (2.3%) were drug abusers. Ten (11.5%) had history of contact with TB patients and the rest had no known contact.

Considering clinical characteristics, out of 87 patients, 13 (14.9%) presented within 2 months of developing symptoms, 34 (39.1%) presented between 3 and 6 months, 25 (28.7%) between 7 and 12 months and 15 (17.2%) of them presented only after one year. In the study, it was found that 71 (81.6%) were taking Category I treatment, 14 (16.1%) Category II and 2 (2.3%) Category IV treatment. It was observed that categorization was correct for all except one. Of the 14 patients who were categorised as Category II, 9 (10.3%) had relapse, 3 (3.4%) were defaulters and 2 (2.3%) had history of treatment failure. It was noted that 65 (74.7%) had pulmonary TB whereas 22 (25.3%) had extra pulmonary TB, of which 11 had pleural effusion, 3 had TB spine, 2 each had bone, miliary and intestinal TB and 1 each had meningeal and pericardial TB.

AFB smear finding showed 53 (60.9%) were positive and 34 (39.1%) were negative. Of those who were sputum positive, 8 (9.2%) had scanty, 24 (27.6%) had 1+, 7 (8%) had 2+ and 14 (16.1%) had 3+ bacilli. Repeat sputum at 2 months was positive for 9 (10.3%) patients and negative for 21 (24.1%), where as 52 patients (59.8%) died before that and not done for 5 (5.7%) patient. 52 patients (59.8%) died before two months of treatment (Intensive Phase) and 35 (40.2%) died after two months of treatment (Continuation Phase). Mean duration was found to be 2.53 months (SD ± 1.87). Median duration was found to be 2.0 months.

Regarding co-morbidities, 34 (39%) had diabetes mellitus, 16 (18.4%) had COPD, and 1 patient (1.1%) suffered from HIV infection. Cause of death was analysed after verbal autopsy for 72 deaths. Among 72 deaths, it was found that 29 (40.3%) had nothing other than TB, where as cause of death for 13 (18.1%) patients was myocardial infarction, 11 (15.3%) had cancer, 2 (2.8%) stroke and 17 (23.7%) other causes which include bronchiectasis, COPD, chicken pox, hepatitis, renal failure, and suicide. Cause of death was analysed for sputum positives (41), sputum negatives (12) and extra pulmonary (19) cases separately. For 15 patients, whose near relatives could not be traced, case records were used to find out the cause of death details and are shown in Table 2.

Three patients died due to hepatitis during treatment for TB, of which one patient had miliary TB who was also an alcoholic, another patient was alcoholic developed hepatitis after 5 months of ATT, one patient was a non-alcoholic but developed portal hypertension during treatment. All the patients who died due to renal failure had diabetes and were diagnosed with kidney disease before the initiation of anti TB treatment (Table 3).

Table 1 – Socio-demographic characteristics of study population.

Variable	Sputum +ve	Sputum −ve	Extrapulmonary
Age			
<60 years	21 (63.6)	5 (15.1)	7 (21.2)
≥60 years	32 (59.3)	8 (14.8)	14 (25.9)
Sex			
Male	47 (70)	9 (13.4)	11 (16.4)
Female	6 (11.3)	4 (30.8)	10 (47.6)
Category I	41 (56.9)	11 (15.3)	20 (27.8)
II	10 (76.9)	2 (15.3)	1 (7.7)
IV	2 (100)	0	0
Smoker			
Yes	38 (71.7)	8 (15.1)	7 (13.2)
No	15 (44.1)	5 (14.7)	14 (41.2)
Alcoholic			
Yes	32 (71.1)	6 (13.3)	7 (15.6)
No	21 (50)	7 (16.7)	14 (33.3)
Co-morbidities			
Nil	26 (61.9)	6 (14.3)	10 (23.8)
DM	15 (53.6)	5 (17.9)	8 (28.6)
COPD	8 (80)	2 (20)	0
DM + COPD	4 (66.7)	0	2 (33.3)
HIV	0	0	1 (4.8)
TRT duration			
≤2months	31 (59.6)	10 (19.2)	11 (21.2)
>2 months	22 (62.9)	3 (8.6)	10 (28.6)

4. Discussion

In Alappuzha district, the case fatality rate of TB was found to be 5.56%. A study done in Andhra Pradesh by Jonnalegade et al. had shown that 6% of patients registered in RNTCP died during treatment.[5] Case fatality rate was more among those had previously treated for TB and lower in those with extrapulmonary TB. In our study, 53 out of 87 (60.9%) were sputum positive. But the study conducted by Mukherjee et al. at West Bengal had shown that deaths were more in new smear negative patients when compared to new smear positive patients.[6] Regarding age of cases of death from TB, a study conducted by Yamamura et al. in Brazil observed that the younger individuals had TB as a cause associated with death.[7] But in our study 62% were above the age of 60 years (54 out of 87 deaths). A study conducted in Valliyur TU of Tamil Nadu by Kolappan et al. had shown that case fatality rate was 20.4% and was more in patients on Category II regimen, treatment failures and defaulters.[8] The excess general

Table 2 – Cause of death in patients during treatment for tuberculosis.

Cause of death		Smear positive		Smear negative		Extrapulmonary		Total
		Verbal autopsy + case records $n = 41$	Case records alone $n = 12$	Verbal autopsy + case records $n = 12$	Case records alone $n = 2$	Verbal autopsy + case records $n = 19$	Case records alone $n = 1$	$n = 87$
NCD related	Myocardial infarction	9	4	2	0	2	0	17
	Cerebrovascular accident	2	0	0	0	0	0	2
	Diabetic ketoacidosis	0	0	0	0	1	0	1
	Aortic aneurysm rupture	1	0	0	0	0	0	1
	Cancer lung	2	2	5	1	2	1	13
	Ca pancreas	0	0	0	0	1	0	1
	Ca larynx	0	0	1	0	0	0	1
Infections related	TB alone	19	5	2	0	9	0	35
	HIV	0	0	0	0	1	0	1
	DVT + cellulitis	0	0	0	0	1	0	1
	Chicken pox	1	0	0	0	0	0	1
Gastro intestinal related	Haematemesis	1	0	0	0	0	0	1
	Hepatitis	3	0	0	0	0	0	3
Renal related	Renal failure	1	0	0	0	2	0	3
Lung related	COPD	0	1	1	1	0	0	3
	Bronchiectasis	0	0	1	0	0	0	1
	Suicide	2	0	0	0	0	0	2
Total		53		14		20		87

mortality for the cohort expressed as SMR was 4.2 (95% CI 3.9–4.5). Kolappan et al. conducted another study at Corporation clinics of Chennai and found that the mortality rate among TB patients was 60 per 1000 person years.[9] The excess general mortality expressed as SMR was 6.1. younger patients, males, those with Category II disease, alcoholics, smokers, defaulters, failure cases, etc. had higher mortality rates when compared to the rest of the cohort. Rao et al. conducted a study in Nagpur city and found that the overall mortality rate for a period of 20 years from 1957 to 1976 was 92.1 per 1 lakh population.[10] Of the total, 32.8% had extra pulmonary TB, 18.6% had TB meningitis, 9.2% had TB intestine and abdomen, 1% had bone TB.

Table 3 – Socio-demographic and clinical characteristics of patients and cause of death.

	TB alone as a cause of death N = 35	Other causes N = 52
Age		
<60	12 (33.4)	21 (63.6)
≥60	23 (42.6)	31 (57.4)
Sex		
Male	27 (40.3)	40 (59.7)
Female	8 (40)	12 (60)
Category		
I	25 (34.7)	47 (65.3)
II	10 (76.9)	3 (23.1)
IV	0	2 (100%)
Smokers	23 (43.4)	30 (56.6)
Alcoholics	18 (40)	27 (60)
Co-morbidities		
DM	10 (35.7)	18 (64.3)
COPD	5 (50)	5 (50)
DM + COPD	3 (50)	3 (50)
HIV	0	1 (100%)
Duration of treatment		
≤2 months	23 (44.2)	29 (55.8)
>2 months	12 (34.3)	23 (65.7)

Gajalakshmi et al. conducted a study in Tamil Nadu and found that smoking which increase the incidence of clinical TB was the cause of half the male TB deaths in india.[11] In our study also 60% were smokers. A study conducted by Abhayneh et al. in Ethiopia showed a case fatality rate of 7.4% and also reported that 56.7% of deaths occurred during intensive phase of treatment and median time of death as 2 months.[12] In the present study also, 59% died in the intensive phase of treatment and the median time of death was 2 months. A study was conducted by Lee et al. in Korea and found that 56% of 36 early deaths were due to TB related causes, where as 84% of 38 late deaths were due to TB-unrelated causes.[13] In the present study only 40% of the total deaths were due to TB alone and the rest 60% had causes other than TB at the time of death.

Regarding cause of death it was found that out of 87 deaths, 36 were non-communicable disease related deaths which included myocardial infarction, stroke, cancers, etc. Four patients had lung related causes, three each had hepatitis and renal failure. Two patients committed suicide. One each suffered from HIV infection, chicken pox and cellulitis. Only in 35 cases nothing other than TB could be suggested as a cause of death. Thus in 52 out of 87 (60%) cases, the causes of death were diseases other than TB.

Analysis of causes of death of TB patients points to causes other than TB in approximately 60% of cases. These are, complications of diabetes, cardiovascular diseases, malignancies, liver and kidney failures, COPD, immune suppression, etc. Presently, screening for HIV and diabetes is a part of TB management policy in the state. However, screening for other co-morbidities are yet to start. All diagnosed TB patients are to be clinically screened for COPD, kidney and liver diseases, and other co-morbidities. This also highlights the need for

clinically reviewing the TB patients periodically to find out any co-morbidities and treat them. Comprehensive assessment of patients at diagnosis is needed to identify any red flag features which may indicate higher risk of complications including death. Death audits to be conducted for all TB deaths and actual causes have to be documented in the case based routine surveillance system.

Strength of the study included using a standardised tool and method to assess the cause of death by visiting all the patients in the community setting. Information has not been collected for cases outside RNTCP programme. The study has got important public health implications, by revealing the real causes of deaths and contributing factors among people who died due to TB.

To summarise, among the TB deaths in Alappuzha district, 60% of deaths were due to diseases other than TB. Along with early diagnosis of all TB cases, screening for co-morbidity, appropriate management of co-morbidity and periodic clinical review of TB patients should also be part of the major strategies to prevent TB related deaths.

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Conflicts of interest

The authors have none to declare.

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REFERENCES

1. World Health Organization. *Global Tuberculosis Report 2017*. Geneva: WHO; 2017.
2. Central TB Division. *Annual TB Report 2017*. New Delhi: Ministry of Health and Family Welfare; 2017.
3. Government of India. *National Strategic Plan for Tuberculosis Elimination 2017–2025*. New Delhi: Ministry of Health and Family Welfare; 2017.
4. WHO Verbal Autopsy Format 2012.
5. Jonnalagada S, Harries AD, Zachariah R, et al. The timing of death in patients with tuberculosis who die during antituberculosis treatment in Andhra Pradesh, South India. *BMC Public Health*. 2011;11:921. http://dx.doi.org/10.1186/1471-2458-11921.
6. Mukherjee A, Singla R, Saha I. Comparing outcomes in new pulmonary sputum positive and sputum negative cases under RNTCP in rural India. *Indian J Tuberc*. 2009;56(3):144–150.
7. Yamamura M, Santos-Neto M, dos Santos RAN, da Cunha Garcia MC, de Almeida Nogueira J, Alexandre Arcêncio R. Epidemiological characteristics of cases of death from tuberculosis and vulnerable territories. *Rev Latino-Am Enfermagem*. 2015;23(5):910–918.
8. Kolappan C, Subramani R, Kumaraswami V, Santha T, Narayanan PR. Excess mortality and risk factors for mortality among a cohort of TB patients from rural south India. *J Tuberc Lung Dis*. 2008;12(1):81–86.
9. Kolappan C, Subramani R, Karunakaran K, Narayanan PR. Mortality of tuberculosis patients in Chennai, India. *WHO Bull*. 2006;84(7):555–560.
10. Rao GR. Tuberculosis mortality in an urban complex in central India: a study of long term trends. *Tubercle*. 1982;63(3):187–193.
11. Gajalakshmi V, Peto R, Kanaka TS, Jha P. Smoking and mortality from tuberculosis and other diseases in India: retrospective study of 43000 adult male deaths and 35000 controls. *Lancet*. 2003;362(9383):507–515.
12. Abhayneh B, Gehnet T, Tariku D, et al. Time to death and associated factors among tuberculosis patients in Danglia Woreda, North West Ethiopia. *PLoS ONE*. 2015;10(12):e0144244. http://dx.doi.org/10.1371/journal pone.0144244.
13. Lee J, Nam HW, Choi SH, et al. Comparison of early and late tuberculosis deaths in Korea. *J Korean Med Sci*. 2017;32(4):700–703.

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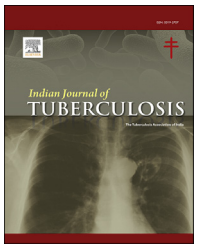

Original Article

Out of pocket expenditure on tuberculosis in India: Do households face hardship financing?

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ABSTRACT

Background: In 2017, India accounted for 27 percent of the global burden on tuberculosis, and the highest among the top 30 countries with high TB burden. Despite the expansion of DOTS programme many households in India incur high expenditure towards TB treatment. Most of the studies in India have focused on measuring catastrophic health expenditure on TB. Catastrophic health expenditure and its impoverishment effects are difficult to calculate and may misrepresent economic hardship.

Methods: This paper uses hardship financing, i.e. when a household sells assets or borrows money on interest to pay for healthcare expenditure, as an indicator of the hardship of the family when it spends on TB treatment using NSSO 71st Round 2014 data.

Results: Using the NSSO national representative sample, the paper estimated that 26.7% of hospitalized cases and 3.5% percent of patients utilising outpatient care experience hardship financing due to TB in the country. 25.9% of the general population had to sell assets or used borrowings for financing TB hospitalization expenses. Education of head of household, income, type of health facility used, and number of hospitalized days were found to be significant factors influencing hardship financing.

Conclusion: Our study highlights that even with free care for tuberculosis, 21.3% were exposed to hardship financing, suggesting the need to re-look at the subsidy coverage of tuberculosis treatment in the country. The study also suggests the use of hardship financing as an alternative to catastrophic spending method as a index of effectiveness of tuberculosis control programme in the country.

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1. Introduction

As per the WHO Global Tuberculosis Report 2018,[1] approximately 10 million persons developed tuberculosis in 2017 worldwide (Men: 5.8 million; Women:3.2 million 1.0 million children). Two-third of these cases occurred in India, China, Indonesia, Nigeria, Pakistan and South Africa. India alone accounted for 27 percent of the global burden in 2017 and being the highest among the top 30 countries with high TB burden in the world.[1] In 2015, it has been estimated that 2.8 million new cases of TB were found in India. The TB mortality has increased from 2.2 lakhs in 2014 to 4.8 lakhs in 2017, and the annual incidence of Multi Drug Resistant (MDR) TB in India was 1.3 lakhs.[2]

The Revised National TB Control Programme (RNTCP) was formally launched in 1997, and expanded in a phased manner to all districts in the country by 2006.[3] The RNTCP adopted the internationally recommended Directly Observed Treatment Short Course (DOTS) strategy based on five principles: political and administrative commitment; good-quality diagnosis; uninterrupted supply of quality drugs; directly observed treatment (DOT); and systematic monitoring and accountability.[4] Using Bayesian evidence synthesis framework, it was estimated that, from 1997 to 2016, RNTCP has saved 7.75 million lives (95% Bayesian credible interval 6.29–8.82 million).[5]

Despite the DOTS, there is evidence that patients with TB symptoms often begin seeking advice in the informal private sector (chemists and unqualified practitioners), then seek care from qualified practitioners, and eventually end up in the public sector for free treatment.[6] A systematic review of tuberculosis care in India revealed that 48% of pulmonary TB and chest symptomatic first visited private/informal sectors. About three healthcare providers (HCPs) were consulted before reaching a diagnosis.[7] Private sector is also known to prescribe twice the amount of anti-TB drugs compared to the public sector.[8] Currently, 261 medical colleges, 150 corporate health units, 2946 NGOs and more than 18,000 private practitioners (PP) are involved in provision of RNTCP services, with the intensified Indian Medical Association public-private mix (IMA PPM) project being undertaken in 167 districts of 6 states.

Tuberculosis affects the most productive age group and thus causes enormous social and economic burden on the family and the society. It was observed that despite free diagnosis and treatment by government under the Revised National Tuberculosis Control Programme (RNTCP), the cost of TB to patients and their families is considerable. Direct costs include transportation, and in the private sector, diagnosis and medical treatment, and indirect costs include work lost or school missed for children. A 2018 study stated that 69% of patients undergoing treatment in the public health system spent half the average monthly individual income ($39.74, 2017 rates) in South India [9]. Most of the studies reporting economic burden of TB have reported that the majority of costs incur during pre-diagnosis and the intensive phase of treatment.[9–11]

In India, where majority of healthcare expenditure is out-of-pocket, the sources of financing are: paying from current income or savings, borrowing with zero interest (e.g. from family and friends), and borrowing with interest or selling assets. The sale of assets or borrowing money with interest entails additional costs, such as depletion of assets or interest.[12,13] Selling of assets may lead to costs, such as losses when assets are sold at less than optimum price or future income loss due to the sale of income-generating assets (like land or livestock). In this article, we assess the exposure of hardship financing that a household faces as a consequence of healthcare expenditure due to TB. This is in line with notions put forward by many recent studies.[13–16] We used the definition as described in John (2017),[14] Binnedjik (2012),[13] Vyas & Kummaranayake, 2006,[17] that 'a household selling assets or borrowing money with interest from bank, microfinance institution or moneylender, was exposed to hardship financing'.

The End TB strategy recommends measuring catastrophic costs incurred when the total costs exceed 20% of the annual household income.[18] Most of the studies in India have focused on measuring catastrophic health expenditure on TB.[19–21].However, catastrophic health expenditure and impoverishment are difficult to calculate and may misrepresent economic hardship, and an indicator such as hardship financing would be a more accurate indicator that captures the hardship of the family when it spends on healthcare.[22] With this backdrop, the present study estimates the out-of-pocket expenditure and exposure to hardship financing due to TB in India.

2. Study setting, data and methods

2.1. *Data source and sample size*

Data related to morbidity, health expenditure and sources of financing was retrieved from nationally representative survey data collected by the National Sample Survey Organisation (NSSO 71st round) during January to June 2014 on 'Social Consumption and Health in India'.[23] NSSO is a national organization under the Ministry of Statistics, established in 1950 to regularly conduct surveys and provide useful statistics on socio-economic status of households, demography, health, industries, agriculture, consumer expenditure, etc. NSSO 71st round survey covered 36 states/union territories 4577 villages, 3720 urban blocks and 65 932 households (36480 household in rural and 29452 household in urban). A total, 333 104 persons were interviewed. A stratified multistage sampling design was adopted. The details of the sampling weights as well as extensive information on survey design, data collection, and management procedures are described in the NSS report.[23]

The survey provides information about OOP health expenditures inpatient and outpatient care along with the various sources of financing. The sources of financing are classified as follows: (1) own income and savings, (2) borrowings (with or without interest), (3) resources from sale of assets, (4) contributions or assistance from friends and relatives (with or without repayment). The survey manual does not clarify whether the borrowings are with or without interest. Similar to approach mentioned in Joe (2015),[24] we have assumed here that borrowings may be mostly with repayment and with interest.

2.2. *Outcome variables*

The outcome variables for this study is mean out of pocket expenditure (OOPE) and sources of health financing for TB.

1. **Direct Medical costs:** Doctor's/surgeon's fee, Medicines, Diagnostic tests, Bed charges
2. **Indirect medical expenses:** Attendant charges, physio-therapy, personal medical appliances, blood, oxygen, etc.
3. **Non-Medical expenditure:** Transport for patient
4. **Productivity loss**: Due to foregone earnings emanating from lost days of work. For the productive work days lost, the analysis was restricted to adults only.
5. **Sources of health financing for TB:** The money may be spent from household income/savings, sale of cattle or draught animals, jewelry or other physical assets, financed by borrowing and contributed by friends and relatives as outright assistance and other sources.
6. **Hardship financing:** Hardship financing is defined as a situation when a household has to borrow money with

Table 1 – Profile of tuberculosis-affected individuals by their selected socioeconomic and demographic characteristics.

Background characteristics	Hospitalization		Outpatient care	
	Sample	Percentage	Sample	Percentage
Individuals characteristics				
Age (in years)				
0–14	55	12.78	33	11.71
15–35	158	31.52	101	35.67
36–59	201	34.36	106	42.12
60 and above	115	21.34	56	10.49
Education				
Illiterate	214	48.52	143	62.12
Up to Primary	141	27.02	58	21.26
Middle	73	10.86	37	7.27
Secondary and above	101	13.60	58	9.35
Gender				
Male	384	63.79	191	61.16
Female	226	36.21	107	38.84
Marital Status				
Never married	134	25.76	80	23.58
Currently married	339	61.06	181	70.58
Others	56	13.18	35	5.84
Household characteristics				
Religion				
Hindu	485	81.51	226	81.61
Muslim	66	14.68	42	13.17
Others	59	3.81	30	5.22
Caste				
ST	106	10.76	44	9.24
SC	143	23.79	78	18.27
OBC	231	41.10	114	60.03
Others	130	24.35	62	12.46
MPCE quintile				
Poorest	123	17.57	21	15.66
Poorer	139	19.33	56	21.43
Middle	115	25.35	49	15.30
Richer	98	16.56	69	20.81
Richest	135	21.19	103	26.80
Community characteristics				
Place of residence				
Rural	412	71.19	198	83.30
Urban	198	28.81	100	16.70
Region				
North	90	13.12	41	11.48
Central	152	22.81	78	29.38
East	141	29.99	57	32.27
Northeast	54	1.95	20	1.42
West	69	9.94	42	10.41
South	79	20.28	49	13.81
Union Territories	25	1.91	08	1.22
India	**610**	**100**	**289**	**100**

Note: All 'n' are unweighted. Total may not be equal due to some missing cases.

interest or to sell assets to pay out-of-pocket healthcare costs. For present study, hardship financing is defined as a situation when a household has to borrow money or to sell assets to pay out-of-pocket healthcare costs.

2.3. *Explanatory variables*

The independent variables included in the analysis are age of persons, education of persons, sex of person, marital status, religion, social group, wealth quintile, level of care, type of ward duration of stay in hospital, place of residence and regions of residence.

2.4. *Analytical approach*

Univariate analyses were conducted to identify the significant variables. In the firstpart of the analysis, estimation of out of pocket expenditure is calculated separately for hospitalization treatment and outpatient treatment by selected background characteristics and productivity loss. In the second step of the analysis, a multilevel regression model was fitted with three levels, individual/household (level 1), community (level 2), and state (level 3), to assess the influence of individual/household, community and state factors (fixed effects) on proportion of total household expenditure for treatment of tuberculosis [106–108]. The predictor variables were screened for multicollinearity. Variables with a Variance inflation factor (VIF) more than 10 were not included in the multilevel model. In the third step of analysis the Multivariate analysis was carried out to know the socio-economic differentials on hardship financing. In the fourth step of the analysis a logistic regression analysis was carried out to estimate the adjusted effects of selected covariates on hardship financing. To take into account the survey design (i.e. sampling weights with clustering and strata) while estimating bivariate and multivariate statistics, the SVY command was used in STATA.

3. Results

3.1. *Profile of tuberculosis-affected individuals*

Table 1 presents the description of tuberculosis-affected individuals by their selected socioeconomic and demographic characteristics in India categorized into utilising hospitalization and outpatient care. Males are affected more compared to females, with 36–59 years age group being more affected compared to other age groups. With respect to educational attainment, 48.5% (95% CI: 38.2–59.0) of hospitalised, and 62.1% (95% CI: 47.7–74.7) of outpatients were illiterate. Majority of those affected with TB resided in rural areas.

3.2. *Health facility utilization and duration of hospital stay for TB care in India*

51% of patients utilized private healthcare facilities for their outpatient care, compared to 36% utilising public hospitals for hospitalized care. Around half of the hospitalised cases received free treatment (57.9%, 95% CI: 48.7–66.5). Around 35.9% (95% CI: 29.2–43.3 of patients had length of stay in hospital for up to 5 days, and 37.4% (95% CI: 28.3–47.5) with length of stay of 6–10 days. Over 8.5% (95% CI: 5.9–12.1) patients had length of stay of 21 days or more in hospitals (Table 2).

3.3. *Out-of-pocket expenditure on TB care in India*

Table 3 presents the average direct medical, non-medical, and transportation cost incurred on outpatient care and hospitalization by selected socioeconomic and demographic characteristics in India. Patients in the age group 36–59 years spend more for hospitalization and outpatient care (₹18213.60 and ₹902.20) as compared to the younger (and older age group. The treatment cost did not differ much between males and females. Patients belonging to other castes who are socially advantaged spent more on hospitalization (₹15474.80) as compared to SC/ST/OBC, whereas for outpatient care ST patients spent the highest (₹1173.90). Persons who attend private hospitals spent three times more on hospitalization, and twice more for outpatient care as, compared to those who attend public hospitals. Urban households spent higher amounts than their rural counterparts on both hospitalization and outpatient care. Patients in special wards spent eight times higher than patients utilising treatment in free wards of public hospitals.

Table 2 – Health facility utilisation indicators for TB care.

Type of facility	Hospitalisation			Outpatient care		
	Sample	Percentage	95% CI	Sample	Percentage	95% CI
PHC/dispensary/CHC/mobile medical unit	33	6.41	[03.00–13.19]	32	12.87	[5.06–29.04]
Public hospital	346	56.86	[48.50–64.84]	126	35.23	[21.51–51.91]
Private hospital	231	36.73	[28.89–45.34]	128	51.90	[35.83–67.59]
Type of ward						
Free	355	57.85	[48.65–66.54]	–	–	–
Paying general	227	38.57	[30.20–47.67]	–	–	–
Paying special	28	3.58	[01.90–06.64]	–	–	–
Duration of stay in hospital						
Up to 5 days	236	35.96	[29.25–43.27]	–	–	–
6–10 days	186	37.39	[28.29–47.48]	–	–	–
11–20 days	112	18.17	[12.99–24.82]	–	–	–
21 and above	76	8.48	[5.88–12.08]	–	–	–

Table 3 – Direct and Indirect cost of illness on tuberculosis by selected socioeconomic and demographic characteristics.

	Hospitalisation (amount in ₹)							Outpatient care (amount in ₹)			
	Direct medical	Non-medical expenses	Transport for patient	Average number of workdays lost	Total OOP	Reimbursed by insurance	Net OOP	Direct medical	Non-medical expenses	Transport for patient	Total
Individuals characteristics											
Age (in years)											
00–14	10998.20	1732.80	277.40	9.10	13008.40	0.00	13008.40	242.20	109.20	88.90	440.30
15–35	10069.40	1439.60	504.50	9.60	12013.50	38.00	11975.50	663.50	71.90	119.70	855.10
36–59	15997.20	1653.30	563.10	10.00	18213.60	12.20	18201.40	500.40	277.10	124.70	902.20
60 and above	9649.80	1209.40	618.60	12.80	11477.80	17.40	11460.40	622.50	86.00	77.70	786.20
Education											
Illiterate	9245.50	1314.50	399.90	10.00	10959.90	15.40	10944.50	487.20	100.90	98.00	686.10
Up to Primary	11961.90	1629.10	466.80	11.30	14057.80	9.70	14048.10	271.80	82.80	96.20	450.80
Middle	13830.10	2049.10	937.80	9.40	16817.00	72.00	16745.00	1686.70	634.70	192.50	2513.90
Secondary and above	19692.70	1611.00	722.90	10.60	22026.60	14.50	22012.10	977.30	157.30	150.10	1284.70
Gender											
Male	12979.70	1715.90	584.20	11.00	15279.80	19.90	15259.90	471.80	117.40	102.70	691.90
Female	11080.10	1469.20	587.10	9.20	13136.40	13.50	13122.90	622.10	137.70	140.90	900.70
Marital Status											
Never married	12787.70	1823.70	523.20	10.10	15134.60	31.50	15103.10	536.60	136.30	120.20	793.10
Currently married	11883.90	1349.40	483.60	10.20	13716.90	17.50	13699.40	542.70	128.40	116.90	788.00
Others	10510.30	1599.60	677.70	11.60	12787.60	8.30	12779.30	386.60	91.80	73.30	551.70
Household characteristics											
Religion											
Hindu	12701.90	1738.00	618.10	10.40	15058.00	8.70	15049.30	460.00	119.10	94.80	673.90
Muslim	8865.80	1040.00	438.70	9.50	10344.50	0.00	10344.50	1052.10	159.50	192.80	1404.40
Others	17443.60	1548.60	421.60	11.70	19413.80	274.00	19139.80	448.30	93.70	120.80	662.80
Caste											
ST	11504.50	1843.40	872.90	15.50	14220.80	126.50	14094.30	283.50	57.10	141.70	482.30
SC	7858.20	1515.60	503.40	9.60	9877.20	0.00	9877.20	520.40	162.10	94.70	777.20
OBC	14039.90	1842.60	615.70	10.40	16498.20	8.30	16489.90	508.50	128.50	86.60	723.60
Others	13721.90	1264.70	490.30	8.80	15476.90	2.10	15474.80	812.60	141.10	220.20	1173.90
MPCE quintile											
Poorest	9923.20	1304.80	547.60	9.20	11775.60	18.10	11757.50	379.70	69.60	85.50	534.80
Poorer	13021.30	1826.10	788.30	10.90	15635.70	0.00	15635.70	654.40	176.70	134.30	965.40
Middle	7808.10	1492.10	594.50	9.50	9894.70	13.50	9881.20	621.60	162.80	76.30	860.70
Richer	9353.60	1551.10	487.80	11.50	11392.50	41.60	11350.90	670.90	105.20	148.90	925.00
Richest	21385.50	1893.10	486.20	10.80	23764.80	19.20	23745.60	399.20	116.80	90.20	606.20
Community characteristics											
Place of residence											
Rural	10381.10	1639.20	626.10	9.70	12646.40	6.90	12639.50	487.40	117.90	118.90	724.20
Urban	16874.50	1575.70	484.00	11.90	18934.20	44.00	18890.20	787.30	194.80	96.40	1078.50
Region											
North	16208.00	2111.20	744.10	12.40	19063.30	4.00	19059.30	511.00	132.90	90.80	734.70
Central	15379.20	1684.40	801.60	9.00	17865.20	0.00	17865.20	464.40	52.00	57.00	573.40
East	8207.80	1397.00	514.10	10.30	10118.90	22.00	10096.90	539.60	151.70	184.80	876.10

Northeast	4658.10	1260.90	380.00	10.00	6299.00	536.80	5762.20	1814.20	481.30	387.20	2682.70
West	14135.80	1345.90	612.10	8.00	16093.80	0.00	16093.80	696.00	125.30	129.70	951.00
South	11634.90	1745.00	351.20	11.50	13731.10	0.00	13731.10	391.00	202.10	57.30	650.40
Union Territories	22246.80	2124.70	760.30	13.50	25131.80	0.00	25131.80	1888.90	393.70	157.60	2440.20
Health related indicators											
Level of care											
PHC/dispensary/CHC/ mobile medical unit	2410.30	437.90	246.60	5.90	3094.80	0.00	3094.80	195.40	50.00	48.10	293.50
Public hospital	6337.20	1486.50	521.80	11.70	8345.50	15.50	8330.00	327.90	167.10	133.80	628.80
Private hospital	21611.60	1940.80	736.10	9.00	24288.50	23.90	24264.60	726.60	133.50	115.30	975.40
Type of ward											
Free	4340.40	1366.80	448.00	10.80	6155.20	9.70	6145.50				
Paying general	18258.90	1958.30	742.50	9.30	20959.70	8.20	20951.50	–	–	–	
Paying special	54862.80	1800.80	1025.80	13.80	57689.40	244.60	57444.80	–	–	–	
Total	**12268.20**	**1621.50**	**585.20**	**10.30**	**14474.90**	**17.50**	**14457.40**	**532.50**	**126.80**	**114.60**	**773.90**

Details of expenditure.
1. Included. Doctor's/surgeon's fee (hospital staff/other specialists), medicines,. Diagnostic tests, Bed charges, Other medical expenses (attendant charges, physiotherapy, personal medical appliances, blood, oxygen, etc.).
2. Other non-medical expenses incurred by the household (Rs.) (food, transport for others, expenditure on escort, lodging charges if any, etc.).
3. Transport for patient.

Table 4 – Fixed and random intercept models predicting the effect of selected characteristics on the proportion of tuberculosis expenditure on hospitalisation over total household expenditure, in India, NSSO 2014.

Background characteristics	Model 1			Model 2		
	Random effects Household and cluster level			Random effects at Household, cluster and State level		
	β (Logit)	Standard Error	*p*-value	β (Logit)	Standard Error	*p*-value
Individuals characteristics						
Age (in years)						
00-14 *(ref)*						
15–35	−0.433	0.849	0.610	−0.063	0.731	0.931
36–59	−1.207	1.061	0.255	−0.823	0.942	0.382
60 and above	−1.255	1.139	0.271	−0.989	1.030	0.337
Education						
Illiterate *(ref)*						
Up to Primary	0.842	0.561	0.133	0.840	0.509	0.099
Middle	0.493	0.737	0.504	0.526	0.669	0.432
Secondary and above	1.204	0.701	0.086	0.786	0.644	0.222
Gender						
Male *(ref)*						
Female	0.761	0.453	0.093	0.814	0.400	0.042
Marital Status						
Never married *(ref)*						
Currently married	0.996	0.721	0.167	0.968	0.628	0.123
Others	0.968	0.976	0.321	0.648	0.851	0.447
Household characteristics						
Religion						
Hindu *(ref)*						
Muslim	−1.179	0.795	0.138	−1.269	0.797	0.112
Others	−0.599	0.843	0.478	−0.458	0.851	0.590
Caste						
ST *(ref)*						
SC	0.175	0.830	0.834	0.481	0.828	0.561
OBC	1.713	0.776	0.027	1.881	0.778	0.016
Others	0.579	0.859	0.500	0.385	0.853	0.652
MPCE quintile						
Poorest *(ref)*						
Poorer	−2.058	0.702	0.003	−1.991	0.666	0.003
Middle	−3.166	0.755	0.000	−3.061	0.728	0.000
Richer	−3.077	0.813	0.000	−2.702	0.776	0.000
Richest	−3.655	0.819	0.000	−3.412	0.810	0.000
Community characteristics						
Place of residence						
Rural *(ref)*						
Urban	−0.252	0.573	0.660	−0.196	0.582	0.736
Health related indicators						
level of care						
PHC/dispensary/CHC/mobile medical unit *(ref)*						
Public hospital	0.523	0.699	0.454	0.531	0.553	0.337
Private hospital	−0.446	0.969	0.645	−1.164	0.809	0.150
Type of ward						
Free *(ref)*						
Paying general	3.310	0.742	0.000	4.067	0.649	0.000
Paying special	5.588	1.087	0.000	5.663	0.913	0.000
Duration of stay in hospital						
Up to 5 days *(ref)*						
6–10 days	1.406	0.371	0.000	1.299	0.298	0.000
11–20 days	2.260	0.423	0.000	1.666	0.345	0.000
21 and above	3.534	0.579	0.000	3.452	0.490	0.000
Constant	0.760	1.203	0.528	0.442	1.092	0.686
Household level variance	15.248	5.911		8.438	3.690	
Cluster level random effect	7.990	6.016		16.844	4.209	
State level random effect				6.10e-19		
Residual	2.187	0.384		1.099	0.203	
log-likelihood/F test		−1514.071			−1497.462	

Table 5 – Socio-economic differentials on sources of financing for expenditure on tuberculosis in India.

Background characteristics	Hospitalization					Outpatient care			
	household income/savings	Borrowings	Sale of physical assets	Contributions from friends and relatives	Other sources	Household income/savings	Borrowings	Contributions from friends and relatives	Other sources
Individuals characteristics									
Age (in years)									
00–14	69.9	25.1	0.0	5.0	0.0	0.0	0.0	0.0	0.0
15–35	75.6	20.6	2.8	0.2	0.7	97.7	2.1	0.2	0.0
36–59	62.5	34.4	0.0	3.2	0.0	94.4	5.2	0.0	0.3
60 and above	74.0	18.4	0.0	7.5	0.0	95.6	0.0	4.1	0.3
Education									
Illiterate	69.3	27.5	0.2	2.9	0.0	97.6	1.7	0.4	0.3
Up to Primary	76.5	16.7	2.9	3.3	0.7	99.7	0.0	0.3	0.0
Middle	46.2	46.5	0.0	7.3	0.0	81.8	16.3	1.8	0.0
Secondary and above	78.7	18.8	0.0	2.2	0.3	92.3	6.9	0.8	0.0
Gender									
Male	65.7	30.2	0.2	3.9	0.1	96.0	3.1	0.8	0.1
Female	76.3	18.4	1.9	2.9	0.5	97.1	2.6	0.1	0.3
Marital Status									
Never married	76.1	21.3	0.0	2.5	0.2	97.3	2.7	0.0	0.0
Currently married	69.0	25.8	1.5	3.5	0.3	96.1	3.2	0.4	0.2
Others	63.0	32.2	0.0	4.8	0.0	96.4	0.0	3.6	0.0
Household characteristics									
Religion									
Hindu	67.3	27.5	1.0	3.9	0.3	95.9	3.4	0.6	0.2
Muslim	81.6	18.0	0.0	0.4	0.0	98.6	1.4	0.0	0.0
Others	70.5	22.9	0.0	6.5	0.1	98.9	0.0	1.1	0.0
Caste									
ST	57.1	28.4	6.4	6.0	2.0				
SC	59.2	35.6	0.4	4.8	0.0	93.9	4.0	1.9	0.1
OBC	70.9	25.4	0.0	3.7	0.0	96.9	2.6	0.3	0.2
Others	82.9	16.3	0.0	0.8	0.0	95.6	4.4	0.0	0.0
MPCE quintile									
Poorest	50.6	35.1	3.9	10.1	0.2	97.0	2.6	0.1	0.3
Poorer	62.6	32.2	0.5	4.6	0.1	90.3	8.3	0.9	0.5
Middle	68.3	30.8	0.0	0.2	0.6	98.5	0.8	0.7	0.0
Richer	85.1	12.0	0.0	2.9	0.0	99.0	1.0	0.0	0.0
Richest	80.9	17.6	0.0	1.5	0.0	97.4	1.8	0.8	0.1
Community characteristics									
Place of residence									
Rural	68.9	25.7	1.1	4.0	0.3	96.4	2.9	0.6	0.1
Urban	71.2	26.5	0.0	2.3	0.0	96.5	3.0	0.2	0.3
Region									
North	80.6	17.1	0.0	2.3	0.0	97.0	2.5	0.5	0.0
Central	73.5	22.5	0.0	3.8	0.2	97.8	1.6	0.2	0.4
East	63.1	29.7	2.6	4.6	0.0	94.6	5.3	0.2	0.0
Northeast	98.8	0.7	0.0	0.2	0.2	100.0	0.0	0.0	0.0
West	76.4	19.8	0.0	2.2	1.6	96.2	3.0	0.9	0.0
South	62.1	34.3	0.0	3.5	0.0	96.4	1.5	1.9	0.2

(*continued on next page*)

Table 5 – (continued)

Background characteristics	Hospitalization					Outpatient care				
	Household income/savings	Borrowings	Sale of physical assets	Contributions from friends and relatives	Other sources	Household income/savings	Borrowings	Contributions from friends and relatives	Other sources
Union Territories	62.0	36.5	0.0	1.2	0.4	100.0	0.0	0.0	0.0
Health related indicators									
Level of care									
PHC/dispensary/mobile medical unit	88.1	11.9	0.0	0.0	0.0	97.7	1.9	0.5	0.0
Public hospital	74.3	20.8	0.8	3.8	0.4	97.0	2.0	0.6	0.5
Private hospital	59.0	36.3	0.9	3.7	0.0	95.5	4.0	0.5	0.0
Type of ward									
Free	75.1	19.9	1.4	3.3	0.4	–	–	–	–
Paying general	62.7	33.2	0.0	4.1	0.0	–	–	–	–
Paying special	54.8	44.0	0.0	1.2	0.0	–	–	–	–
Duration of stay in hospital									
Up to 5 days	75.8	20.2	0.5	3.3	0.1	–	–	–	–
6–10 days	69.9	28.3	0.0	0.4	0.4	–	–	–	–
11–20 days	72.3	19.3	1.0	7.4	0.0	–	–	–	–
21 and above	35.7	53.8	5.2	5.2	0.0	–	–	–	–
Total	**69.6**	**25.9**	**0.8**	**3.5**	**0.2**	**96.3**	**3.0**	**0.5**	**0.2**

3.4. *Effect of tuberculosis expenditure over total household expenditure*

Table 4 shows the result of fixed and random intercept models predicting the effect of selected characteristics on the proportion of tuberculosis expenditure on hospitalization over total household expenditure, in India. All differences in the multilevel model are due to the variations between states rather than within states. This is confirmed in the three-level random intercept model where the cluster level random effect is not significant (Model 1), whereas it is significant in the two-level model (Model 2) after adjusting for the state effect. The results appear similar irrespective of whether we consider the fixed effect (not shown here) or random effect model. Further the Log-likelihood ratio test also suggest Model 2 as a better model compared to Model 1. As expected patient from the poor have a higher cost burden than patient from rich economic strata. Results indicate that, wealth quintile is negatively associated with proportion of tuberculosis expenditure over total household expenditure. Patients in the poorest quintile had higher proportion of tuberculosis expenditure over total household expenditure as compared to patient from the higher wealth quintile. (Richest, $\hat{a} = -3.655$, p-value 0.000), richer ($\hat{a} = -3.077$, p-value 0.000), Middle ($\hat{a} = -3.166$, p-value 0.000) and Poorer ($\hat{a} = -2.058$, p-value 0.003) Patients from the urban area have a lower cost burden than their rural counterparts but it was not statistically significant.

3.5. *Sources of financing for TB treatment*

Major share (around 96%) of healthcare expenditure comes from the bank account/savings of those who were seeking treatment from OPD compared to 69.6%% of those who were hospitalized (Table 5). In the overall population 25.9% had to sell assets or used borrowings for financing TB hospitalization expenses, while the percentage among SC and ST population stood at 70.8% in comparison to 16.3% among general population. The poorer and poorest had significantly higher use of sale of assets or borrowings compared to richer or richest groups for managing both outpatient and inpatient hospitalization expenses for TB treatment.

3.6. *Exposure to hardship financing*

Results indicates, that almost one-fourth (26.7%) of those who were hospitalized are exposed to hardship financing as compared to 3.0% percent of OPD patients (Table 5). Thirty seven percent of TB patients getting treatment in private facilities were exposed to hardship financing for hospitalization as compared to 21.6% of patients taking treatment in public facilities. 35.85% of lowest two wealth quintiles were exposed to hardship financing due to hospitalization.

3.7. *Determinants of hardship financing*

Further, this study explores the factors associated with hardship financing when paying for treatment cost (Table 6). It was observed that education of patient had a significant association with hardship financing. Only patients with middle level education were 3.2 times more likely to face hardship

Table 6 – Binary logistic regression results of determinants of hardship financing due to TB expenditure on hospitalisation as per socio-economic status (Dependent variable: exposure to hardship financing).

Background characteristics	Odds Ratio	95% CI	P-value
Individuals characteristics			
Age (in years)			
0-14 *(ref)*			
15–35	0.781	0.154–3.957	0.765
36–59	1.338	0.239–7.490	0.740
60 and above	0.509	0.065–3.983	0.519
Education			
Illiterate *(ref)*			
Up to Primary	0.900	0.388–2.087	0.805
Middle	3.199	1.202–8.519	0.020
Secondary and above	1.091	0.294–4.051	0.897
Gender			
Male *(ref)*			
Female	0.637	0.275–1.477	0.293
Marital Status			
Never married *(ref)*			
Currently married	2.009	0.522–7.730	0.310
Others	3.002	0.653–13.795	0.157
Household characteristics			
Religion			
Hindu *(ref)*			
Muslim	0.550	0.151–2.001	0.364
Others	0.613	0.104–3.610	0.588
Caste			
ST *(ref)*			
SC	1.016	0.305–3.382	0.979
OBC	0.966	0.350–2.668	0.947
Others	0.456	0.124–1.672	0.235
MPCE quintile			
Poorest *(ref)*			
Poorer	0.335	0.110–1.015	0.053
Middle	0.586	0.205–1.679	0.319
Richer	0.096	0.023–0.396	0.001
Richest	0.078	0.020–0.302	0.000
Sanitation facility			
Unsafe *(ref)*			
Safe	0.583	0.265–1.285	0.181
Drinking water			
Unsafe *(ref)*			
Safe	0.760	0.239–2.421	0.642
Cooking fuel			
Unsafe *(ref)*			
Safe	0.780	0.291–2.093	0.621
Community characteristics			
Place of residence			
Rural *(ref)*			
Urban	3.354	1.322–8.510	0.011
Region			
North *(ref)*			
Central	1.026	0.231–4.566	0.973
East	2.772	0.760–10.106	0.122
Northeast	0.082	0.009–0.736	0.026
West	1.333	0.319–5.574	0.693
South	2.280	0.628–8.282	0.210
Union Territories	3.994	0.187–85.393	0.375
Health related indicators			
level of care			
PHC/dispensary/CHC/mobile medical unit *(ref)*			
Public hospital	3.155	0.691–14.400	0.138
Private hospital	12.217	1.852–80.607	0.009
Type of ward			
Free *(ref)*			
Paying general	1.383	0.400–4.780	0.608
Paying special	1.207	0.213–6.833	0.831
Duration of stay in hospital			
Up to 5 days *(ref)*			
6–10 days	4.347	1.849–10.222	0.001
11–20 days	1.378	0.518–3.668	0.520
21 and above	16.404	4.776–56.338	0.000
Constant	0.092		
−2 Log likelihood	225.290	With chi2 92.43, p-value 0.000	
Nagelkerke R Square	0.178		
Hosmer and Lemeshow Test	5.71	With chi2 5.71, degree of freedom 8 p-value <1%	
Classification accuracy	77.07		

financing as compared to less educated or illiterate patients (OR = 3.2, CI = 1.2–8.5, p-value 0.02). The MPCE quintile showed a significant inverse association with hardship financing. Patient from the richer (OR = 0.096, CI = 0.023–0.396, p-value 0.001), richest (OR = 0.078, CI = 0.020–0.302, p-value 0.000) MPCE quintiles are less likely to experience hardship financing as compared to patient from the poorest MPCE quintile. There was no impact of sex of the patient on hardship financing. Length of stay in hospital had a significant relationship with hardship financing. Hospital stay of more than twenty days resulted in seven times more hardship financing (OR = 7.5, CI = 4.78–15.33, p-value 0.000), as compared to 5 days stay.The risk of experiencing hardship financing among patients whose stay was for 11–20 days (OR = 4.35, CI = 1.85–10.22, p-value 0.001) was four times more than those who stayed up to 5 days. Patients who undertook treatment from private healthcare facilities had a higher risk of hardship financing (OR = 10.22, CI = 1.85–60.61, p-value 0.009) as compared to those who took the treatment in PHC/dispensary/CHC/mobile medical unit facilities. The risk of seeking hardship financing for treatment was found to be higher (OR = 3.35, CI = 1.32–8.51, p-value 0.011) in urban areas as compared to rural areas. The northeast region showed less risk of hardship financing (OR = 0.08, CI = 0.009–0.73, p-value 0.026) as compared to North regions of India.

4. Discussion

Rising burden of tuberculosis, increasing healthcare costs and household health spending, warrants disaggregated analysis of the financial hardship faced by households in India. This paper is a first ever attempt by providing disaggregated estimates of OOPE and financial hardship faced by households due to tuberculosis. We have used the NSSO 2014 which is the latest nationally representative survey for our analysis.

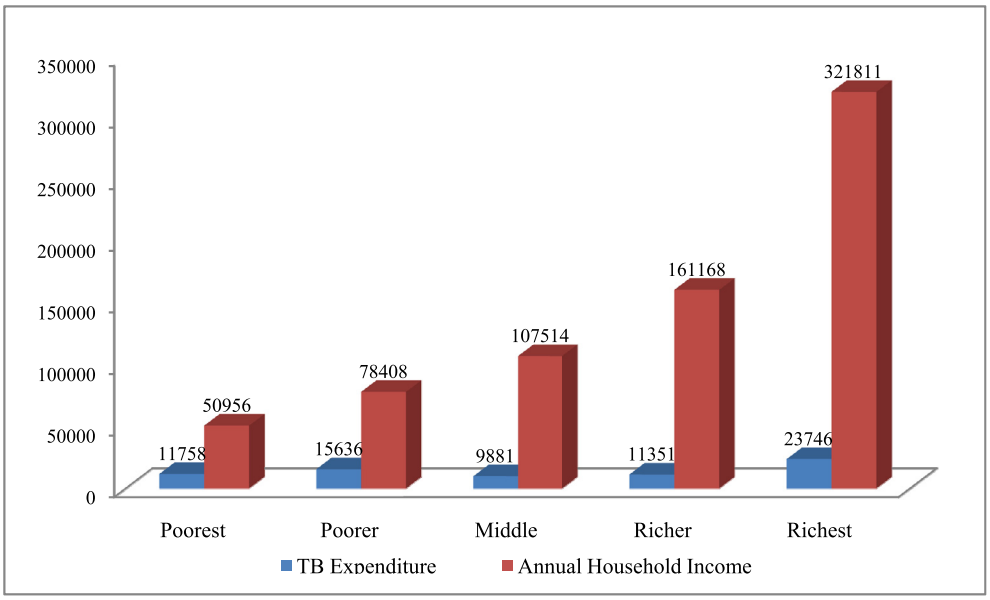

Fig. 1 – TB expenditure and average annual household income* (*- Author's analysis using IHDS-II data).

799 individuals (Hospitalised, n = 610, and Outpatient, n = 289) were reported to have tuberculosis within the overall sample. Proportionately more males than females were reported with tuberculosis among both hospitalised and outpatient cases. This is similar to other studies where TB prevalence is seen to be significantly higher among men than women in low- and middle-income countries,[25] and NFHS surveys,[26] although in cities such as Mumbai a higher proportion of women are reported to suffer from TB, as compared to others.[27] More males (30.4%) were exposed to hardship financing than females (19.3%). About 48.5% of hospitalised cases and 62.1% outpatient care patients were illiterates. This group spent the lowest on hospitalisation as compared to literate patients. However, illiterates constituted the second highest group exposed to hardship financing (29.4%) Educational attainment and literacy have been identified as barriers for accessing TB services by other studies.[28–30]

Scheduled Castes and Scheduled Tribes constituted 34.4% of those reporting tuberculosis in the sample. Though the outpatient expenditure was the lowest for scheduled castes, their hospitalisation expenses were the second highest, in comparison with other castes (ST – ₹14094.30, SC – ₹9877.20, OBC – ₹16489.90, Others – ₹15475.80). These groups also had higher exposure to hardship financing compared to other castes for hospitalisation (ST- 34.4%, SC– 36%, OBC-25.4%, Others-16.3%). These findings are important given the fact that the SC/ST groups have been found to have prolonged delays in seeking care for seeking tuberculosis treatment.[31] With regards to income categories, the lowest bottom two quintiles contributed to 36.8% and 37% of total hospitalisation and outpatient cases. In terms of healthcare expenditure, these two categories had average expenditures of ₹11757.50 and ₹15635.70 for hospitalisation, and ₹534.80 and ₹965.40 for outpatient care respectively These expenditures represent 23.07% and 19.94% of the total household income in these two categories (Fig. 1). Similar figures for the richer and richest quintiles were 7.04% and 7.37% respectively, whereas for middle income category the figure was 12.5%. The poorest and poorer categories, had 39% and 32.7% of hospitalised cases, and 2.7%, and 9.2% of outpatient cases respectively, exposed to hardship financing. In contrast, the upper two quintiles, i.e. richer and richest categories, had 12% and 17.6% for hospitalisation, and 1%, and 2.6% for outpatient care, were exposed to hardship financing. This is similar to many other studies that have reported the higher costs for TB of poorest populations.[32,33] Our regression analysis also shows that patients from richer MPCE quintiles are less likely to experience hardship financing as compared to patients from the poorest MPCE quintile.

In terms of healthcare utilisation, 56% of patients utilised private healthcare facilities for their outpatient care, compared to 57% utilising public hospitals for hospitalised care. Patients utilising hospital care in private facilities spent 3 times than those attending public facilities (₹8330 in private facilities, ₹24264.60 in public facilities). Patients attending private hospitals had higher odds of exposure to hardship financing as compared to public hospitals (37.2% in private, and 21.6% in public; OR: 12.2 95% CI: 1.8–80.6),) and were found to be significant $p < 0.009$). Majority (57.8%, 95% CI: 48.6–66.5 received free hospitalization. Those who reported spending for hospitalisation spent an average of ₹14457.40. Kastor & Mohanty (2018) found that only 0.1% of expenditure in private facilities and 0.2% of public of expenditure in public facilities were reimbursed.[34] This could be the reason that almost 21.3% of the patients who got free treatment were exposed to hardship financing.

WHO's End TB Strategy[35] while proposing aggressive action to reduce tuberculosis incidence and mortality, also highlights the need to reduce the related out-of-pocket costs and impoverishment, which can be catastrophic on households. Although the economic burden of tuberculosis of households in known to be high, most studies have focused on cross-sectional studies in one region or another.[19,20] A 2018 published study[34] looked into the healthcare utilisation, OOPE and catastrophic expenditure of TB among hospitalised cases

using NSSO 71st Round data. However, this is the first study that conducted a detailed analysis of NSSO 71st Round data of disaggregated data of TB cases utilising outpatient and inpatient care in private and public facilities.

In this article, we defined hardship financing as being exposed to a less stable or worsened financial state brought about by additional costs/losses due to borrowing or selling assets.[14] Since the questions about amount borrowed from each source and the rate of interest was not analysed we cannot quantify losses due to selling assets. In this study, we found that around one-fourth, i.e. 26.7 percent of the hospitalized cases and 3% percent of patients utilising outpatient care experience hardship financing. The association between selected household characteristics and exposure to hardship financing was assessed alongside individual socio-demographic characteristics that predict hardship financing. As an alternative to the catastrophic spending method, our study could play an important role in advancing the notion of hardship financing as a measure of effectiveness of health financing policy for tuberculosis in the country. However, there are some limitations to this study. The same findings would not apply elsewhere without adequate data. As with any health services utilization study, our study would also be influenced by the regular limitations of self-reporting of incidence of illness and costs of care with regard to data interviews with respondents.

5. Conclusion

This paper presents the disaggregated analysis of OOPE and exposure to hardship financing, i.e use of sale of assets or borrowing for financing hospitalisation or outpatient care, due to tuberculosis in the country. Our study presents that even with free care for tuberculosis 21.3% were exposed to hardship financing, suggesting the need to re-look at the subsidy coverage of tuberculosis treatment in the country. The recently announced Prime Minister Jan Arogya Yojana (PMJAY) with a hospitalisation coverage of ₹500,000 could provide some support.[36] However, the higher utilisation of private health facilities in comparison to public care for outpatient care prompts the need to conduct intensive social marketing efforts of DOTS programme. These efforts may be helpful in preventing many households from falling into the poverty trap due to tuberculosis in the country.

Author contributions

Conceptualization: Denny John & Geetha Menon.
Formal analysis: Jitendra Yadav.
Methodology: Denny John.
Supervision: Denny John & Geetha Menon.
Writing-original draft: Denny John & Jitendra Yadav.
Writing-review and editing: Denny John, Jitendra Yadav, and Geetha Menon.

Ethical approval

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Conflicts of interest

The authors have none to declare

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REFERENCES

1. *Global Tuberculosis Report 2018*. Geneva: World Health Organization; 2018. Licence: CC BY-NC-SA 3.0 IGO.
2. Central TB Division. *TB India 2017*. Central TB Division, Ministry of Health & Family Welfare, Government of India; 2017.
3. World Health Organisation. *A Brief History of Tuberculosis Control in India*. Geneva: World Health Organisation; 2010.
4. Raviglione MC, Pio A. Evolution of WHO policies for tuberculosis control, 1948-2001. *Lancet*. 2002;359(9308):775–780. https://doi.org/10.1016/S0140-6736(02)07880-7.
5. Mandal S, Chadha VK, Laxminarayan R, Arinaminpathy N. Counting the lives saved by DOTS in India: a model-based approach. *BMC Med*. 2017:15–47.
6. Finnie RK, Khoza LB, van den Borne B, Mabunda T, Abotchie P. Mullen PD Factors associated with patient and health care system delay in diagnosis and treatment for TB in sub-Saharan African countries with high burdens of TB and HIV. *Trop Med Int Health*. 2011;16(4):394–411.
7. Sreeramareddy CT, Qin ZZ, Satyanarayana S, Subbaraman R, Pai M. Delays in diagnosis and treatment of pulmonary tuberculosis in India: a systematic review. *Int J Tuberc Lung Dis*. 2014;18(3):255–266.
8. Arinaminpathy N, Batra D, Khaparde S, et al. The number of privately treated tuberculosis cases in India: an estimation from drug sales data. *Lancet Infect Dis*. 2016;16(11):1255–1260. pmid:27568356.
9. Veesa KS, John KR, Moonan PK, et al. Diagnostic pathways and direct medical costs incurred by new adult pulmonary tuberculosis patients prior to anti-tuberculosis treatment – Tamil Nadu, India. *PLoS One*. 2018;13(2):e0191591.
10. Foster N, Vassall A, Cleary S, Cunnama L, Churchyard G, Sinanovic E. The economic burden of TB diagnosis and treatment in South Africa. *Soc Sci Med*. 2015;130:42–50.
11. Ukwaja KN, Alobu I, Abimbola S, Hopewell PC. Household catastrophic payments for tuberculosis care in Nigeria:

incidence, determinants, and policy implications for universal health coverage. *Infectious Diseases of Poverty*. 2013;2:21.
12. Steinhardt LC, Waters H, Rao KD, Naeem AJ, Hansen P, Peters DH. The effect of wealth status on care seeking and health expenditures in Afghanistan. *Health Policy Plan*. 2009;24(1):1–17.
13. Binnendijk E, Koren R, Dror D. Hardship financing of healthcare among rural poor in Orissa, India. *BMC Health Serv Res*. 2012;12(1):23. https://doi.org/10.1186/1472-6963-12-23.
14. John D, Kumar V. Exposure to hardship financing for healthcare among rural poor in Chhattisgarh, India. *J Health Manag*. 2017;19(3):1–14.
15. Flores G, Krishnakumar J, O'Donnell O, van Doorslaer E. Coping with health-care costs: implications for the measurement of catastrophic expenditures and poverty. *Health Econ*. 2008;17(12):1393–1412.
16. Kruk ME, Goldmann E, Galea S. Borrowing and selling to pay for health care in low- and middle-income countries. *Health Aff (Millwood)*. 2009;28(4):1056–1066.
17. Vyas S, Kumaranayake L. Constructing socio-economic status indices: How to use principal components analysis. *Health Policy Plan*. 2006;21(6):459–468.
18. World Health Organisation. *The End TB Strategy: Global Strategy and Targets for Tuberculosis Prevention, Care and Control after 2015*. Geneva: World Health Organization; 2014.
19. Prasanna T, Jeyashree K, Chinnakali P, Bahurupi Y, Vasudevan K, Das M. Catastrophic costs of tuberculosis care: a mixed methods study from Puducherry, India. *Glob Health Action*. 2018;11(1):1477493.
20. Muniyandi M, Rao VG, Bhat J, Yadav R, Sharma RK. Household catastrophic health expenditure due to tuberculosis: analysis from particularly vulnerable tribal group, Central India. *Med Mycol Open Access*. 2015;2:9. https://doi.org/10.21767/2471-8521.100009.
21. Vergeut S, Riumall-Heri, Gomez GB, et al. Catastrophic costs potentially averted by tuberculosis control in India and South Africa: a modelling study. *Lancet Glob Health*. 2017;5(11):e1123–e1132.
22. John D. *As India Plans Healthcare Privatization, New Study From Rural Chhattisgarh Reveals Pitfalls*. Indiaspend; 2017. www.indiaspend.com.
23. National Sample Survey Organisation. *Key Indicators of Social Consumption in India, Health NSS 71st Round. National Sample Survey Organisation, Ministry of Statistics and Programme Implementation*. Government of India; 2015.
24. William J. Distressed financing of household out-of-pocket health care payments in India: incidence and correlates. *Health Policy Plan*. 2015;30:728–741.
25. Horton KC, MacPherson P, Houben Rein MGJ, White RG, Corbett EL. Sex differences in tuberculosis burden and notifications in low- and middle-income countries: a systematic review and meta-analysis. *PLoS Med*. 2016;13(9), e1002119.
26. Sharma PP, Kumar A, Singh P. A study of gender differentials in the prevalence of tuberculosis based on NFHS-2 and NFHS-3 data. *Indian J Community Med*. 2010;35(2):230–237.
27. Why There Might Be More Women Suffering from Tuberculosis in India than We Think. www.scroll.in, Accessed on October 11 2018.
28. Yang Wei-Tang, Gounder CR, Akande T, et al. Barriers and delays in tuberculosis diagnosis and treatment services: does gender matter? *Tuberc Res Treat*; 2014, 461935. https://doi.org/10.1155/2014/461935.
29. Storla DG, Yimer S, Bjune GA. A systematic review of delay in the diagnosis and treatment of tuberculosis. *BMC Public Health*. 2008;8(15).
30. Vissandjee B, Pai B. The socio-cultural challenge in public health interventions: the case of tuberculosis in India. *Int J Public Health*. 2007;52(4):199–201.
31. Rao V, Muniyandi M, Bhat J. Research on tuberculosis in tribal areas in India: a systematic review. *Indian J Tuberc*. 2017;65(1). https://doi.org/10.1016/j.ijtb.2017.06.001.
32. Oxlade O, Murray M. Tuberculosis and poverty: why are the poor at greater risk in India? *PLoS One*. 2012;7(11):e47533. https://doi.org/10.1371/journal.pone.0047533.
33. Muniyandi M, Ramachandran R. Socioeconomic inequalities of tuberculosis in India. *Expert Opin Pharmacother*. 2008;9(10). https://doi.org/10.1517/14656566.9.10.1623.
34. Kastor A, Mohanty SK. Disease and age pattern of hospitalisation and associated costs in India: 1995–2014. *BMJ Open*. 2018;8:e016990. https://doi.org/10.1136/bmjopen-2017-016990.
35. WHO. *End TB Strategy*. Geneva: WHO; 2015.
36. www.pmjay. Accessed October 11, 2018.

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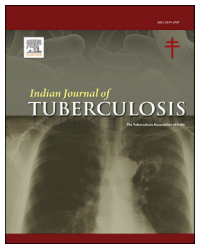

Original article

Profile of patients with pulmonary non-tuberculous mycobacterial disease mimicking pulmonary tuberculosis

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ABSTRACT

Introduction: With the introduction of newer molecular diagnostic tools, an increasing number of Non-tuberculous Mycobacteria (NTM) affecting the respiratory system and mimicking symptoms of pulmonary tuberculosis (PTB) are being identified. They may be misdiagnosed and treated as PTB, often categorized as treatment failures if they do not respond to treatment. This manuscript aims to characterize patients with pulmonary NTM disease.

Methods: Patient characteristics of bacteriologically confirmed pulmonary NTM disease, attending the ICMR-National Institute for Research in Tuberculosis, Chennai were prospectively compiled over a two-year period (2017–2018).

Results: A total of 122 patients with recurrent chest symptoms and not responding to anti-tuberculosis treatment were screened for NTM. Thirty-nine cases (26 males and 13 females) of symptomatic pulmonary NTM were diagnosed. The mean (SD) patient age and body mass index were 48.6 ± 11 years and 16.3 ± 3. All male participants were smokers, had at least one episode of previous ATT. *Mycobacterium kansasii* (48.7%) was the most frequently isolated species followed by *Mycobacterium intracellulare* (20.5%), *Mycobacterium abscessus* (7.6%) followed by *Mycobacterium avium, Mycobacterium fortuitum, Mycobacterium kyorinense, and Mycobacterium simiae*. Infection with multiple NTMs was seen in four patients. Isoniazid resistance was identified in 20 patients. Based on species identified, treatment was initiated as per American Thoracic Society guidelines and continued up to 12 months of culture negativity.

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Conclusions: *M. kansasii* is the commonest pulmonary NTM isolated in Tamilnadu with a higher prevalence in males and elderly. Sensitization of both patients and providers is essential to avoid misdiagnosis and delay in diagnosis of pulmonary NTM disease as pulmonary TB.

1. Introduction

Non-tuberculous Mycobacteria (NTM) is ubiquitous in nature and have been isolated from a variety of source like dust, soil, water etc.,.[1] Infection to humans is acquired from the environment and can affect various parts of the body including lymph nodes, lungs, skin, spleen, gastrointestinal tract.[2] It is reported that more than 90% of the NTM infections are pulmonary in origin with both geographic and ethnic variations.[3] Globally, the incidence of NTM ranges between 7.2 and 13.6/100,000 persons.[4]

Until recent times, the culture was not a routine part of diagnosing TB in India and hence is difficult to predict the exact magnitude of pathogenic NTM in our country. The evidence that they are present in our environment - *Mycobacterium avium-intracellulare* (MAI) being the most frequently isolated species (22.6% of all NTM) followed by *Mycobacterium terrae* (12.5%) and *Mycobacterium scrofulaceum* (10.5%) was shown very early by the Tuberculosis Research Centre, Chennai.[5,6] Later in the 2000s, many studies from other parts of the country have tried to correlate the presence of environmental NTMs with clinical samples from patients suspected of having pulmonary tuberculosis (PTB), but their role as pathogen was always doubtful.[7,8] In recent times, with the availability of improved molecular diagnostic testing, NTM infections are increasingly being diagnosed. The prevalence of NTM and identification rate in pulmonary diseases varied from 0.7% to 34% in India.[9,10] With the emergence of human immunodeficiency disease, a few studies have shown the presence of NTM in HIV infected patients in India.[11,12] Many NTM species are pathogenic to humans causing clinically significant disease requiring treatment. As the treatment for NTM varies with the type of species, rapid and reliable identification of NTM species is important.

For this to happen, early diagnosis of the correct mycobacterial species is the first step in treatment initiation and curing the patient. Treatment should be initiated based on the NTM species and the drug susceptibility test for a better response. However, treatment for symptomatic pulmonary NTM disease is not widely available through the Revised National Tuberculosis Control Programme (RNTCP). We report here a profile of patients with pulmonary NTM and their response to species-specific treatment, secondary to the identification of a species.

2. Methods

A prospective cohort of adults with symptomatic pulmonary NTM disease, where NTM was isolated on at least two consecutive sputum specimens, were being followed up at the ICMR-National Institute for Research in Tuberculosis (NIRT), Chennai from March 2017 to 2018. Patients referred for diagnosis of MDRTB using Line Probe Assay (LPA, Genotype MTBDR*plus* 2.0) under RNTCP, who were smear positive but were negative for MTB by LPA and culture were contacted through the referring center. These presumptive pulmonary NTM patients were further evaluated at NIRT. The study was approved by the institutional ethics committee of NIRT.

AT NIRT, symptomatic patients were screened and after obtaining an informed written consent, data were collected that included demographics including occupation, co-morbidities like diabetes, HIV and use of immunosuppressive agents, current symptoms of cough, fever, shortness of breath, fatigue, weight loss, hemoptysis etc., along with prior TB treatment history. Chest x-ray and blood for liver and renal function were done. After cleansing the mouth with lukewarm water, three consecutive sputum samples (2 early mornings and 1 spot specimen) were collected for AFB smear, culture, and species identification.

2.1. Sputum sample processing

All samples received from presumptive NTM patients, were processed using the N-acetyl-L-cysteine-sodium citrate-NaOH (NALC-NaOH) method.[13] Resultant sediments were re-suspended in 1 ml of phosphate buffer solution. The deposit inoculated onto Lowenstein–Jensen media (LJ) for mycobacterial culture. Any growths on the slopes were subjected to AFB smear and rapid immunochromatography test (ICT) (TBc ID, Becton Dickinson, Sparks, MD) as per standard or manufacturer's protocol. Cultures that were positive by AFB smear but negative by ICT were subjected to speciation using LPA (GenoType Mycobacterium CM/AS, Hain Lifescience GmbH, Nehren, Germany).[14] $H_{37}Rv$ was included as a positive control. The presence of distinct bands at positions 10 and 16 indicated a positive test for *Mycobacterium tuberculosis* complex. In case of growth exhibiting more than one type of morphology, speciation was done for all.

2.2. Treatment of pulmonary NTM

Based on the species identified, symptomatic patients were started on treatment as per the guidelines of American Thoracic Society (ATS) if they fulfilled any of the two criteria - clinical, bacteriological and radiological criteria.[15] Clinical criteria included combination of pulmonary symptoms of cough, fever, shortness of breath, fatigue, weight loss, hemoptysis with radiological criteria of nodular or cavitary opacities on chest x-ray or CT scan AND appropriate exclusion

of other diagnosis PLUS microbiological criteria of positive culture results from at least two separately expectorated sputum samples (If results from these were non-diagnostic, sputum AFB smear and culture were repeated) OR positive culture results from at least one bronchial wash. Treatment is being continued for 12 months post-culture negativity and patients followed for 12 months post-treatment completion.

2.3. *Drug susceptibility test*

Susceptibility of NTMs to drugs was done for the following - rifampicin, isoniazid, ethambutol, amikacin, kanamycin, ciprofloxacin, levofloxacin, moxifloxacin, linezolid, and clofazimine, depending on the species identified and the recommended treatment regimen by MGIT960 and/or microbroth dilution method. Sputum isolates have been stored for performing clarithromycin DST retrospectively, once the kit becomes available.

3. Results

3.1. *Characteristics of the study population*

One hundred and twenty-two patients were referred to as a presumptive case of pulmonary NTM from RNTCP centers, of which only 102 patients registered for further testing. Fifty-eight patients were referred back due to various reasons, species identification is awaited for five patients while 39 patients were started on appropriate treatment after the NTM species were identified (Fig. 1). Of the 39 patients started on treatment, there were 26 males and 13 females. The mean age and body mass index of the study population was 48.6 (SD: 10.7) and 16.3 (SD: 3.1) respectively. Age-wise categorization of the patients is shown in Table 1. In this cohort, 16 patients were current smokers; 22 patients had were alcohol users earlier of which 14 continued to consume alcohol during the current period also. A major proportion of this cohort were daily laborers (34%), home-makers (32%), involved in the textile business (13%) and drivers (11%). Two patients were air conditioner mechanics, one each of a farmer and watchman.

Table 1 – Demographic and Clinical Characteristics of the Study cohort (n = 39).

S. No.	Characteristics	Frequency N (%)
1	Age	
	21–30 years	3
	31–40 years	6
	41–50 years	11
	51–60 years	14
	61–70 years	5
2	Male Gender	26 (66%)
3	Height; mean (SD)	161.2 (10.7)
4	Weight; mean (SD)	42.6 (8)
5	Body mass index	
	<18	26 (67%)
	≥18	13 (33%)
6	Diabetes mellitus	
	Yes	4 (10%)
	No	35 (90%)
7	Smoking	
	Ever Smoked	22 (56%)
	Current Smoker	17 (44%)
8	Alcohol	
	Ever consumed	22 (56.4%)
	Current consumer	17 (43.6%)
9	Previous treatment for TB	
	Once	13 (33%)
	Twice	15 (39%)
	Thrice	10 (26%)
	Four times	1 (3%)

The commonest non-pulmonary co-morbidities in this cohort were diabetes mellitus (10%) and human immunodeficiency virus (HIV) infection (5%). Majority of them had been treated at least once previously for PTB and declared as either relapse or non-responders – 10 patients were treated with ATT once, 14 twice, 7 thrice and one patient was treated with ATT 4 times previously (Table 1).

3.2. *Clinical Presentation*

All patients presented with symptoms similar to PTB – cough, breathlessness, expectoration, and weight loss. Hemoptysis was reported in only seven patients (Fig. 2). Sputum smear by

Fig. 1 – Flowchart of Patient enrolled in NTM study.

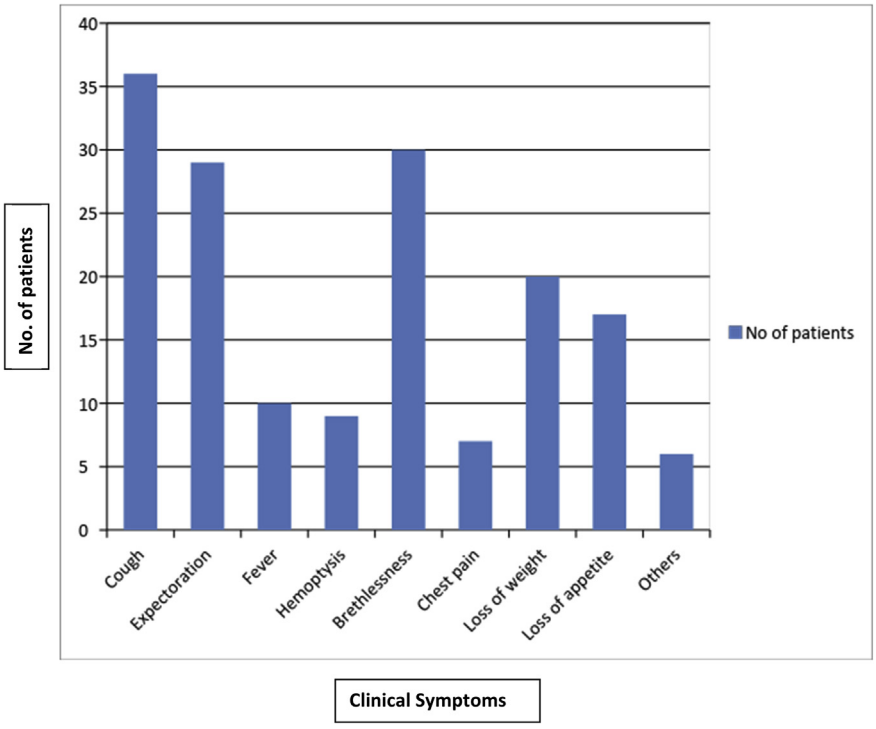

Fig. 2 – Clinical Presentation of Patients with Pulmonary NTM disease.

Fluorescence microscopy was positive in all patients. Chest x-ray showed bilateral lung involvement in 68.5% of patients and more than two zones were involved in 89% of the patients.

3.3. *Pulmonary NTM species isolated*

A total of 10 species of NTM were identified in this study. The three most frequently isolated pulmonary NTM were *M. kansasii* (49%), *Mycobacterium intacellulare* (21%) and *Mycobacterium abscessus* (8%). Six patients (15%) had multiple species identified in their sputum specimen – *M. abscessus* and *Mycobacterium intracellulare* were most frequently associated with multiple other species. The frequencies of the rest of the NTMs are shown in Table 2.

3.4. *Drug susceptibility*

Drug susceptibility testing was done only for *M. kansasii, M. avium, and M. intracellulare*. Of the 19 *M. kansasii* samples, 17 showed resistances to isoniazid with six being resistant to both isoniazid and ethambutol while one was resistant to isoniazid, ethambutol, and rifampicin (2 samples DST not done). Of the 8 *M. intracellulare* samples, six showed resistance to rifampicin and fluoroquinolones (moxifloxacin) and only one was sensitive to all drugs. *M. avium* identified was resistant to isoniazid, rifampicin, and ethambutol. DST was not done for *Mycobacterium simiae, Mycobacterium kyorinense, and M. abscessus*.

3.5. *Species-specific treatment regimens*

After identification of the species, appropriate treatment was initiated based on ATS guidelines (Table 3). During the course of treatment, results of the drug susceptibility test (DST) were received and if the patient was not responding to the current regimen, treatment was modified based on the DST profile. But, if the patient had become asymptomatic and his cultures had converted to negative, the same regimen was continued. Two patients died during the course of the study – one was a case of pulmonary *M. abscessus* and patient was irregular with her treatment, while the other was a case of mixed infection with 4 species, not responding to treatment. All patients were followed up for 12 months of post-culture conversion.

3.6. *Association of NTM isolates and age*

Most NTM isolates were found in male patients and those aged above 45 years. However, statistical significance was

Table 2 – Frequency of Pulmonary NTM species isolated from the study cohort.

S.No	NTM Species	Frequency N (%)
1	*M.abscessus*	3
2	*M.avium*	1
3	*M.intracellulare*	8
4	*M.kansasii*	19
5	*M. kyroninese*	1
6	*M.simiae*	1
7	*M.abscessus, M.gordoneae*	1
8	*M.abscessus, M.kansasii,*	1
9	*M.abscessus, M.fortuitum*	1
10	*M.abscessus, M.fortuitum, M.intracellulare,*	1
11	*M.abscessus, M.fortuitum, M.intracellulare, M.peregrinum,*	1
12	*M.kansasii, M.intracellulare, M.malmoense*	1

found only between the type of NTM isolate and gender of the patient and alcohol intake (Table 4). There was no statistically significant difference noted among NTM species and age groups.

4. Discussions

We demonstrate a unique profile of pulmonary NTM disease in Tamilnadu state. *M. kansasii* was the commonest pulmonary NTM isolate, followed by *M. intracellulare* and *M. abscessus*. The high prevalence of pulmonary *M. kansasii* in our cohort could be the result of its abundance in this region unlike that reported for northern parts of the country. Umrao et al, reported a higher prevalence of *M. abscessus*, *M. fortuitum* and *M. intracellulare* in the pulmonary specimen, while Maurya et al, reported *M. fortuitum and M. intracellulare* as the common NTM species in their respective cohorts from north India.[16,17] Our study portrays the diversity of NTM species in pulmonary specimens when compared with other published reports, highlighting the varied geographical distribution of NTM throughout India. Even in the international arena, there is much diversity in the NTM species causing pulmonary disease. A study involving 30 different countries from six different continents documented a higher prevalence of *M. avium* complex from North and South America and Europe. *M. intracellulare* was predominantly reported from South Africa and Australia.[18] It highlights the regional variability of various species of NTM.

In our cohort, we observed a higher proportion of males and alcohol users have a higher risk for NTM pulmonary disease. This is in agreement with previous studies considering gender and age as significantly associated with pulmonary

Table 4 – Prevalence of NTM isolates by Gender and Age.

	M. kansasii (n = 21)	*M.intracellulare* (n = 10)	Other species (n = 8)
Gender			
male	18*	3	5
female	3	7	3
Age			
≤ 40	7	2	1
>40	14	8	7
BMI			
< 18	14	7	5
≥18	5	2	3
Diabetes			
Yes	2	2	-
No	19	8	8
Smokers			
Yes	12	3	2
No	9	7	6
Alcohol			
Yes	13*	1	3
No	8	9	5
Prior ATT			
> 2 courses	6	4	1
≤2 courses	15	6	7

* = significance value of $p < 0.05$ between *M. kansasii* and the other two groups.

Table 3 – Species based Treatment regimens as per ATS guidelines.

Species	Regimen with dose	Duration and rhythm of treatment	Alternative regimen for resistance or failure
Mycobacterium avium complex – Fibrocavitary or Nodular disease	Clarithromycin* (500 mg bd or 1000 mg od) + Rifampicin (10 mg/d, max. of 600 mg/d) + Ethambutol (15 mg/kg/d)		Azithromycin (250 mg/d) instead of Clarithromycin or Rifabutin**(150–300 mg) instead of rifampicin
Mycobacterium avium complex – severe & extensive multilobar fibrocavitary disease	Clarithromycin* (500 mg bd or 1000 mg od) + Rifampicin (10 mg/d, max. of 600 mg/d) + Ethambutol (15 mg/kg/d) + Inj.Amikacin or Streptomycin for first 2–3 months		
Mycobacterium kansasii	Isoniazid (5 mg/kg/day, max.300 mg) + Rifampicin (10 mg/kg/d, max. 600 mg) + Ethambutol (15 mg/kg/d)	Daily for 12 months of negative sputum culture while on therapy	For H or E resistance: Clarithromycin, TMP-SFX, Ciprofloxacin, Levofloxacin For R resistance: Clarithromycin, TMP-SFX Ethambutol, Moxifloxacin,
Mycobacterium fortuitum	Clarithromycin + Doxycycline + TMP-SFX or levofloxacin	12 months of negative sputum culture while on therapy	
Mycobacterium abscessus	Clarithromycin (1000 mg) + Amikacin (10–15 mg/kg/d) + Cefoxitin (or Imipenem 500 mg bd or qid)	Daily. Intermittent Rx suggested in view of toxicity	Surgical resection
Mycobacterium malmoense	Optimal therapy is not known, but some microbiologic improvement has occurred with the use of combinations of INH, rifampin, and ethambutol, with and without quinolones and macrolides		

* = significance value of $p < 0.05$ between *M. kansasii* and the other two groups.

NTM, though we did not find a significant association with age.[4,19] The role of older age as a demographic risk factor for NTM infection has been described previously.[4] This could be either because of the anticipated rise in global aging or because older people are more prone to preexisting lung disease, which may favor NTM colonization and infection. With better and affordable healthcare facilities in the country, the population aged 55 years and above is expected to increase. Hence it is important to recognize pulmonary NTM infection and its association with age as an important public health issue with potentially significant consequences for affected patients and resources. Conditions that suppress cellular immunity like diabetes mellitus, malnutrition or HIV infection are known to predispose individuals to NTM infection and considered as important risk factors. In our cohort, we found a higher positivity rate of diabetes mellitus (10%) and lower HIV positivity rate (5%), in agreement with previous studies.[16] The higher prevalence of diabetes mellitus in this part of the country could also be another reason for the higher diabetic patients in our cohort.[20]

Furthermore, similar to the Singapore cohort, 40% of our study population had been treated previously for pulmonary tuberculosis with the suggestion of non-response to 6-months of short-course chemotherapy and recurrence.[19] This history suggests an underlying pulmonary disorder with bronchiectasis or other structural lung damage making them more prone to NTM infection. Risk factors for NTM pulmonary disease include prior TB, chronic obstructive pulmonary disease, cystic fibrosis, occupational lung disease etc.

NTM related diseases are on the rise now globally mainly due to improved isolation/identification techniques. The prevalence and type of pulmonary NTM isolated vary in different parts of the country.[21] Clinical presentations due to pulmonary NTM infections often mimic PTB. Hence they are often misrecognized and misdiagnosed as drug-resistant TB leading to undue delay in initiation of the correct treatment with a poor treatment outcome. In addition, a subclinical NTM infection that gets demonstrated in a patient on ATT is likely to be considered a treatment failure or a relapse. The clinical outcome of this cohort was not very satisfactory, further emphasizing the fact of recognizing pulmonary NTM early and treating them.

NTM isolated in culture can be identified by conventional biochemical methods which are elaborate and time-consuming. Chromatographic method like High Pressure Liquid Chromatography (HPLC) can also be used for speciation of NTM but it needs expertise and is also time-consuming. WHO introduced commercial, GenoType Mycobacterium common mycobacteria/additional species (CM/AS) assay (Hain Life science, Nehren, Germany) that differentiates and identifies different species of NTM from cultures. The CM kit identifies 15 mycobacterium species along with *M. tuberculosis* complex and the AS kit identifies 16 additional species which also covers the rare NTM species.

5. Conclusion

Our study presents the profile of patients with pulmonary NTM in Tamil Nadu, with *M. kansasii* being the commonest NTM isolated and a prediction towards older men and prior history of TB treatment. With an increasing capability to diagnose pulmonary NTM, it is necessary to treat them appropriately with species-specific treatment. This highlights the need to better understand the epidemiology, clinical response and economic burden of treating pulmonary NTM disease in the country.

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Conflicts of interest

The authors have none to declare.

Appendix A. Supplementary data

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REFERENCES

1. Falkinham 3rd JO. Environmental sources of nontuberculous mycobacteria. *Clin Chest Med*. 2015;36:35–41.
2. Piersimoni Claudio, Scarparo Claudio. Extrapulmonary infections associated with nontuberculous mycobacteria in immunocompetent persons. *Emerg Infect Dis*. 2009 Sep;15(9):1351–1358.
3. Kendall BA, Winthrop KL. Update on the epidemiology of pulmonary nontuberculous mycobacterial infections. *Semin Respir Crit Care Med*. 2013;34(1):87–94.
4. Cassidy PM, Hedberg K, Saulson A, McNelly E, Winthrop KL. Non-tuberculous mycobacterial disease prevalence and risk factors: changing epidemiology. *Clin Infect Dis*. 2009;49:e124–e129.
5. Paramasivan CN, Govindan D, Prabhakar R, Somasundaram PR, Subbammal S, Tripathy SP. Species-level identification of non-tuberculous mycobacteria from South Indian BCG trial area during 1981. *Tubercle*. 1985;66:9–15.
6. Kamala T, Paramasivan CN, Herbert D, Venkatesan P, Prabhakar R. Evaluation of procedures for Isolation of

nontuberculous mycobacteria from soil and water. *Appl Environ Microbiol*. 1994;60(3):1021–1024.
7. Parashar D, Chauhan DS, Sharma VD, Chauhan A, Chauhan SVS, Katoch VM. Optimization of procedures for isolation of mycobacteria from soil and water samples obtained in northern India. *Appl Environ Microbiol*. 2004;70(6):3751–3753.
8. Agarwal A, Jindal N. Isolation rates of nontuberculous mycobacteria from Amritsar. *Indian J Med Microbiol*. 2001;19:230–231.
9. Thomson RM. Changing epidemiology of pulmonary nontuberculous mycobacteria infections. *Emerg Infect Dis*. 2010;16:1576–1583.
10. Narang P, Narang R, Mendiratta DK, et al. Isolation of *Mycobacterium avium complex* and *M.simiae* from the blood of AIDS patients from Sevagram, Maharashtra. *Indian J Tuberc*. 2005;52:21–26.
11. Swaminathan S, Padmapriyadarsini C, Ramachandran R, et al. Localized pulmonary Mycobacterium avium disease in HIV-infected patients without access to HAART. *J Int Assoc Physicians AIDS Care (Chic)*. 2007;6(4):264–268.
12. Shah A, Stani A, Adalja M, George A. Immune reconstitution disease or mycobacteria other than tuberculosis or both: a dilemma in a patient of AIDS. *Indian J Sex Transm Dis AIDS*. 2012;33(1):44–46.
13. Morcillo N, Imperiale B, Palomino JC. New simple decontamination method improves microscopic detection and culture of mycobacteria in clinical practice. *Infect Drug Resist*. 2008;1:21–26.
14. Bruker-Hain Diagnostics, GenoType Mycobacterium CM VER 2.0. Accessed on 28th February 2019 from https://www.hain-lifescience.de/en/products/microbiology/mycobacteria/ntm/genotype-mycobacterium-cm.html.
15. Griffith DE, Aksamit T, Brown-Elliott BA, et al. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. Official statement of the American thoracic society (ATS). *Am J Respir Crit Care Med*. 2007;175:367–416.
16. Umrao J, Singh D, Zia A, et al. Prevalence and species spectrum of both pulmonary and extrapulmonary nontuberculous mycobacteria isolates at a tertiary care center. *Int J Mycobacterial*. 2016;5(3):288–293.
17. Maurya AK, Nag VL, Kant S, et al. Prevalence of nontuberculous mycobacteria among extrapulmonary tuberculosis cases in tertiary care centers in northern India. *BioMed Res Int*. 2015;2015:465403.
18. Hoefsloot W, van Ingen J, Andrejak C, et al. The geographic diversity of nontuberculous mycobacteria isolated from pulmonary samples: an NTM-NET collaborative study. *Eur Respir J*. 2013;42(6):1604–1613.
19. Lim AYH, Chotirmall SH, Fok ETK, et al. Profiling non-tuberculous mycobacteria in an Asian setting: characteristics and clinical outcomes of hospitalized patients in Singapore. *BMC Pulm Med*. 2018;18(1):85.
20. Anjana RM, Deepa M, Pradeepa R, et al. Prevalence of diabetes and prediabetes in 15 states of India: results from the ICMR-INDIAB population-based cross-sectional study. *Lancet Diabetes Endocrinol*. 2017;5(8):585–596.
21. Myneedu VP, Verma AK, Bhalla M, et al. Occurrence of non-tuberculous mycobacterium in clinical samples - a potential pathogen. *Indian J Tuberc*. 2013;60:71–76.

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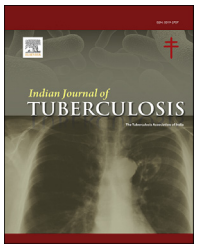

Original article

Is sterile pyuria another minor diagnostic criterion in urinary tuberculosis?

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ABSTRACT

Introduction: Composite reference standard (CRS) is used for diagnosis of urinary tract tuberculosis (UTB). We examined if addition of a new 'component test' as minor criterion in the form of SP could improve the yield.

Methods: We identified patients admitted with a diagnosis of UTB from January 2009 to February 2016 from our patient database. We performed the validation of addition of a new 'component' "sterile pyuria" to the existing basic CRS.

Results: SP was seen in 50 patients (65.7%). Forty (52.6%) of these patients had one major criterion positive and 10 (13.1%) were diagnosed based on minor criteria. If SP was added as a minor criterion, an additional 8 (9.2%) patients would have been diagnosed based on minor criteria alone without the need for a histopathology.

Conclusions: SP could improve the diagnostic yield of existing CRS by 8% with a 70% decrease in reliance on histopathology for diagnosis.

1. Introduction

Tuberculosis (TB) of the urinary system (UTB) constitutes 15–20% of extra pulmonary TB.[1] A high index of suspicion is necessary for timely diagnosis of UTB to reduce morbidity and mortality.[2] Chaudhary et al proposed diagnostic criteria in 2004 to aid in the diagnosis of UTB.[1] This composite reference standard (CRS) is being employed in UTB because of inherent difficulty in demonstrating mycobacteria by microbiological or histopathological methods in all patients.[1,2] Empiric anti-tuberculous therapy (ATT) is associated with seriousside effects like hepatotoxicity and optic neuritis and prolonged periods of ATT intake.[3] 'CRS' is formulated using a fixed rule to establish the final diagnosis based on the results of two or more 'component tests'.[1,4]

While employing these criteria, the urologist is faced with the problem that none of the major criteria or only a single minor

Abbreviations: TB, Tuberculosis; GUTB, Genitourinary tuberculosis; LUTS, Lower urinary tract symptoms; HIV, Human immunodeficiency virus; ESR, Erythrocyte sedimentation rate; IVU, Intravenous urogram; CECT, Contrast enhanced Computed Tomography; PCN, percutaneous nephrostomy; DJ, double J; VUJ, Vesicoureteric junction; DOTS, Directly observed treatment shortcourse; PCR, Polymerase chain reaction; ATT, Anti tubercular treatment.

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criterion is present in some patients and the treatment becomes empirical. Bladder biopsy in UTB has low sensitivity, needs general anesthesia and utmost care to prevent catastrophic complications like bladder perforation.[5] Subtle radiologic findings of UTB on intravenous urography (IVU) and treated pulmonary TB may be missed at times. Though sterile pyuria (SP) is frequently seen with UTB, interestingly, it has not found its way into the CRS yet. We aimed to identify the diagnostic yield of the existing criteria in suspected UTB and also examined if addition of a new 'component test' as minor criterion in the form of SP could improve the utility of the existing CRS.

2. Patients and methods

This was a hospital-based study performed at a tertiary care referral urological centre in South India. We identified patients admitted with a diagnosis of UTB from January 2009 to February 2016 from our patient database based on the Chaudhary et al CRS.[1] UTB treated empirically and patients with exclusive genital tuberculosis were excluded. Data pertaining to demographics, clinical presentation, blood and urine investigations, contrast radiological investigations including IVU or contrast enhanced computed tomography of kidney, ureter and bladder (CECT KUB), diagnostic cystoscopy with or without biopsy, surgical procedures and histopathology were recorded.

Major criteria include urine acid fast bacilli (AFB) positivity, urine positivity for polymerase chain reaction (PCR) and granulomatous lesion on histopathology examination (HPE). Minor criteria included radiological features suggestive of tuberculosis, hematuria, elevated erythrocyte sedimentation rate (ESR) and pulmonary changes consistent with healed pulmonary tuberculosis. Presence of one major or two minor criteria should be considered as UTB.[1]

We performed the validation of addition of a new 'component' "sterile pyuria" to the existing basic CRS proposed by Chaudhary et al, to formulate a new CRS based on appropriate statistical principles.[1,4,6] We identified the proportion of patients that could be diagnosed based on major criteria alone or various combinations of two minor criteria. We employed these criteria in a stepwise fashion and identified the number that was positive for major criteria and those patients who could be diagnosed when minor criteria are applied. Standard radiologic criteria suggestive of UTB included calyceal or infundibular stenosis, ureteric stricture, hydroureteronephrosis, shrunken bladder and poorly functioning kidney.[5,7,8] Cystoscopic findings suggestive of UTB included cystitis with tubercles on mucosa, ureteric orifice abnormalities and reduced capacity bladder.[5,8] We identified how many patients were diagnosed based on granulomatous pathology on HPE using cystoscopic biopsy and in how many patients diagnosis was reached only after nephrectomy when the other two major and all minor criteria were negative.

We then added SP as a new minor criterion and identified how many patients could be additionally diagnosed when only a single minor criterion was positive. We evaluated if including microscopic hematuria was useful in improving the diagnostic yield. We also examined in how many patients this addition could have avoided a cystoscopic biopsy for diagnosis of UTB when other criteria were negative. Based on these findings, we developed an algorithm to aid in the clinical diagnosis in patients suspected to have UTB.

3. Results

During the period, 76 patients with UTB conformed to the existing CRS.[1] The mean (±SD) age was 41 ± 13 years at presentation and 50 (65.7%) were males.

3.1. *Clinical presentation*

The most frequent symptoms in decreasing order of occurrence were irritative lower urinary tract symptoms (LUTS) constituted by increased frequency and/or nocturia and urgency in 49 (64.5%), dysuria in 42 (55.3%), pain abdomen in 26 (34.2%), low grade fever in 25 (32.9%) and hematuria in 23 (30.3%) patients. Eleven (14.5%) were treated for pulmonary TB in the past.

3.2. *Investigations*

Sterile pyuria (SP) was observed in 50 (65.7%) of patients. Microscopic hematuria was seen in 43 (56.6%) patients. The median (IQR) ESR was 40 (50.75) mm at the end of one hour. Elevated ESR (ESR >20 mm at one hour for males and >30 mm at one hour for females) was observed in 54 (71%) patients. Urine was positive for AFB in 23 (30.2%) and for PCR in 11 (14.5%) patients. Radiological changes on IVU or CECT KUB characteristic of UTB were seen in 59 (77.6%) patients. Diagnostic cystoscopy was performed in 40 (52.6%) patients and 34 (44.7%) had positive findings suggestive of UTB. HPE was positive in 15 (19.7%) out of 30 patients in whom cystoscopic biopsy was done.

3.3. *Applying diagnostic criteria (Fig. 1)*

Applying major and minor criteria in our patients, we were able to diagnose 57 (75%) patients on the basis of major criteria alone and 19 (25%) patients on the basis of minor criteria alone. Of the 57 patients diagnosed on major criteria, 3 (5.2%) had all 4 minor criteria positive, 18 (31.5%) had 3 minor criteria, 20 (35%) had 2 minor criteria and 8 (14%) had atleast one minor criterion positive. In 8 (14%) patients, none of the minor criteria were seen. The distribution of minor criteria in these 57 patients was raised ESR in 39 (68.4%) patients, radiological changes in 33 (43.4%), macroscopic hematuria in 18 (23.6%) and CXR changes of past pulmonary TB in 5 (6.5%) patients. The commonest minor criteria positive were radiological changes and raised ESR in 15 (78.9%) each, 3 (15.7%) had macroscopic hematuria and 6 (31.5%) had changes suggestive of TB in chest X-ray. Of note, radiological changes on IVU/CTU and elevated ESR were the commonest minor criteria positive across the whole data set and a combination of atleast these two was positive in 50 (65.7%) patients. We propose an algorithm in a stepwise manner based on the existing diagnostic criteria (Fig. 1).

3.4. *Addition of sterile pyuria (SP) (Fig. 2)*

SP was seen in 50 patients (65.7%). Forty (52.6%) of these patients had any one of the major criterion positive and 10

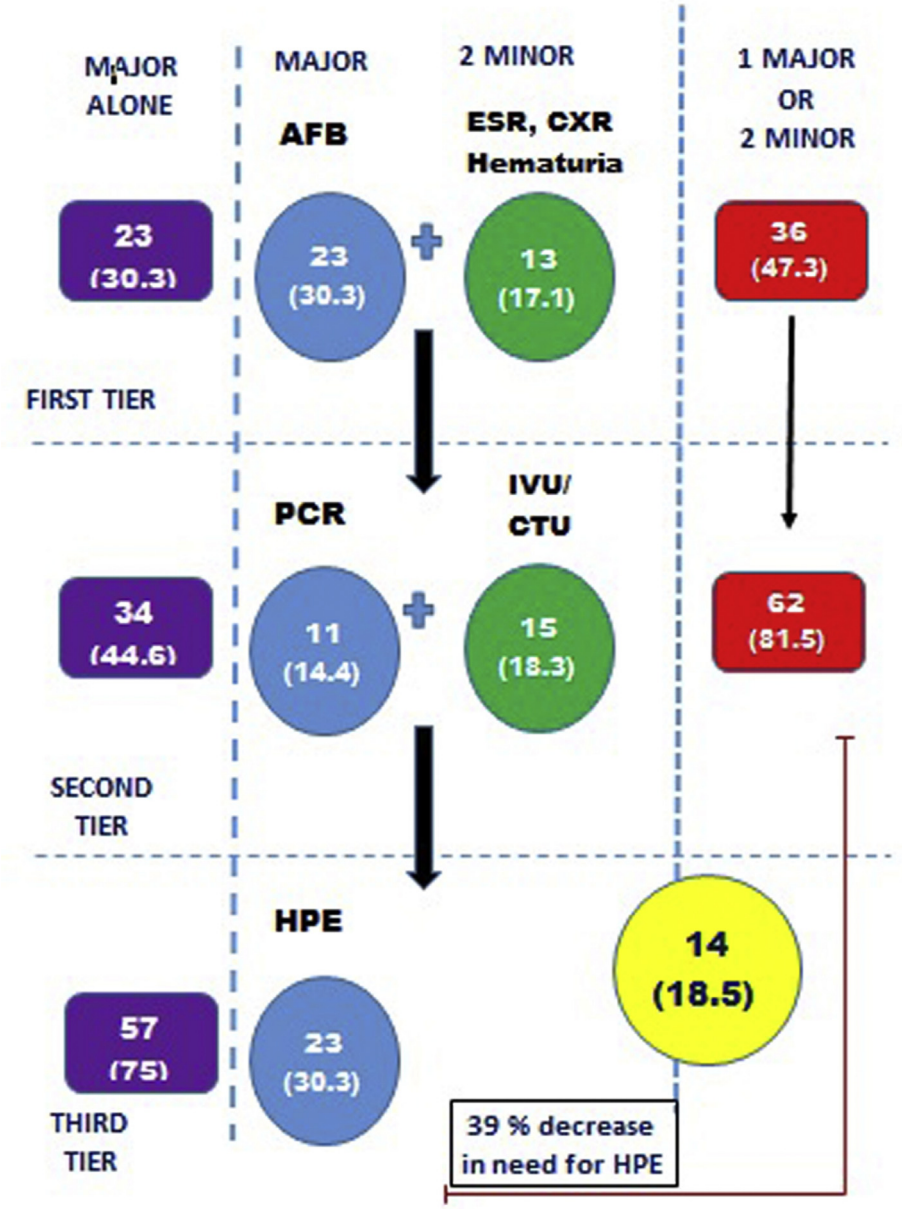

Fig. 1 – Flow chart depicting three investigational tiers for suspected urinary tuberculosis. Number of patients is indicated and percentages in parantheses. Numbers in boxes indicate the cumulative yield of diagnosis using major criteria alone (purple) or minor criteria also (red) as we investigated in a sequential approach. Numbers in yellow circle depicts the number of patients requiring HPE if minor criteria are strictly used for diagnosis. There is a decrease of 39% in patients requiring HPE to diagnose TB. AFB = Acid fast bacilli in urine; ESR = erythrocyte sedimentation rate; CXR = Chest X ray findings suggestive of past pulmonary tuberculosis; PCR = Urine TB-Polymerase chain reaction; IVU = Intravenous urogram; CTU = Computed tomography urogram; HPE = Histopathological examination.

(13.1%) were diagnosed based on minor criteria. If SP was added as a minor criterion to aid in diagnosis, it was observed that an additional 8 (9.2%) patients would have been diagnosed based on minor criteria alone without the need for a histopathological diagnosis. This increases the yield of minor diagnostic criteria to 26 patients (34.2% of total cohort), from the earlier 19 patients thereby precluding an invasive procedure like cystoscopic biopsy in 5 patients and waiting for histopathology of surgical specimen in 2 patients. Thus dependence on HPE as a major diagnostic criterion was brought down to 21.05% compared to the earlier 30.2%.

4. Discussion

Empirical treatment of UTB with ATT is associated with problems. There is no randomized trial examining the duration of ATT. There is often poor compliance to ATT due to its

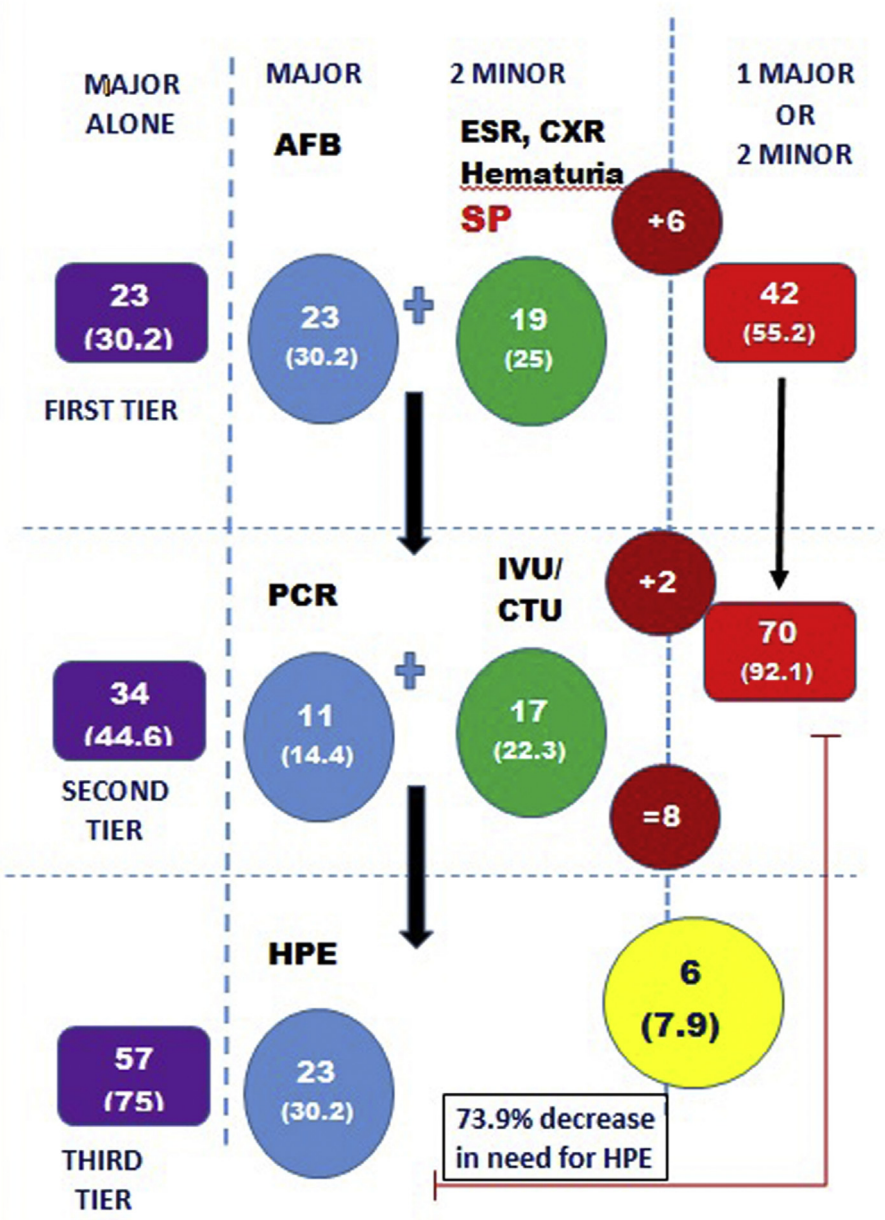

Fig. 2 – Effect of sterile pyuria(SP) added to minor diagnostic criteria. Number of patients is indicated and percentages in parantheses. Numbers in maroon circles indicate additional patients diagnosed if sterile acid pyuria is added as one of the minor diagnostic criteria. Number in yellow circle depicts the number of patients requiring HPE if sterile acid pyuria is added as one of the minor criteria. Close to 74% decrease in the utilization of HPE in diagnosis of TB. AFB = Acid fast bacilli in urine; ESR = erythrocyte sedimentation rate; CXR = Chest X ray findings suggestive of past pulmonary tuberculosis; PCR = Urine TB-Polymerase chain reaction; IVU = Intravenous urogram; CTU = Computed tomography urogram; HPE = Histopathological examination.

side effects. Drug-induced hepatotoxicity is an important complication necessitating temporary stoppage of its intake. Incidence of drug resistance and prolonged ATT intake in these patients also calls for proper diagnosis of UTB.[3] Before surgical management of UTB, ideally ATT is started 4–6 weeks prior to reduce bacillary load.[8] Cystoscopic biopsy has 18–52% sensitivity but is associated with chances of bladder perforation and morbidity.[5] These make the preoperative diagnosis of UTB imperative.

Most tests lack either sensitivity or specificity thus making diagnosis of UTB difficult. To overcome this problem, CRS is employed in UTB. CRS is formulated using a fixed rule to combine the results of two or more 'component' tests. This circumvents the problem associated with imperfect reference standard bias to generate a pseudo-reference. However CRS cannot completely eliminate this bias.[4,9] We tested the addition of SP as an additional 'component' test.

Table 1 – Composite reference standard for diagnosis of urinary tuberculosis with suggested revision.

Major Criteria	Minor Criteria
1. Urine positive for acid fast bacilli	1. Radiological (CECT/IVU) features suggestive of UTB
	2. Hematuria
2. Urine polymerase chain reaction positive	3. Elevated ESR
	4. Chest X ray suggestive of old healed pulmonary tuberculosis
3. Granuloma on histopathology	5. Sterile pyuria[a]

[a] Added by authors.

4.1. *Diagnostic criteria*

Chaudhary et al CRS are widely followed in our country. We applied these criteria and found them to be useful with 75% of cases diagnosed based on major criteria alone and minor criteria alone being diagnostic in 25%. However for the purpose of the current study, we did not include patients who were empirically treated as UTB and only one minor criterion was positive. In addition, we found that a combination of raised ESR and radiological changes was present in over 65% of the patients. We also found that if minor criteria had also been considered strictly, we could have possibly avoided diagnosis by biopsy in an additional 9 patients (11.7%) and only 14 (18.5%) patients would have required histopathological proof of tuberculosis.

Kapoor et al performed a Medline database literature search in 2008 and reviewed over 100 articles published from 1998-2007.[2] They used the criteria proposed in 2004 and proposed an algorithm to diagnose UTB in suspected cases.[1,2] The Association of Southern Urologists (ASU) published consensus guidelines in 2015 after reviewing a large number of available national and international publications and have recommended the use of these criteria.[10]

4.2. *CBNAAT*

Card based Nucleic Acid Amplification test (CBNAAT) is recently being reported to be a rapid and useful diagnostic test for tuberculosis. The sensitivity of Gene-Xpert MTB/RIF ranges from 83 to 95% and specificity ranges between 79 and 99% based on a systematic review in two good quality studies. Based on pooled analysis, this review reported a sensitivity of 87% and specificity of 91%.[11] In a recent report, the reported sensitivity was 69% and specificity was almost 100% in comparison with CRS.[12] This is a rapid test in which results are available as early as three hours. However cost is a limiting factor for Gene-Xpert in developing nations.[13] Results of PCR can be influenced by contaminants, drugs, metabolites and urea in urine.[11] CBNAAT reduces cross contamination and helps in rapid turnover of samples.[12] CBNAAT has been employed in peripheral centres for public health programs with good success.[14]

4.3. *Addition of sterile pyuria (SP)*

UTB is an important cause of SP after ruling out calculi, prior antibiotic therapy and tumor which can be diagnosed during evaluation. When we added SP as an additional minor criterion, we could diagnose 7.9% patients at first level when urine AFB was negative and ESR was elevated. When urine PCR and contrast radiological investigations were done, SP was able to detect an additional 10.6% in combination with radiology. We observed SP offered an increase in 18.5% which was beneficial to detect patients diagnosed on HPE (73.9% decrease) using cystoscopic biopsy or a diagnosis reached postoperatively after nephrectomy. This could reduce the number of cystoscopic biopsies to diagnose UTB. We propose the addition of sterile pyuria as an additional minor criterion to the existing CRS (Table 1).[1] A combination of positive CECT abdomen/IVU findings along with sterile pyuria can be the two key minor criteria to clinch the diagnosis of UTB.

4.4. *Limitations*

Our study had a few limitations. It was a retrospective record review and hence we included only those patients who were diagnosed to have UTB based on the standard criteria for UTB and assessed the effect of adding SP. Urine PCR/CBNAAT was underutilised in our study because of the non-availability and expense in the earlier period in the study.

5. Conclusions

We identified that the addition of SP could improve the diagnostic yield of existing criteria by 8% with a 70% decrease in reliance on histopathology for diagnosis. With modifications of the existing criteria, the use of cystoscopic biopsy as a tool to diagnose UTB in the absence of sufficient yield on other investigations or diagnosis only on postoperative HPE can be reduced substantially. Addition of SP, adding weightage for IVU and cystoscopy findings, microscopic or macroscopic hematuria and increasing the number of minor criteria necessary to diagnose UTB will increase the sensitivity and specificity of the existing diagnostic criteria. This should be validated at many urological centres after approval by experts.

Conflicts of interest

All authors have none to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijtb.2019.08.004.

REFERENCES

1. Chaudhary H, Mandhani A, Dubey D, Srivastava A, Kapoor R, Kumar A. Is contralateral renal involvement in genitourinary tuberculosis primary? *Indian J Urol*. 2004;20:19.
2. Kapoor R, Ansari MS, Mandhani A, Gulia A. Clinical presentation and diagnostic approach in cases of genitourinary tuberculosis. *Indian J Urol*. 2001;24(3):401–405.
3. Kadhiravan T, Sharma SK. Medical management of genitourinary tuberculosis Indian. *J Urol*. 2008;24:362–368.
4. Naaktgeboren CA, Bertens LC, van Smeden M, de Groot JA, Moons KG, Reitsma JB. Value of composite reference standards in diagnostic research. *BMJ*. 2013;347:f5605.
5. Figueiredo AA, Lucon AM. Urogenital tuberculosis: update and review of 8961 cases from the world literature. *Rev Urol*. 2008;10(3):207–217.
6. Alonzo TA, Pepe MS. Using a combination of reference tests to assess the accuracy of a new diagnostic test. *Stat Med*. 1999;18(22):2987–3003.
7. Merchant S, Bharati A, Merchant N. Tuberculosis of the genitourinary system-Urinary tract tuberculosis: renal tuberculosis-Part I. *Indian J Radiol Imaging*. 2013;23(1):46–63.
8. Chang AH, Blackburn BG, Hsieh MH. Tuberculosis and parasitic infections of the genitourinary tract. In: Wein AJ, Kavoussi LR, Partin AW, eds. *Campbell-walsh Urology*. 11th ed. Peters CA: Elsevier Philadelphia; 2016.
9. Tang S, Hemyari P, Canchola J. Composite reference standard in diagnostic research: a new approach to reduce bias in the presence of imperfect reference tests. *Biometrics Rev*; 2016. Available from: https://www.researchgate.net/profile/Jesse_Canchola4/publication/289376735_Composite_reference_standard_in_diagnostic_research_a_new_approach_to_reduce_bias_in_the_presence_of_imperfect_reference_tests/links/568c08e608ae197e42689358.pdf. Accessed June 27, 2019.
10. *South Indian Consensus on the Diagnosis and Management of Genito-Urinary Tuberculosis*; 12 July 2015. Available from: http://szusi.com/brochures/10.PUBLICATIONS/GUTB%20CONSENSUS.pdf. Accessed June 27, 2019.
11. Altez-Fernandez C, Ortiz V, Mirzazadeh M, Zegarra L, Seas C, Ugarte-Gil C. Diagnostic accuracy of nucleic acid amplification tests (NAATs) in urine for genitourinary tuberculosis: a systematic review and meta-analysis. *BMC Infect Dis*. 2017;17(1):390, 5.
12. Samuel BP, Michael JS, Chandrasingh J, Kumar S, Devasia A, Kekre NS. Efficacy and role of Xpert® Mycobacterium tuberculosis/rifampicin assay in urinary tuberculosis. *Indian J Urol*. 2018;34(4):268–272.
13. Pang Y, Shang Y, Lu J, et al. GeneXpert MTB/RIF assay in the diagnosis of urinary tuberculosis from urine specimens. *Sci Rep*. 2017;7(1):6181.
14. Boehme CC, Nicol MP, Nabeta P, et al. Feasibility, diagnostic accuracy, and effectiveness of decentralised use of the Xpert MTB/RIF test for diagnosis of tuberculosis and multidrug resistance: a multicentre implementation study. *Lancet*. 2011;377(9776):1495–1505.

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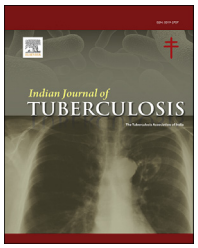

Original article

Phenotypic isoniazid resistance and associated mutations in pediatric tuberculosis

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ABSTRACT

Background and objectives: Tuberculosis (TB) remains one of the most challenging global health problems as resistance to first-line antimycobacterial drugs continues to rise in many countries worldwide. Isoniazid-resistant TB without MDR-TB poses a serious threat to the management and control of TB across the world. The aim of this study was to investigate the extent of *katG*315 and *inhA*-15 mutations in *Mycobacterium tuberculosis* strains isolated from pediatric TB patients from a tertiary care hospital.

Material and methods: A total of 51 pulmonary and extra pulmonary specimens were collected from clinically suspected pediatric TB cases, who were microbiologically confirmed. Resistance to INH was detected by 1% proportion method. *katG*315 and *inhA*-15 genes were amplified by PCR and detection of mutations in *katG*315 and *inhA*-15 genes was done by sequencing.

Result: A sample size of only 51 could be achieved due to short duration of the study. 36/51 (70.6%) culture isolates were obtained and put for drug susceptibility test, 5(13.89%) were resistant for isoniazid. *M. tuberculosis* DNA was found in fifty samples. Mutations in either *katG*315 or *inhA*-15 genes were found in 7/50 (14%) samples. Six of seven (85.7%) had mutation in *katG*315 gene and 1/7 (14.2%) had mutation in *inhA*-15 gene.

Conclusion: INH resistance not only reduces the probability of treatment success, but may also facilitate the spread of MDR-TB and reduce the effectiveness of INH preventive therapy (IPT) therefore quantification of the magnitude of INH resistant TB and variation in frequency of isoniazid resistance associated mutations is important.

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1. Introduction

Tuberculosis (TB) remains one of the most challenging global health problems as resistance to first-line antimycobacterial drugs continues to rise in many countries worldwide.Multidrug-resistant (MDR) TB and extensively drug-resistant (XDR) TB are increasing globally, with almost 4,80, 000 new MDR-TB cases and 1,90, 000 estimated deaths due to MDR-TB worldwide in 2017.Among the new TB cases, an estimated 3.3% have multidrug-resistant TB and this proportion is much higher (up to 20%) among the previously treated cases for TB. At least 1 million children become ill with TB each year and represent about 10–11% of all TB cases worldwide. According to World Health Organization (WHO) estimates 2, 10,000 children died of TB in 2017, hence the urgency to combat TB in children cannot be underestimated.[1]

Today, throughout the world isoniazid (INH) and rifampicin(RMP) together form the backbone of short course chemotherapy for *Mycobacterium tuberculosis (M. tuberculosis)* infection. Several studies have pointed out that strains resistant to INH and RMP already develop resistance to other antimicrobials; therefore, resistance to these antimicrobials is considered as marker for the detection of strains of MDR-TB. About 9.5% of TB cases globally (14% previously treated and 8.1% of newly diagnosed cases) are estimated to have isoniazid resistant TB without coexisting MDR TB.[2] This poses a serious threat to the management and control of TB across the world. Quantification of the magnitude of INH resistant TB is therefore important because INH resistance not only reduces the probability of treatment success, but may also facilitate the spread of MDR-TB and reduce the effectiveness of INH preventive therapy (IPT).[3]

INH exhibits mycobactericidal activity by inhibiting mycolic acid biosynthesis.[4] For isoniazid, mutations mainly in *katG* and *inhA* gene promoter, and infrequently in *ahpC*, *oxyR*, *kasA*, *furA* and *ndh* genes, confer resistance to the drug.[5] Approximately 64% of the phenotypic resistance to isoniazid globally is attributed to the *katG*/Ser315Thr mutation.[6] As mutations in *katG*, particularly at codon 315, confer high-level INH resistance, INH is ineffective for the treatment of *M. tuberculosis* with this mutation profile. The *inhA* regulatory region encodes nicotin-amide adenine dinucleotide-dependent enoyl-acyl carrier protein reductase, the primary target of active INH, as well as ethionamide and prothionamide.[6] *inhA* mutations cause low-level resistance to the drug, which means that high doses of INH may be effective against *M. tuberculosis*.[7]

TB control programs in many countries rely on rapid identification of cases for effective treatment of the disease. Importantly, the drug-resistant forms of TB require accurate diagnosis to guide therapy and interrupt transmission.[8] The conventional culture-based diagnostics for TB, often not available in the developing countries; are slow, labor intensive and expensive. The demand for rapid TB diagnostics led to the development and introduction of commercial molecular tests into practice. Two commonly used tests are the "Xpert MTB/RIF", which diagnoses TB and detects rifampicin resistance, and the GenoTypeMTBDRplus (line probe assay), which detects *M. tuberculosis* and its resistance to both rifampicin and isoniazid.[9,10] Molecular tests for TB target spontaneous point mutations in specific genes and/or loci in the *M. tuberculosis* chromosome that are associated with drug resistance. Regional variation in the frequencies of rifampicin and isoniazid resistance-conferring mutations has been reported and this could limit the sensitivity of molecular tests detecting resistance.[6,8]

The aim of this study was to investigate the extent of *katG*315 and *inhA*-15 mutations in *M. tuberculosis* strains isolated from pediatric TB patients from a tertiary care hospital.

2. Material and methods

2.1. Study design and setting

This was a cross sectional observational study conducted at the Departments of Microbiology, Pediatrics and DOTS centre; University College of Medical Sciences (UCMS) &Guru Teg Bahadur (GTB) Hospital, Delhi; during one and half year of the study period (2017–2019): All newly diagnosed pediatric TB cases ≤12 years of age were included in the study. Cases with a previous history of TB or taking antitubercular therapy were excluded from the study. Ethical Clearance was obtained from the Institutional Ethics Committee-Human Research.- Informed written consent was taken from the parents/ guardian of the study subjects prior to conducting the study and from children >7 years informed written assent was also obtained.

2.2. Specimen collection and processing

A total of 51 pulmonary (sputum, gastric lavage aspirate) and extra pulmonary (cerebrospinal fluid, pus, pleural fluid and lymph node aspirate) specimens were collected from clinically suspected pediatric TB cases, who were microbiologically confirmed by Zeihl Neelsen staining for acid fast bacilli and/or culture for M. tuberculosis and/or cartridge-based nucleic acid amplification test (CB-NAAT). Culture was accomplished on Lowenstein-Jensen (LJ) medium and the isolates were identified by standard microbiological methods such as Ziehl-Neelsen staining, colony morphology, pigment production, growth rate, para nitro benzoic acid test and MPT 64 antigen detection test. Specimens were decontaminated with N-acetyl L-cysteine (NALC) – 4% Sodium Hydroxide (NaOH) method, cultured on LJ medium and incubated at 37 °C for 3–10 weeks, until *M. tuberculosis*colonies appeared on the surface. Resistance to INH was detected by culturing bacterial suspensions (0.5 McFarland) on Lowenstein solid medium containing INH (0.2 μg/mL) according to 1% proportion method. *M. tuberculosis* was considered to be resistant to a drug only if the number of colonies obtained on drug containing medium was at least 1% of those obtained on drug free medium.[11] For all experiments, *M. tuberculosis* H37RV was used as the standard.

2.3. DNA extraction

DNA was extracted from clinical specimens or culture isolates (where required). HiPurA™*M. tuberculosis* DNA Purification Kit (HiMedia Laboratories Pvt. Limited, Nashik MH)

Table 1 – Microbiological profile of isoniazid resistant isolates showing phenotypic drug resistance by 1% proportion method.

S. No.	Type of TB (clinical specimen)	Smear microscopy finding for acid fast bacilli	CBNAAT result
1	Pulmonary TB (gastric aspirate)	Positive	Positive
2	Pulmonary TB (gastric aspirate)	Positive	Positive
3	Extra pulmonary TB (cerebrospinal fluid)	Negative	Positive
4	Pulmonary TB (gastric aspirate)	Negative	Positive
5	Pulmonary TB (gastric aspirate)	Positive	Positive

was used for DNA extraction according to the manufacturer's instructions.

2.4. PCR amplification

Preliminary detection of *M. tuberculosis* was done by the amplification of a 130 bp fragment of the insertion sequence *IS6110*. Primers used were: *IS6110F* (CTCGTCCAGCGCCGCTTCGG) and *IS6110R* (CCTGCGAGCG-TAGGCGTCGG). The primers used for PCR amplification and detection of mutations in *kat*G315 and *inh*A-15 genes were 250 bp and 245 bp respectively. Primers used were: *kat*G315F (GGCCCCGAACCCGAGGCTGC), *kat*G315R (AACGGGTCCGG-GATGGTGCCG) and *inh*A-15F (CCGCCGATGAGAGCGGTGAGC), *inh*A-15R (CCACTGCTTTGCCGCCACCGC).[12] The following thermocycler parameters were applied with initial denaturation at 95 °C for 5 minutes; 35 cycles of denaturation at 95 °C for 30 seconds; primer annealing at 60 °C for 30 seconds; extension at 72 °C for 30 seconds; and a final extension at 72 °C for 5 minute. The PCR product was amplified and purified again and checked on the gel electrophoresis. The final purified DNA obtained was used for sequencing.

2.5. DNA sequencing and data analysis

PCR products of the *kat*G315 and *inh*A-15 genes were purified using QIAquick PCR Purification Kit to remove contaminants. Purified DNA bands were run on agarose gel and quantified comparing the intensity of band with the DNA ladder (100ng/ul). Forward and reverse DNA sequencing reaction of PCR amplicon was carried out with gene specific forward and reverse primers using BDT v3.1 Cycle sequencing kit on ABI 3730xl Genetic Analyzer.

The obtained sequencing files were analyzed by sequencing analysis software, freely available web-based software NCBI Basic Local Alignment Search Tool (BLAST) (assessable at: http://blast.ncbi.nlm.nih.gov/). The sequencing data were compared with the corresponding sequences of *M. tuberculosis* strain H37Rv (http://genolist.pasteur.fr/TuberCuList/)

3. Result

Out of 51 clinical specimens 36 (70.6%) culture isolates were obtained and put for drug susceptibility testing for isoniazid by 1% proportion method. Out of the 36 culture isolates on which DST was done,5 (13.89%) were resistant for isoniazid. Table 1 shows the microbiological profile of these five phenotypically resistant isolates. Out of the five, 2 (40%) were smear negative.

DNA was extracted from fifty one clinical samplesor culture isolates (where required). Preliminary detection of *M. tuberculosis* was done by the amplification of a 130 bp fragment of the insertion sequence IS6110, found in fifty samples used for detection of*kat*G315 and *inh*A-15 genes. *kat*G315 and *inh*A-15 genes were detected in all fifty samples.

Mutations in either *kat*G315 or*inh*A-15 genes were found in seven (14%) samples out of the 50 PCR products subjected to

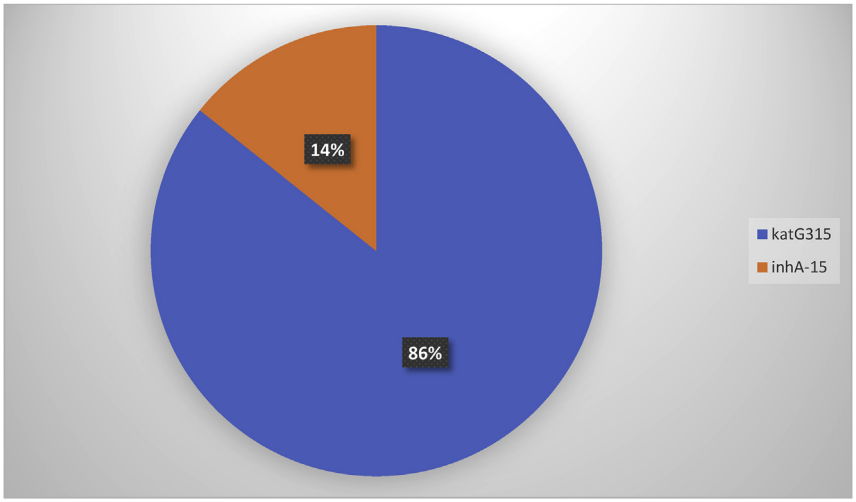

Fig. 1 – Frequency distribution of *kat*G315 &*inh*A-15 mutations for isoniazid resistance (n = 7).

sequencing. Six of seven (85.7%) had mutation in*katG*315 gene, causingAGC to ACC substitution and 1/7 (14.2%) had mutation in *inh*A-15 gene with C to T substitution (Fig. 1).

Out of these seven samples five (71.4%) were culture positive and demonstrated isoniazid resistance phenotypically. These five samples found only *katG*315 mutation. No mutations for *katG*315 and *inh*A-15 genes were detected in thirty one isoniazid drug susceptible isolates by phenotypic method. Two samples which were negative for culture were found to have isoniazid resistance associated mutation, one for *katG*315 andthe other for*inh*A-15 genes. Four out of seven samples (57.1%) that showed mutations for isoniazid resistance were smear negative (Table 2).

4. Discussion

This study addressed the extent of isoniazid resistance and associated mutations in *M. tuberculosis* among pediatric TB patients from a tertiary care hospital.Isoniazidresistance was found in 14% of culture positive pediatric TB casesby phenotypic method. These results were almost similar to an Indian study, which reported 8.7% resistance to isoniazid.[13] Results of a study from Pune among adults,in agreement with our study, reported 25% isolates resistant to isoniazid in combination with other drugs.[14] A recent study from Mumbai reported 6.6% prevalence of drug resistant TB among children. Among the total resistant isolates, isoniazid resistance was reported to be 96.8%.[15] In a study among the 148 isolates in whom drug susceptibility testing was undertaken, the overall prevalence of isoniazid resistance was 14.2%.[16] In a recent systematic review of 95 studies that included 8351 pediatric TB cases, the median proportion of children with isoniazid resistance was 8%.[17] Among the 51 microbiologically confirmed pediatric TB cases in our study, the proportion of children who had isoniazid resistance was 9.8%.The higher prevalence of isoniazid resistance has important implications. Isoniazid remains the cornerstone drug throughout the course of treatment for non-MDR-TB. It is also the drug of choice for chemoprophylaxis of TB in developing countries for treating latent TB infection and child contacts of infectious tuberculosis cases. So, the preventive therapy as well as the treatment would get compromised, if this drug is no longer effective. The widespread presence of isoniazid resistance in children also points to the need for alternative regimens to treat isoniazid-resistant tuberculosis in children. A significant proportion of children with latent tuberculosis infection (LTBI) may require alternative prophylactic regimens in terms of preventive treatment. Moreover, it is a predictor for MDR-TB in the future since MDR-TB has been reported to often develop from initial isoniazid mono-resistant strains.[18] A recent study reported a high proportion of treatment failure in INH-monoresistant patients, underscoring the importance of early detection and close monitoring of these patients with rapid diagnosis.[19] In comparison, identical outcomes were achieved between patients with INH-monoresistant TB and those with drug-susceptible TB when early diagnosis of resistance and tailored therapy were implemented.[20,21]

Isoniazid resistance associated mutation in *katG*315 and *inh*A-15 genes were present in 14% of our samples. *katG*315 mutation accounted for 85.7%.Hence, and as per RNTCP guidelines too, in children found to be resistant to isoniazid; isoniazid needs to be stopped and replaced by levofloxacin without further sequencing for inhA mutations if sufficient data suggest the same. Variation in frequency of isoniazid resistance associated mutations may be because of varied geographical distribution, circulating strain patterns and demographic, ethnic or epidemiological differences. Previous studies have identified highly variable frequencies of these mutations; with katG315 mutations accounting for 42 to 95% and inhA-15 mutations accounting for 6 to 43% of the phenotypic INH resistance.[22,23] In our case katG315 mutation accounted for 100% of the phenotypic isoniazid resistance and inhA-15 mutation was not present in any one of them, though, studies on greater sample size would be able to elucidate this further. In another study, out of 251 isoniazid resistant strains, 227 (90.4%) had detectable mutations: 75.3% in *kat*G codon 315 (*katG*315) and 28.2% in the *inh*A promoter region. *katG*315 mutations were significantly associated with pretreatment resistance to streptomycin, rifampicin, and ethambutol.Unfavourable treatment outcome was, however, significantly associated with *katG*315 mutations.[24] There is a higher probability of intra macrophage survival of bacteria having an *inh*A mutation than for the strains having *katG*315 mutation because of full catalase-peroxidase expression. So there is increased risk of relapse, in particular for *inh*A mutations, because the catalase-peroxidase release is a component of the bacterial *oxy*Rresponse which helps the bacteria to survive inside macrophages.[24]

Table 2 – Clinico-microbiological correlation among seven PCR products showing mutations for isoniazid resistance.

	Type of TB (clinical specimen)	Smear microscopy finding for acid fast bacilli	CBNAAT result	Culture finding on LJ medium	Phenotypic isoniazid resistance	Mutation on sequencing of *katG*315 and *inh*A-15 genes
1	Pulmonary TB (gastric aspirate)	Positive	Positive	Positive	Resistant	*katG*315
2	Pulmonary TB (gastric aspirate)	Positive	Positive	Positive	Resistant	*katG*315
3	Pulmonary TB (sputum)	Negative	Positive	Negative	*	*katG*315
4	Extra pulmonary TB (cerebrospinal fluid)	Negative	Positive	Positive	Resistant	*katG*315
5	Pulmonary TB (gastric aspirate)	Negative	Positive	Positive	Resistant	*katG*315
6	Pulmonary TB (gastric aspirate)	Positive	Positive	Positive	Resistant	*katG*315
7	Extra pulmonary TB (pus)	Negative	Positive	Negative	*	*inh*A-15

*2 samples were negative for culture.

Low-level resistance to INH can also confer resistance to ETH, while *M. tuberculosis* with high-level INH resistance is susceptible to ETH. Many studies have demonstrated that high doses of INH (16–18 mg/kg) may be safely used without increased risk of toxicity for the treatment of MDR- and XDR-TB in cases of low-level INH resistance.[6,7] The most significant finding of our study is the S315T mutation which seems to represent a mechanism of development of resistance to INH in the circulating strains in our environment. This biological behaviour could provide us with the opportunity to use S315T mutation in rapid diagnostic tools on newer platforms that would potentially detect at least 88% of resistant strains, which is particularly relevant in patients with treatment failure.Nearly 90% of INH resistance in India is caused by *kat*G mutations, associated with high-level resistance and poor treatment outcomes; the development of MDR-TB is preceded by development of resistance to INH. Our study being time bound, patients could not be followed up to know the treatment outcome. INH resistance at the time of initiation of treatment leads to an increased incidence of treatment failure and relapse as compared to the pan sensitive strains. Data from the most recent National workshop on DST-guided treatment in India reveals poor treatment success rates for INH mono resistant TB, ranging from 31% to 53%.[25] Studies will need to define clinical risk factors for INH mono resistance, perform universal DST to allow detection of INH resistance in all cases, and conduct prospective trials to determine optimal treatment regimens for patients with INH mono resistance.

Drug resistant TB is challenging to diagnose in a sick child because of the difficulty of obtaining a sample containing enough bacteria to enable drug susceptibility testing. Undiagnosed drug resistance can lead to the inadvertent use of ineffective treatment regimens for children, increasing their risk for treatment failure and death.Recognition of INH resistance patterns and the frequency of *kat*G and *inh*A mutations in different geographic areas may help to guide decision making about standardisation of treatment regimens or individualised treatment, mainly in MDR or XDR-TB cases as for such situations the availability of effective drugs is limited.

Conflicts of interest

The authors have none to declare.

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REFERENCES

1. World Health Organization. *Global Tuberculosis Report 2018*. Geneva: World Health Organization; 2018 [cited 27 February 2019]. Available from: https://www.who.int/tb/publications/global_report/en/.
2. World Health Organization. *WHO Treatment Guidelines for Isoniazid-Resistant Tuberculosis*. Geneva: World Health Organization; 2017 [cited 27 February 2019]. Available from: https://www.who.int/tb/areas-of-work/drug-resistant-tb/treatment/gdg-meeting-izoniazid-resistant-tb/en/.
3. Jenkins HE, Zignol M, Cohen T. Quantifying the burden and trends of isoniazid resistant tuberculosis, 1994–2009. *PLoS One*. 2011;6(7), e22927.
4. Takayama K, Wang L, David HL. Effect of isoniazid on the in vivo mycolic acid synthesis, cell growth, and viability of *Mycobacterium tuberculosis*. *Antimicrob Agents Chemother*. 1972;2:29–35.
5. Unissa AN, Selvakumar N, Narayanan S, Suganthi C, Hanna LE. Investigation of Ser315 substitutions within katG gene in isoniazid-resistant clinical isolates of Mycobacterium tuberculosis from south India. *BioMed Res Int*. 2015;20:15–36.
6. Seifert M, Catanzaro D, Catanzaro A, Rodwell TC. Genetic mutations associated with isoniazid resistance in Mycobacterium tuberculosis: a systematic review. *PLoS One*. 2015;10(3), e0119628.
7. Bollela VR, Namburete EI, Feliciano CS, Macheque D, Harrison LH, Caminero JA. Detection of katG and inhA mutations to guide isoniazid and ethionamide use for drug-resistant tuberculosis. *Int J Tuberc Lung Dis*. 2016;20(8):1099–1104.
8. Campbell PJ, Morlock GP, Sikes RD, et al. Molecular detection of mutations associated with first- and second-line drug resistance compared with conventional drug susceptibility testing of Mycobacterium tuberculosis. *Antimicrob Agents Chemother*. 2011;55(5):2032–2041.
9. Sekadde MP, Wobudeya E, Joloba ML, et al. Evaluation of the Xpert MTB/RIF test for the diagnosis of childhood pulmonary tuberculosis in Uganda: a cross-sectional diagnostic study. *BMC Infect Dis*. 2013;13:133–142.
10. Albert H, Bwanga F, Mukkada S, et al. Rapid screening of MDR-TB using molecular Line Probe Assay is feasible in Uganda. *BMC Infect Dis*. 2010;10:41–47.
11. Central TB Division. *Government of India. Revised National TB Control Programme Training Manual for* Mycobacterium tuberculosis *Culture & Drug Susceptibility Testing*. New Delhi: Central TB Division, Directorate General of Health Services, Ministry of Health and Family welfare, New Delhi, India; 2009:1–76.
12. Khosravi AD, Goodarzi H, Alavi SM. Detection of genomic mutations in katG, inhA and rpoB genes of *Mycobacterium tuberculosis* isolates using polymerase chain reaction and multiplex allele-specific polymerase chain reaction. *Brazilian J infect dis*. 2012;16(1):57–62.
13. Prajapati S, Upadhyay K, Mukherjee A, et al. Delhi Pediatric TB Study Group. High prevalence of primary drug resistance in children with intrathoracic tuberculosis in India. *Paediatr Int Child Health*. 2016;36(3):214–218.
14. Pereira M, Tripathy S, Inamdar V, et al. Drug resistance pattern of Mycobacterium tuberculosis in seropositive and seronegative HIV-TB patients in Pune, India. *Indian J Med Res*. 2005;121(4):235–239.
15. Shah I, Shah F. Changing prevalence and resistance patterns in children with drug-resistant tuberculosis in Mumbai. *Paediatr Int Child Health*. 2017;37(2):135–138.
16. Fairlie L, Beylis NC, Reubenson G, Moore DP, Madhi SA. High prevalence of childhood multi-drug resistant tuberculosis in Johannesburg, South Africa: a cross sectional study. *BMC Infect Dis*. 2011;11(1):28–36.
17. Yuen CM, Tolman AW, Cohen T, Parr JB, Keshavjee S, Becerra MC. Isoniazid-resistant tuberculosis in children: a systematic review. *Pediatr Infect Dis J*. 2013;32(5):e217–e226.
18. Abdella K, Abdissa K, Kebede W, Abebe G. Drug resistance patterns of Mycobacterium tuberculosis complex and associated factors among retreatment cases around

Jimma, Southwest Ethiopia. *BMC Public Health*. 2015;15(1):599–609.
19. Jacobson KR, Theron D, Victor TC, Streicher EM, Warren RM, Murray MB. Treatment outcomes of isoniazid-resistant tuberculosis patients, Western Cape Province, South Africa. *Clin Infect Dis*. 2011;53(4):369–372.
20. Bang D, Andersen PH, Andersen ÅB, Thomsen VØ. Isoniazid-resistant tuberculosis in Denmark: mutations, transmission and treatment outcome. *J Infect*. 2010;60(6):452–457.
21. Cattamanchi A, Dantes RB, Metcalfe JZ, et al. Clinical characteristics and treatment outcomes of patients with isoniazid-monoresistant tuberculosis. *Clin Infect Dis*. 2009;48(2):179–185.
22. Zhang Y, Yew WW. Mechanisms of drug resistance in Mycobacterium tuberculosis. *Int J Tuberc Lung Dis*. 2009;13:1320–1330.
23. Rattan A, Kalia A, Ahmad N. Multidrug-resistant Mycobacterium tuberculosis: molecular perspectives. *Emerg Infect Dis*. 1998;4:195–209.
24. Huyen MN, Cobelens FG, Buu TN, et al. Epidemiology of isoniazid resistance mutations and their effect on tuberculosis treatment outcomes. *Antimicrob Agents Chemother*. 2013;57(8):3620–3627.
25. Chatterjee S, Poonawala H, Jain Y. Drug-resistant tuberculosis: is India ready for the challenge? *BMJ global health*. 2018;3(4), e000971.

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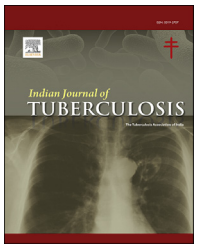

Original article

Fifth year of a public-private partnership to improve the case detection of tuberculosis in India: A role model for future action?

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ABSTRACT

Background: There is limited access to radiology facilities in most parts of India leading to significant under diagnosis and underreporting of smear negative clinically diagnosed tuberculosis (CDTB). Public Private Partnership (PPP) has a lot to contribute towards addressing this gap through providing access to chest x-ray (CXR) in far-off locations.

Method: Mobile vans equipped with digital CXR equipment and support staff were provided by a Corporate Hospital working closely with government, with scheduled visits to government peripheral health institutes. Patients received upfront CXR and sputum microscopy along with GeneXpert in accordance with the revised TB diagnostic algorithm prescribed by the national program, Following a successful pilot in 2014 in district Rewari, "TB free Haryana" was launched in November 2015 with a phased roll out in 16 districts by 2018.

Results: The pilot initiative in 2014 confirmed practical and clinical feasibility and revealed a high rate (30% of people screened) of CDTB i.e. symptomatic cases with radiologic abnormalities compatible with Pulmonary TB. In the first year (2016), 5 districts were covered and a total of 3340 CXRs were carried out. There was an increase in the case notification rates of new CDTB (smear negative) in 2016 compared to 2015 ($p = 0.036$); yielding an additional 180 cases and an 11.67% increase in case detection. Scale up to a total of 13 and 16 districts took place successfully in 2017 and 2018 respectively; with 6268 CXRs and 8021 CXRs done in the respective years.

Conclusion: PPP can involve Corporate Hospitals to improve the existing diagnostic infrastructure and provides access to CXR in a not-for-profit sustainable collaboration, with scale-up to the state level; and potential to replicate this initiative in other states.

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1. Introduction

India is one of the 20 high tuberculosis (TB) burden countries with an estimated 2740 000 new cases of TB and 421 000 TB deaths in 2017.[1] The Revised National Tuberculosis Control Program (RNTCP) reported a 35% gap in case detection in 2017.[1] This means we are missing millions of cases every year. Until we plug this gap, our dream of Ending TB will remain far from reality.

One of the strategies recommended by the national program is to actively identify these missing undiagnosed cases from the community, also known as active case finding (ACF). However, most of the ACF approaches have used sputum microscopy to identify bacteriologically confirmed cases, thereby missing smear negative cases also known as clinically diagnosed TB who continue to infect others. To target these missing cases who escape bacteriological tests, World Health Organization (WHO) has recommended CXR in combination with laboratory based diagnostic tests to contribute to earlier and accurate diagnosis of TB.[2]

In accordance with the global consensus, the recent Revised National Tuberculosis Control Program (RNTCP) guidelines in India have recommended a revised diagnostic algorithm in 2016, placing CXR early in the algorithm to be done simultaneously with sputum.[3] But this has remained in principle only as there is limited access to CXR facilities.

Private sector can play a crucial role in addressing this gap in diagnostic infrastructure. The role of the private sector in early diagnosis and improved case finding is outlined in the National Strategic Plan of the RNTCP. However, the precise future configuration of the Private Public Mix (PPM) in India is unclear and many such projects fail to sustain. Our goal was to contribute to improved TB diagnostic services within the state of Haryana alongside existing GOI health workers and algorithms through a PPM model.

As part of a PPM model, chest radiography facilities were provided by a corporate hospital to complement the microscopy and Xpert facilities available in the public sector in the state of Haryana. Using the digital chest x-ray (CXR) unit mounted on a mobile van and an enhanced case finding approach, the revised RNTCP algorithm was implemented to screen patients with presumptive TB for the presence of active TB under the TB-Free Haryana campaign. All patients with presumptive TB (i.e. cough more than two weeks) underwent sputum examination and digital CXR simultaneously. Patients eligible for Xpert according to the RNTCP guidelines were also referred for Xpert testing.

The project started as a pilot in Mewat district of Haryana in 2014 following its launch in 2015. During the period 2016–18, the project was expanded to 16 district of the state. We discuss here the development of this PPM during the period 2014–18 and the yields of this activity which promises early success and benefits that may be replicated elsewhere.

2. Method

2.1. Local setting

Haryana is a north Indian state with a population of 25.4 million in 21 districts, with very low HIV rates. Majority of the population (65%) lives in rural villages.[4] The notification rate of TB is 150/100,000 population, with a lower than expected level of smear negative rate of PTB.[5] The difficulty in accessing Chest x-ray (CXR) in rural villages was an identified gap in the diagnosis of PTB.

2.2. Project 'TB Free Haryana'

a) Pilot

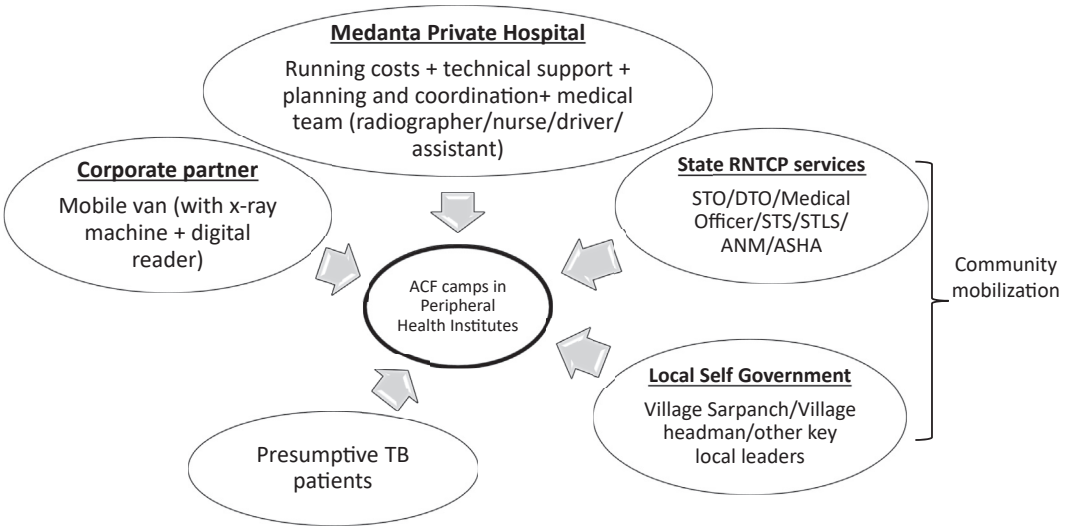
A pilot study was initiated to look at the potential benefit of improving access to CXR by employing a mobile digital X-ray van, the cost being met by the Corporate Hospital, along with a radiographer, driver, and administrator to collect basic patient information. A timetable for visits to Peripheral Health Institutes (PHIs) was prepared. Rural remote villages which have vehicular access were chosen by the District TB Officer (DTO). Using the RNTCP algorithm for the diagnosis of PTB,[3] villagers were identified by the local Accredited Social Health Activists (ASHAs) with cough lasting for more than 2 weeks, 2 negative sputum smear tests, and not-responding to antibiotics. CXR was recommended for all. The patient was asked to attend the local PHI for a timetabled van visit to get the CXR done. This pilot study ran from May to December 2014 and was evaluated as a worthwhile exercise.[6] This led to further engagement with various stakeholders including the corporate partners, GOI Central TB Division, USAID, and The Union, who were also very supportive of the project.

b) Expansion: "TB Free Haryana"

The project which started as a pilot in one district, was scaled up to 5 districts in 2016 following its launch in 2015. A dedicated mobile CXR van was funded with sponsorship from commercial partners which formed part of the State initiative "TB free Haryana". The 5 districts were chosen for their proximity to the hospital providing the van. The van was based, serviced and run from Medanta Hospital, with daily rotating timetabled visits on a "hub and spoke" model to PHIs (Fig. 1). Approval of individual Civil Surgeons (CS), and DTO's of each of the new districts, with clear written allocation of the respective duties of each party was agreed.

The first strategy for integration of X-ray into the district RNTCP program followed the protocol as outlined in the pilot phase. 4–5 PHIs in a district were identified by the DTO and the van went on a fixed day of the week to each district, rotating among the PHIs. Low case attendance at some of the PHIs led to a simultaneous trial of another strategy of Enhanced Case Finding (ECF) in the five districts. This involved intensive promotion by local ASHAs and Panchayati Raj members, with banners, posters and local media, 3–6 weeks prior to the planned van visits (Fig. 2). Along with CXR, simultaneous sputum microscopy was also introduced in the diagnostic algorithm based on the new RNTCP guidelines in 2016.[3] In this second strategy, all local residents with cough more than 2 weeks, were called for the "X-Ray camp", where they were subjected to both X-ray and sputum collection. The two strategies operated simultaneously over an 11-month period.

Regular meetings were held to support and engage the DTOs to mutually discuss operational issues, educational needs, and feedback of results from individual districts.



STO=State Tuberculosis Officer; DTO=District Tuberculosis Officer; STS=Senior Treatment Supervisor; STLS=Senior Tuberculosis Laboratory Supervisor; ANM=Auxiliary Nurse Midwife; ASHA=Accredited Social Health Activist; ACF=Active Case Finding; IEC=Information Education Communication

Fig. 1 – Framework of collaboration and different partners involved in the Public Private Mix.

Administrative support from the State TB Officer (STO) and Deputy Director General (DDG) of India were crucial in promoting mutual understanding between the two agencies.

In 2017, a total of 13 districts were covered, with 2 further X-ray vans financed for this planned scale up, along similar guidelines in a spoke and hub outreach model. In 2018, 16 districts were covered. Roll out to the whole state with one further van (total 4 vans) is anticipated in 2019. The state-wide expansion of the PPM initiative is depicted in Fig. 3.

c) Statistical analysis

The key study outcomes such as number screened for TB (x-ray), number of x-rays suggestive of TB and number started on DOTS have been presented year-wise in terms of absolute numbers and percentages.

Case notification rates (CNR) for new smear negative (NSN), new smear positive (NSP) and total TB for each of the five districts and combined have been presented for the year 2015 (baseline) and 2016 (study period). To take into account any biases caused by seasonality, comparison has been made between the respective quarters of the two years. The change in these parameters has been tested for significance using two sample proportion test. Data analysis was done using SPSS software, version 13.0.

3. Results

3.1. *Pilot phase (2014)*

In the pilot during May to Dec 2014, 355 presumptive TB patients with smear negative status attended the camp for CXR

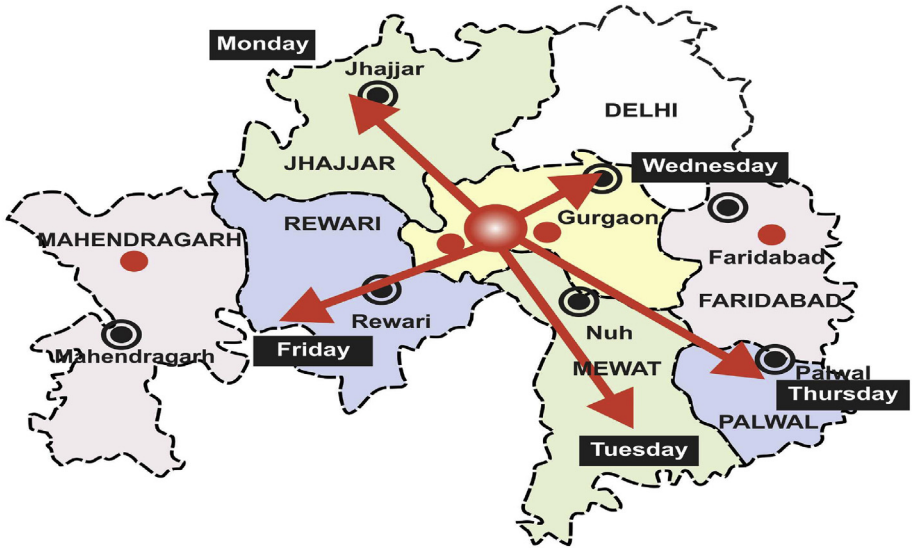


Fig. 2 – Hub and spoke model of the mobile van visit schedule to five districts of Haryana.

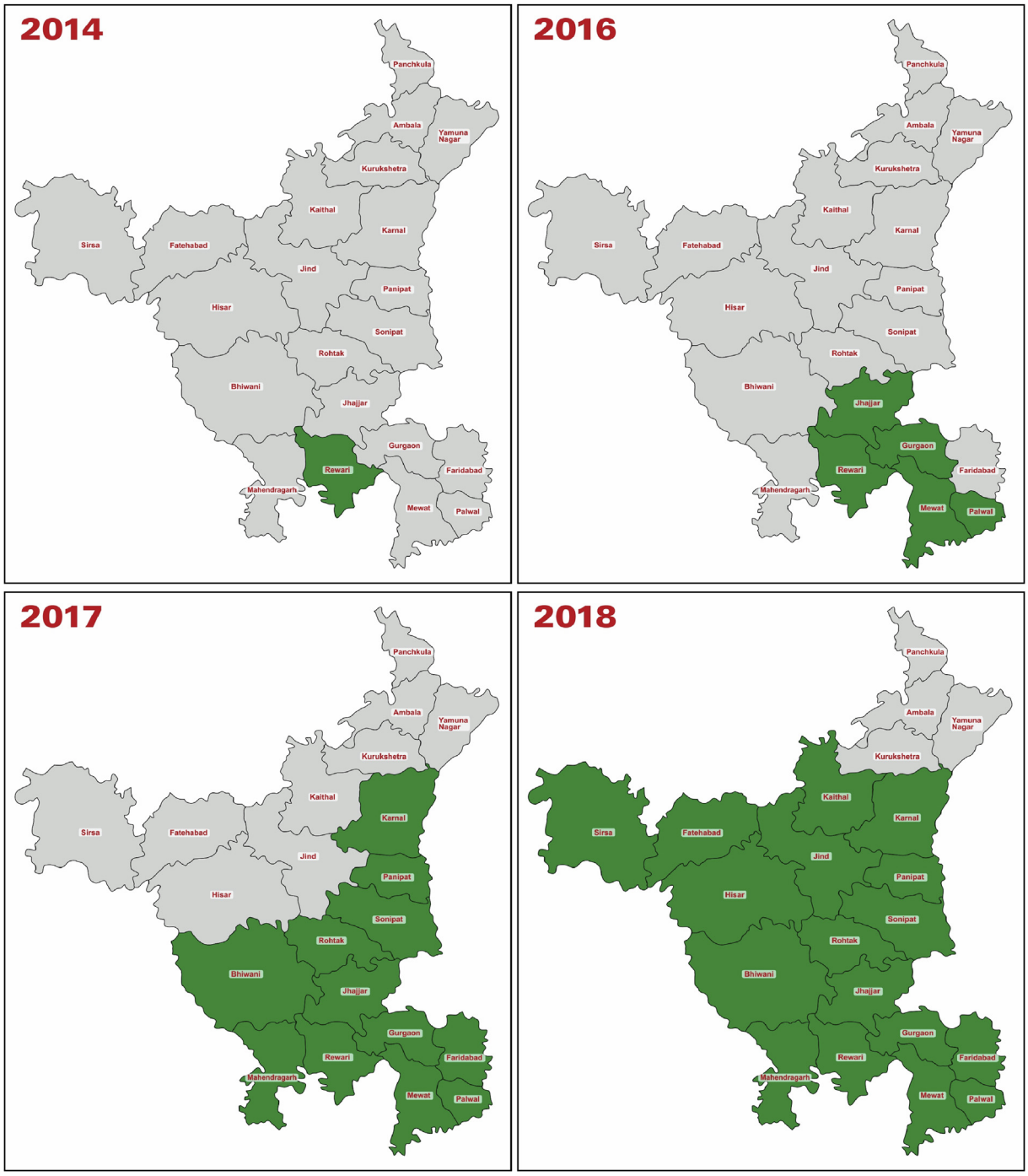


Fig. 3 – Expansion of TB-Free Haryana project throughout the state during 2014–18.

in 19 van visits. A total of 122 (34%) had abnormal CXR suggestive of active PTB as determined by the DTO who is a qualified chest specialist. Those cases without previous PTB, and clinically likely to have active PTB, were notified, and put on anti-tubercular treatment (ATT) as per the standard national guidelines (5) within the RNTCP. A total of 45 patients (45/355, 12.7%) were put on anti-TB treatment. Success of the pilot initiative and feasibility of its expansion has been previously reported.[6]

3.2. *First year of project (2016)*

Following the project launch in 2015, five districts were covered in 2016. A total of 77 PHIs were covered over 182 camps. Of 3340 who had a CXR, 1094 (32.75%) had abnormal X ray findings, half of which were suggestive of TB requiring clinical review, and careful selection for referral for ATT. The decision to start ATT rested with the DTO. A total of 328 (9.8%) were initiated on anti-TB treatment. Two different strategies

Table 1 – Comparison of strategy 1 and 2 in terms of numbers of patients attending the camp and number initiated on TB treatment in 2016.

Parameters	Strategy 1	Strategy 2	p-value
Total patients attending the camp	1609	1731	–
Total CXR suggestive of TB	572 (35.6%)	522 (30.1%)	0.003
Patients initiated on DOTS	169 (10.5%)	139 (8%)	0.2
Total camps held	119	63	–
Average CXR per camp	13	28	–

DOTS = Directly Observed Treatment Short Course; CXR=Chest X-Ray.

were used in different districts: In strategy 1 (used in the pilot phase in 2014), adult patients (18 years and above) who, according to the RNTCP diagnostic algorithm were eligible but not able to get a CXR (chest symptomatic with sputum smear negative) underwent CXR. Out of 1609 cases with presumptive TB, 572 (35.6%) had abnormal chest x-rays; 169 (10.5%) were considered for ATT. In strategy 2, all chest symptomatic patients (cough > 2 weeks) were called for chest x-ray, regardless of their smear status. Patients with abnormal x-ray findings were recalled for sputum testing. However, because of drop-out of patients for sputum examination, it was decided to offer x-ray and sputum examination simultaneously afterwards. This strategy also involved active information, education and communication (IEC) and community mobilization few weeks prior to the case finding activity. Under this, 1731 patients with presumptive TB were identified, of whom 522 (30.1%) had abnormal CXR; 139 (8%) were identified for DOTS (Table 1).

There was an increase in the CNR for new smear negative (NSN) cases of TB in 2016 compared to 2015 i.e. before the launch of the project (Table 2). The total number of NSN increased from 1542 (17.5% of total notified TB) to 1722 (18.7% of total notified TB), yielding a statistically significant result ($p = 0.03$); thus yielding an additional 180 cases and an 11.67% increase in case detection, in the pooled data from 5 districts in the first year of the intervention in 2016.

3.3. *Project expansion (2017)*

In 2017, strategy 2 was used in all the districts; this was done in accordance with the revised RNTCP guidelines with upfront CXR and sputum microscopy simultaneously (8). 13 districts were covered, 6268 x-rays were done, with 2567 (40.95%) suggestive of TB and 989 (15.78%) referred for DOTS. Referrals for CBNAAT were made as per RNTCP guidelines, although access to this test was available in the District hospitals of most but not all districts during this period. The number of tests performed was not available at this time. The CNR is awaited for the year 2017, a deferral caused by an overhaul and systematic change of the notification system of the national program.

3.4. *Further expansion (2018)*

16 districts have been covered. A total of 8021 patients with presumptive TB were screened, 2677 (33.37%) had x-ray suggestive of TB and 885 (11.03%) were referred for DOTS in the same year.

Successful scale up led from a pilot study in a single district, to 5 districts in the first year, 13 districts in the second year, and 16 in the third year. Expansion is planned to all the districts in the state of Haryana by the end of 2019. Fig. 4 shows the figures for each year in the project starting from 2014 to 18.

4. Discussion

There are two main aspects to this discussion; firstly the description of the process of development and operational flexibility of this arguably successful model of a PPM sustained for more than four years with scale up to the state level. Secondly, there are operational challenges of the program which uses mobile X-ray vans and its current and potential impact on the diagnosis of PTB in "hard to reach" areas of India.

While a number of PPM projects have been active in India, we believe that this is the first such initiative to originate from a commercial Corporate Hospital to fill a gap in provision of a government diagnostic radiology service.[7] It has involved large numbers of cases, has had a long term commitment, with many of the collaborative features that have been shown to be predictive of an effective and sustainable programme.[8,9] An effective sustenance and scale up in PPM has been seen to result from sincere collaboration, regulation and use of innovation.[9] All these attributes were present in this model. Regulation by strict adherence to the national program and use of mobile digital CXR technology helped reach and screen large numbers in a short period of time, demonstrating the

Table 2 – Annual case notification rates of tuberculosis by the type of TB in five districts of Haryana during 2015–2016.

District	NSP			NSN			EPTB		
	2015	2016	p-value	2015	2016	p-value	2015	2016	p-value
Gurgaon	777 (30.8%)	780 (28.7%)	0.09	479 (19.0%)	580 (21.3%)	0.03*	702 (27.9)	777 (28.5)	0.6
Jhajjhar	621 (40.2%)	542 (36.1%)	0.02*	264 (17.1%)	255 (17.0%)	0.9	297 (19.2)	307 (20.5)	0.4
Mewat	668 (38.9%)	704 (36.2%)	0.09	262 (15.3%)	323 (16.6%)	0.3	305 (17.8)	382 (19.6)	0.2
Palwal	580 (36.5%)	620 (36.6%)	0.9	251 (15.8%)	294 (17.4%)	0.2	293 (18.5)	279 (16.5)	0.1
Rewari	465 (32.0%)	412 (30.2%)	0.3	286 (19.7%)	270 (19.8%)	0.9	349 (24.1)	358 (26.3)	0.2
Total	3111 (35.3%)	3058 (33.2%)	0.003*	1542 (17.5%)	1722 (18.7%)	0.03*	1946 (22.1)	2263 (22.8)	0.3

NSP=New Smear Positive; NSN=New Smear Negative; EPTB = Extra Pulmonary Tuberculosis.

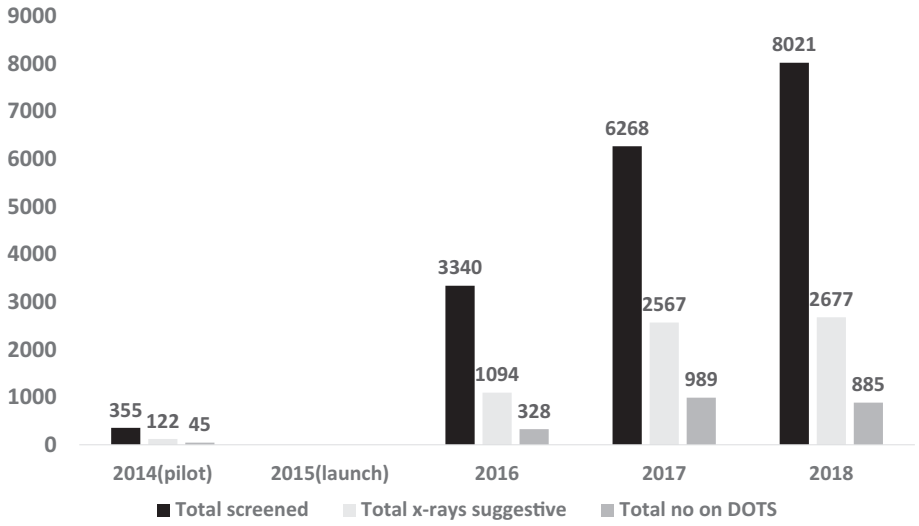


Fig. 4 – Annual x-ray screening for TB and numbers put on anti-TB treatment in each year of the TB-Free Haryana project 2014–18.

effectiveness of the model. Linkage of the private partner to the local public sector TB program is the recommended approach and reflected in this model, which complemented (via X-ray) existing government facilities (sputum and subsequently GeneXpert).[10]

The support of key State GOI officers was essential in promoting data sharing and suitable senior medical attendance at mobile van visits. Financial commitment to the staffing and running of the vans comes from an institution with an organisational history of community outreach. The high profile of the partners in this collaboration is likely to have facilitated major commercial partners to sponsor new vans and the digital technology required.

In the execution of the mobile digital X-ray program in the first year, the second strategy was considered more efficient in terms of numbers screened per van visit, although the numbers finally identified for DOTS was similar in both the strategies. Analysis of one District, Mewat, supported the cost effectiveness of the second strategy and led to the adoption of this approach from that point in time.[11] While the project was structured as pragmatic and clinical rather than as a research model, we hope to continue to provide field operational data, which appears to support the recently introduced diagnostic algorithm including CXR and sputum testing simultaneously, which was criticised for its lack of basis in field research prior to introduction.[12] There was a modest but statistically significant increase in the CNR in the diagnosis of NSN over 5 districts over the period reported, which can be at least partly attributed to the mobile X-ray program; data from subsequent years is necessary to substantiate this hypothesis.

It was observed that despite a coordinated effort of both teams in the camps, procuring the final result of how many actually went onto treatment proved to be a challenge. While multiple levels of losses are acknowledged in the cascade of diagnosis and treatment of TB in India[13] the capacity to minimise this in the field remains the major challenge. While accepting the central concern of NSP cases in public health, NSN cases are also important and associated with infectivity.[14] A substantial number of - X-rays were reported as strongly suggestive of TB in smear negative symptomatic patients who fulfilled the RNTCP criteria for smear negative pulmonary TB, but there were limited registrations as NSN cases and therefore of ATT.

CBNAAT is recommended along the current algorithm or clinical diagnosis and treatment if microbiological confirmation is not available with suitable follow up. The review of the role of modern digital CXR in diagnosis, along with the impact of possible future incorporation of CBNAAT in point-of-care field trials of this type are being currently supported in screening initiatives in other circumstances[15] and modification, research support, and data collection from similar initiatives to this may be of great value in improving outcomes in the diagnosis of PTB in hard to reach areas of India. With the advent of the portable single module GeneXpert Edge, efforts are on to incorporate this tool in the mobile X-ray van, to provide a Point of Care diagnostic model.

In this article we have concentrated on the process of development of this on-going not for profit PPM project, with supporting data which has shown significant benefits for patients at this early stage and the potential for new shared initiatives and working relationships between GOI and Commercial Hospitals. We have at this point not included an evaluation of the clinical or cost effectiveness of the project, patient clinical outcomes, quality assurance or compliance with current algorithms but this would be important before the potential longer term public health impact can be fully assessed.

5. Conclusion

We report a new initiative within a PPM to improve the diagnosis of PTB within the existing RNTCP pathway. This collaboration has helped to fill a gap in current diagnostic

infrastructure, and established new, productive, and mutually benefitting working relationships between the Corporate and the Government sector in Haryana state. We believe there is potential for replication of similar projects in other states. The model of mobile digital X-ray vans could be executed successfully with encouraging results.

Conflicts of interest

The authors have none to declare.

Author's contributions

DJF, BD, AJ and NT conceptualized the project, were involved in the planning and implementation of the project. DJF, BD and JPT analysed and interpreted the data, wrote and edited the manuscript. BD, AKP, PG, PC, VS were involved in collection of data and critically reviewed the manuscript. AJ and NT critically reviewed the manuscript. All the authors have read and approved the final version of the manuscript.

Ethics approval

The study received ethics approval from the Institute Review Board of The Medanta - The Medicity Hospital, Gurugram, Haryana. Administrative approval to conduct the study was obtained from the State RNTCP, Haryana and the District TB Officers.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijtb.2019.09.005.

REFERENCES

1. World Health Organisation. *Global Tuberculosis Report 2018*. 2018. Geneva, Switzerland.
2. World Health Organization. *Chest Radiography in Tuberculosis Detection-Summary of Current WHO Recommendations and Guidance on Programmatic Approaches*. 2016.
3. Central TB Division, Ministry of Health and Family Welfare Technical and operational guidelines for TB Control in India. *Case Finding and Diagnosis Strategy*. Delhi, India: Ministry of Health and Family Welfare, Government of India; 2016 [Chapter 3].
4. Haryana Population Census 2011-2018. Available at: https://www.census2011.co.in/census/state/haryana.html [Last accessed on 12 Mar 2019].
5. *India TB report 2018. Revised National TB Control Programme. Annual Status Report*. New Delhi India: Central TB Division, Ministry of Health and Family Welfare; 2018. Available at: https://tbcindia.gov.in/showfile.php?lid=3314. Accessed March 12, 2019.
6. Datta B, Hazarika A, Shewade HS, Ayyagiri K, Kumar AMV. Digital chest X-ray through a mobile van: public private partnership to detect sputum negative pulmonary TB. *BMC Res Notes*. 2017;10(1):96.
7. Dewan PK, Lal SS, Lonnroth K, et al. Improving tuberculosis control through public-private collaboration in India: literature review. *BMJ*. 2006;332:574–578.
8. Lei X, Liu Q, Escobar E, et al. Public-Private Mix for tuberculosis care and control: a systematic review. *Int J Infect Dis*. 2015;34:20–32.
9. Uplekar M. Public-Private Mix for tuberculosis care and prevention. What progress? What prospects? *Int J Tuberc Lung Dis*. 2016;20(11):1424–1429.
10. World Health Organization. *Engaging All Health Care Providers in TB Control: Guidance on Implementing Public-Private Mix Approaches*. 2006. WHO/HTM/TB/2006.360. Geneva, Switzerland.
11. Datta B, Prakash AK, Ford D, et al. Comparison of clinical and cost-effectiveness of two strategies using mobile digital X-ray to detect Pulmonary Tuberculosis in rural India. *BMC Public Health*. 2019;19(1):99.
12. Sharath BN, Shastri S. India's new TB diagnostic algorithm-far from reality? *Public Health Action*. 2016;6(3):206.
13. Subbaraman R, Nathavitharana RR, Satyanarayana S, et al. The tuberculosis cascade of care in India's public sector: a systematic review and meta-analysis. *PLoS One*. 2016;13(10). e1002149.
14. Tostmann A, Kik SV, Kalisvaart NA, et al. Tuberculosis transmission by patients with smear-negative pulmonary tuberculosis in a large cohort in The Netherlands. *Clin Infect Dis*. 2008;47:1135–1142.
15. *High tech trucks to carry out targeted TB screening in high-risk communities*; 2018. Available at: https://www.theunion.org/news-centre/news/zimbabwe-high-tech-trucks-to-carry-out-targeted-tb-screening-in-high-risk-communities. Accessed March 11, 2019.

Available online at www.sciencedirect.com

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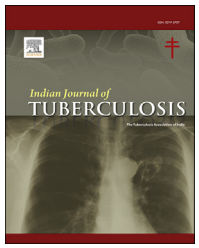
journal homepage: http://www.journals.elsevier.com/indian-journal-of-tuberculosis/



Review article

The roles of latency-associated antigens in tuberculosis vaccines

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ABSTRACT

Tuberculosis (TB) is a re-emerging disease and is caused by *Mycobacterium tuberculosis* (*M. tuberculosis*). TB is currently one of the leading causes of morbidity and mortality, worldwide. The only available vaccine against TB infection, Bacillus Calmette–Guérin (BCG), fails to adequately protect against reactivation of latent infections in adults. Furthermore, recently developed subunit vaccines, which are in various stages of clinical trials, are all prophylactic vaccines based on proteins expressed in replicating stage of *M. tuberculosis* and they are not preventive of reactivation of latent TB infection. Thus, an appropriate subunit post-exposure vaccine needs to be developed to control all forms of TB infection. To produce a multi-stage subunit vaccine, scientists should combine the early secreted *M. tuberculosis* antigens with latency antigens. For this purpose, some latency proteins are known which could be important antigens in the production of specific humoral and cellular immune responses in latent *M. tuberculosis* infected individuals. Several studies have evaluated the immunogenicity of these proteins in improving the TB vaccines. The present study is a comprehensive review of several studies on the role of the latency antigens in the development of TB vaccines. Overall, the studies indicate that the latency-associated antigens including the resuscitation-promoting factors, the Dormancy of survival regulon (DosR) proteins and the starvation stimulant proteins are potential candidates for the development of subunit vaccines against TB infection.

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1. Introduction

Tuberculosis (TB), caused by *Mycobacterium tuberculosis* (*M. tuberculosis*), is a re-emerging infectious disease and is one of the leading causes of morbidity and mortality in many countries, especially in developing countries.[1] According to the latest report by the World Health Organization (WHO) in 2018, about 10 million people had TB, which led to1.3 million deaths. This state is further exacerbated due toTB/HIV co-infection, multidrug-resistant (MDR) *M. tuberculosis* strains and the appearance of extremely drug-resistant (XDR) *M. tuberculosis* strains.[2] Currently, vaccination is one of the most effective approaches in prevention and control TB infection. The TB vaccine, Bacillus Calmette–Guérin (BCG), is the only available approved vaccine against TB and has been widely used in many countries for decades.[3] BCG provides highly variable efficacies against adult pulmonary TB infection with a range of 0–80% protection. BCG also fails to adequately protect against reactivation of latent infections in adults. Furthermore, the current vaccine suffers from inability to eliminate latent TB infection, and loss of efficacy over time and in immune compromised patients.[4,5] One of the important differences between *M. tuberculosis* and other pathogens is the survival of bacteria in an intracellular habitat in the human cells for decades and its establishment as a latent infection. About one-third of the global population has latent TB infection and about 5–10% of them will eventually progress active TB infection whenever their immune status suppresses. Patients with latent TB infection are the major reservoir of adult TB infection.[6,7] Most TB vaccines that recently entered different phases of clinical trials were based on proteins expressed in replicating stages. Such TB vaccines can prevent active TB infection (prophylactic vaccine) but not latent TB infection.[6] Thus, a more effective subunit post-exposure vaccine is needed to control all forms of TB infection in adults, especially latent infection. To produce a multi-stage subunit vaccine, researchers should combine early secreted antigens such as Ag85B with *M. tuberculosis* latency antigens such as HspX.[6] Recently, some multi-stage subunit vaccines *i.e.* Hybrid 56 + IC31 and ID93+GLA-SE, containing dormancy antigens, have entered clinical trials.[8,9] Latency-associated antigens have shown to elicit appropriate and strong immune and protective responses.[10] These antigens include: 1) the Dormancy of survival regulon (DosR) proteins which are responsible for adaptation to hypoxia. These constitute the latency expressing proteins; 2) nutrient starvation proteins; and 3) enduring hypoxic response (EHR) genes which comprise many genes of the DosR regulon.[11,12] Recently, scientists have used several *M. tuberculosis* proteins homologous to the resuscitation-promoting factor (rpfa-A-E) of *Micrococcus luteus*. These proteins are involved in resuscitation and reactivation of dormant TB infection and to control reactivated *M. tuberculosis*. These proteins lead to specific humoral and cellular immune responses in latently *M. tuberculosis* infected individuals. Thus, *M. tuberculosis* resuscitation-promoting factors proteins (Rpf), particularly RpfB which memory T-cells able to respond to them can be used as antigens for novel TB subunit vaccines.[13,14] DosR-regulated protein HspX is an important antigen that leads to specific humoral and cellular immune responses in latently *M. tuberculosis* infected individuals.[15] This protein is known to be targeted by $CD4^+$ and $CD8^+$ T cells. On the other hand, several of other latency antigens such as RV2628c, RV1813, RV2660, RV0072, RV1737 and RV2031c have been shown to induce strong Th1-mediated immune responses.[16,17] Some previous studies have suggested that latency-associated antigens in all kinds of TB vaccines can induce strong humoral and/or cellular Th1-mediated immune responses.[16–18] Therefore, it could be hypothesized that a heterologous prime boost vaccine, including a combination of dormant antigens to induce a specific immune response, is more protective than the homologous prime boost vaccine. The present review article focuses on dormancy-related antigens of *M. tuberculosis* as potentially ideal candidates in the development of new vaccine against TB.

2. Resuscitation-promoting factors

Resuscitation-promoting factors (Rpf) are proteins with peptidoglycan-hydrolyzing activity and are vital for mycobacterial virulence, especially for resuscitation from dormancy. These proteins were first reported in *M. luteus* as a secretory protein. Mutant *M. tuberculosis* strains with a deficiency in Rpf show inability in replication, reactivation and in resistance to stress probably due to changes in their cell wall structure.[19] There are five *rpf* genes in the *M. tuberculosis* genome (*rpf*A-E) which are very similar to those of Rpf from *M. luteus*.[14] Rpf proteins are potential targets for the host immune response. Rpf are key virulence factors for *M. tuberculosis* and responses to Rpf could be protective. These have been evaluated in cellular experiments and mouse models.[14] Previous studies have demonstrated that RpfB and RpfE produce protective immune responses *in-vitro* and are potential candidates for the development of vaccine.[20] RpfB and RpfE induce the maturation of dendritic cells (DCs) and these activated DCs polarize T-cell proliferation toward Th1 phenotype. RpfE also induces Th17 development which in addition to Th1 is needed for appropriate protection against *M. tuberculosis*.[20,21] The immune responses induced by Rpf antigens and their protective efficacy against challenge with virulent *M. tuberculosis* have been evaluated in animal models.[22] Lee *et al* demonstrated that when C57BL/6 mice were vaccinated intramuscularly with RpfB using a plasmid DNA vector, it can elicit a significant poly functional $CD8^+$T cell responses in mice, suggesting that RpfB DNA immunization may be protective against TB infection.[21] In another study RpfB and RpfD were reported to be the most antigenic in the tested models. It was also indicated that RpfB protein is the most immunogenic antigen among the five Rpf proteins of *M. tuberculosis*, implying that Rpf proteins can be used as an antigen in new TB vaccines.[14] In conclusion, RpfB and RpfE induce immune responses associated with resistance to *M. tuberculosis* and provide some levels of protection in animal models. Further human-based studies are needed to evaluate if the observation could be replicated in humans and whether Rpf should be considered as

antigens for development of a subunit vaccine against *M. tuberculosis*.[22]

3. Dormancy of survival regulon (DosR)

A region in the genome of *M. tuberculosis* called DosR regulon contains 50 latency-associated genes and is active during latency. Most latency-associated antigens related to DosR regulon including Rv2031c, Rv2029c, Rv2628c, Rv1737c, Rv1733c and Rv0081 were evaluated for their immunogenic characteristics in different studies.[16] This review summarizes the possible role of DosR regulon proteins as effective candidates for development of subunit vaccines against TB infection.

3.1. *Rv2031c (gene name:* hspX*; gene length: 435 bp; 144 amino acids)*

An important antigen from the DosR regulon is a stress protein induced by hypoxia and nutrient scarcity is called heat-shock protein X orα-crystallin ((14 kDa antigen) (HSP16.3)).[23] The expression of HspX protein is regulated by DosR regulon in different environmental conditions.[24] HspX is associated with bacterial growth, escape from the host immune system and prolonged bacterial survival in macrophages during latent infections.[25,26] One of the most crucial immune responses against *M. tuberculosis* infection is activation of T helper1 (Th1) and cytotoxic T (Tc) cells. HspX strongly induces Th1 cytokines such as IFN-γ (interferon gamma) and TNF-α (tumor necrosis alpha) followed by induction of cellular and humoral immune responses in the latent phase of TB infection.[27,28] Several studies have shown the efficacy of HspX protein for the induction of strong Th1-medited immune responses and its potential to be a suitable antigen candidate for vaccination against TB infection. As an example, in a study conducted by Yuan *et al*, a DNA vaccine was constructed expressing a fusion protein of *M. tuberculosis* antigens including Ag85B, Esat6 and HspX. After vaccination of mice with DNA vaccine, a significant increase in antigen-specific IFN-γ against HspX antigen and higher levels of HspX specific T cell proliferation was observed, compared to vaccination with BCG.[29] Geon *et al* evaluated immune responses against Ag85A and HspX antigens in the mice model. Ag85A and HspX increased the level of IFN-γ responses. Also, after mice challenge with *M. tuberculosis*, HspX subunit vaccine induced significant protective immunity.[30] In another study, Yuan *et al* developed a new recombinant BCG expressing high levels of Ag85B and HspX. After vaccination of mice with this vaccine, the immunization of new vaccine compared to BCG. It was observed that the new vaccine was able to protect mice against intranasal infection of *M. tuberculosis* better than that of BCG.[31] Similar results were shown by Xin *et al*, Marongiu *et al*, de Sousa *et al*, Geluk et *al* and Costa *et al* confirmed the immunogenicity of HspX antigen.[9,25,28,32,33] Several studies indicated that HspX protein either in combination with adjuvants or as encapsulated with nanoparticles can strongly induce the immune system. In a study conducted by Khademi *et al*, HspX antigen was shown to efficiently induce mucosal and systemic immune responses in BALB/c mice, when combined with a replicating bacilli antigen, as multi-stage subunit vaccine (HspX/EsxS-fused protein), alone or as encapsulated in PLGA and PLGA:DDA hybrid nanoparticles.[34] Additionally, they showed that adding DOTAP and MPLA adjuvants to HspX/EsxS-fused protein could enhance immune responses after subcutaneous and nasal immunization of BALB/c mice.[34,35] In another study by Mansury *et al*, HspX protein in combination with PPE44 and EsxV proteins were encapsulated into DOTAP liposome. They showed that this formulation was able to induce a strong Th1-mediated response.[36] Amini *et al* reported a multi-component vaccine containing HspX in combination with PPE44 and EsxV antigens adsorbed on calcium phosphate nanoparticles could induce strong cellular immunity in an animal model.[37] Niu *et al* developed a new multi-sage subunit vaccine against TB infection containing ESAT6-Ag85B-MPT64-Mtb8.4-HspX antigens along with two adjuvants, DDA and Poly I:C. They showed that this new vaccine could induce a stronger immunity compared to traditional BCG vaccine.[38]

3.2. *Rv2029c (gene name:* pfkB*; gene length: 1020 bp; 339 amino acids)*

M. tuberculosis pfkB gene encodes a 35 kDa-latency protein with kinase and phosphotransferase activity. This *M. tuberculosis* latency antigen is DosR-regulon-encoded antigen and as a probable 6-phosphofructokinase (*pfkB*) is involved in glycolysis: converts sugar-1-P to sugar-1, 6-P.[39] The immunogenicity of this latency protein was evaluated in different studies. Arroyo *et al* reported that *M. tuberculosis* latency antigen Rv2029c was able to induce higher immune responses of T cells ($CD4^+$ or $CD8^+$) producing IFN-γ and TNF-α in latently *M. tuberculosis* infected individuals.[39] The immunogenicity profile of Rv2029c antigen has also been investigated by Mensah and colleagues.[40] They reported that latency antigen Rv2029c was able to induce higher levels of IFN-γ, Granzyme B, TNF-α and IL-17 and also low levels of IL-10 and sIL-2R-α in peripheral blood mononuclear cell.

3.3. *RV2628c (gene name:* Rv2628*; gene length: 363 bp; 120 amino acids)*

M. tuberculosis Rv2628 gene encodes a 13 kDa-latency antigen RV2628c protein with unknown function. It was reported that this *M. tuberculosis* DosR-regulon-encoded antigen can induce strong long-term IFN-γ responses. As an example, Goletti *et al* study showed that this latency antigen may induce immune-mediated protection against TB infection.[17] Similar results DosR-regulon-encoded protein Rv2029c, Mensah and colleagues were reported for DosR-regulon-encoded protein Rv2628.[40]

3.4. *Rv1737c(gene name:* narK2*; gene length: 1188 bp; 395 amino acids)*

The protein expressed by this gene *i.e.* nitrate/nitrite transporter NarK2 is involved in the excretion of nitrite across the membrane. Arroyo *et al* assessed the DosR antigens Rv1737c

immunogenicity and reported that it is capable of promoting T cells responses.[39]

3.5. *Rv1733c (gene name:* Rv1733c*; gene length: 633 bp; 210 amino acids)*

Rv1733c is a probable conserved trans membrane protein with unknown function. It was indicated as a potent inducer of T cell antigen in bioinformatics analysis.[16] However, this DosR-regulon-encoded antigen is also known to be immunogenic *in vitro* experiments conducted by Mensah *et al*, Kassa *et al* and Commander *et al*[40–42]

3.6. *Rv0081 (gene name:* Rv0081*; gene length: 345 bp; 114 amino acid)*

Twelve kDaRv0081 antigens belong to the latency-associated antigens and is encoded by DosR regulon.[16] This *M. tuberculosis* sDosR-regulon-encoded antigen is a probable transcriptional regulatory protein and involved in transcriptional mechanism. Kassa *et al* reports on the immune response against Rv0081 antigen confirmed Rv0081 antigen as a potent immunogenic antigen.[41]

4. The starvation regulon

4.1. *Rv2660c (gene name:* Rv2660c*; gene length: 228 bp; 75 amino acid)*

A collection of genes including Rv2660 and Rv2659 called the starvation regulon and expressed in response to nutrient deprivation by *M. tuberculosis*.[16] Govender *et al* suggested that the starvation stimulon gene product Rv2660 is a suitable antigenic candidate in a post-infection vaccine against TB infection. They showed that Rv2660 induced IFN-γ production in latently *M. tuberculosis* infected individuals.[43]

5. Conclusion

In all literature reviewed in the current study, it has been shown that the latency-associated antigens including resuscitation-promoting factors, the DosR regulon encoded antigens and the starvation regulon encoded antigens can stimulate cellular immune responses against latent TB infection. Therefore, they could be potential candidate antigens for immunization as a prophylactic vaccine against the latent stage of TB infection and could prevent the reactivation of latent infection.

REFERENCES

1. Steingart KR, Ng V, Henry M, et al. Sputum processing methods to improve the sensitivity of smear microscopy for tuberculosis: a systematic review. *Lancet Infect Dis*. 2006;6(10):664–674.
2. Organization World Health (WHO). *Global Tuberculosis Report 2018*. 2018.
3. Lucia S, Mihaescu T. History of BCG vaccine. *Medicina*. 2013;8(1):53–58.
4. Mosavat A, Soleimanpour S, Farsiani H, et al. Fused Mycobacterium tuberculosis multi-stage immunogens with an Fc-delivery system as a promising approach for the development of a tuberculosis vaccine. *Infect Genet Evol*. 2016;39:163–172.
5. Farsiani H, Mosavat A, Soleimanpour S, et al. Fc-based delivery system enhances immunogenicity of a tuberculosis subunit vaccine candidate consisting of the ESAT-6: CFP-10 complex. *Mol Bio Syst*. 2016;12(7):2189–2201.
6. Soleimanpour S, Farsiani H, Mosavat A, et al. APC targeting enhances immunogenicity of a novel multistage Fc-fusion tuberculosis vaccine in mice. *Appl Microbiol Biotechnol*. 2015;99(24):10467–10480.
7. Ohara N. Current status of tuberculosis and recombinant bacillus Calmette-Guérin vaccines. *J Oral Biosci*. 2012;54(2):92–95.
8. Khademi F, Derakhshan M, Yousefi-Avarvand A, Tafaghodi M, Soleimanpour S. Multi-stage subunit vaccines against *Mycobacterium tuberculosis*: an alternative to the BCG vaccine or a BCG-prime boost? *Expert Rev Vaccines*. 2018;17(1):31–44.
9. Xin Q, Niu H, Li Z, et al. Subunit vaccine consisting of multi-stage antigens has high protective efficacy against *Mycobacterium tuberculosis* infection in mice. *PLoS One*. 2013;8(8), e72745.
10. Moradi J, Tabrizi M, Izad M, Mosavari N, Feizabadi MM. Designing a novel multi-epitope DNA-based vaccine against tuberculosis: in silico approach. *Jundishapur J Microbiol*. 2017;10(3), e43950.
11. Sun X, Zhang L, Jiang J, et al. Transcription factors Rv0081 and Rv3334 connect the early and the enduring hypoxic response of *Mycobacterium tuberculosis*. *Virulence*. 2018;9(1):1468–1482.
12. Bose T, Das C, Dutta A, Mahamkali V, Sadhu S, Mande SS. Understanding the role of interactions between host and Mycobacterium tuberculosis under hypoxic condition: an in silico approach. *BMC Genomics*. 2018;19(1):555.
13. Zhu W, Plikaytis BB, Shinnick TM. Resuscitation factors from mycobacteria: homologs of *Micrococcus luteus* proteins. *Tuberculosis*. 2003;83(4):261–269.
14. Romano M, Aryan E, Korf H, et al. Potential of *Mycobacterium tuberculosis* resuscitation-promoting factors as antigens in novel tuberculosis sub-unit vaccines. *Microb Infect*. 2012;14(1):86–95.
15. Silva BD, Tannus-Silva DG, Rabahi MF, Kipnis A, Junqueira-Kipnis AP. The use of *Mycobacterium tuberculosis* HspX and GlcB proteins to identify latent tuberculosis in rheumatoid arthritis patients. *Memórias do Instituto Oswaldo Cruz*. 2014;109(1):29–37.
16. Meier NR, Jacobsen M, Ottenhoff TH, Ritz N. A systematic review on novel *Mycobacterium tuberculosis* antigens and their discriminatory potential for the diagnosis of latent and active tuberculosis. *Front Immunol*. 2018;9:2476.
17. Goletti D, Butera O, Vanini V, et al. Response to Rv2628 latency antigen associates with cured tuberculosis and remote infection. *Eur Respir J*. 2010;36(1):135–142.
18. Su H, Zhu S, Zhu L, et al. *Mycobacterium tuberculosis* latent antigen Rv2029c from the multistage DNA vaccine A39 drives TH1 responses via TLR-mediated macrophage activation. *Front Microbiol*. 2017;8:2266.
19. Kana BD, Gordhan BG, Downing KJ, et al. The resuscitation-promoting factors of *Mycobacterium tuberculosis* are required for virulence and resuscitation from dormancy but are collectively dispensable for growth in vitro. *Mol Microbiol*. 2008;67(3):672–684.
20. Choi HG, Kim WS, Back YW, et al. *Mycobacterium tuberculosis* RpfE promotes simultaneous Th1-and Th17-type T-cell

immunity via TLR4-dependent maturation of dendritic cells. *Eur J Immunol*. 2015;45(7):1957–1971.
21. Lee J, Kim J, Lee J, Shin SJ, Shin EC. DNA immunization of *Mycobacterium tuberculosis* resuscitation-promoting factor B elicits polyfunctional CD8+ T cell responses. *Clin Exp Vaccine Res*. 2014;3(2):235–243.
22. Rosser A, Stover C, Pareek M, Mukamolova GV. Resuscitation-promoting factors are important determinants of the pathophysiology in *Mycobacterium tuberculosis* infection. *Crit Rev Microbiol*. 2017;43(5):621–630.
23. Khademi F, Yousefi-Avarvand A, Derakhshan M, et al. *Mycobacterium tuberculosis* HspX/EsxS fusion protein: gene cloning, protein expression, and purification in *Escherichia coli*. *Rep Biochem Mol Biol*. 2017;6(1):15–21.
24. Aagaard C, Dietrich J, Doherty M, Andersen P. TB vaccines: current status and future perspectives. *Immunol Cell Biol*. 2009;87:279–286.
25. Marongiu L, Donini M, Toffali L, Zenaro E, Dusi S. ESAT-6 and HspX improve the effectiveness of BCG to induce human dendritic cells-dependent Th1 and NK cells activation. *PLoS One*. 2013;8, e75684.
26. Wang X, Zhang J, Liang J, et al. Protection against *Mycobacterium tuberculosis* infection offered by a new multistage subunit vaccine correlates with increased number of IFN-γ+ IL-2+ CD4+ and IFN-γ+ CD8+ T cells. *PLoS One*. 2015;10, e0122560.
27. Li Q, Yu H, Zhang Y, et al. Immunogenicity and protective efficacy of a fusion protein vaccine consisting of antigen Ag85B and HspX against *Mycobacterium tuberculosis* infection in mice. *Scand J Immunol*. 2011;73:568–576.
28. de Sousa EM, da Costa AC, Trentini MM, de AraújoFilho JA, Kipnis A, Junqueira-Kipnis AP. Immunogenicity of a fusion protein containing immunodominant epitopes of Ag85C, MPT51, and HspX from *Mycobacterium tuberculosis* in mice and active TB infection. *PLoS One*. 2012;7, e47781.
29. Yuan W, Dong N, Zhang L, et al. Immunogenicity and protective efficacy of a tuberculosis DNA vaccine expressing a fusion protein of Ag85B-Esat6-HspX in mice. *Vaccine*. 2012;30:2490–2497.
30. Jeon B-Y, Kim S-C, Eum S-Y, Cho S-N. The immunity and protective effects of antigen 85A and heat-shock protein X against progressive tuberculosis. *Microb Infect*. 2011;13:284–290.
31. Yuan X, Teng X, Jing Y, et al. A live attenuated BCG vaccine overexpressing multistage antigens Ag85B and HspX provides superior protection against *Mycobacterium tuberculosis* infection. *Appl Microbiol Biotechnol*. 2015;99:10587–10595.
32. Geluk A, Lin MY, van Meijgaarden KE, et al. T-cell recognition of the HspX protein of *Mycobacterium tuberculosis* correlates with latent *M. tuberculosis* infection but not with *M. bovis* BCG vaccination. *Infect Immun*. 2007;75:2914–2921.
33. da Costa AC, de Oliveira Costa-Junior A, de Oliveira FM, et al. A new recombinant BCG vaccine induces specific Th17 and Th1 effector cells with higher protective efficacy against tuberculosis. *PLoS One*. 2014;9, e112848.
34. Khademi F, Derakhshan M, Yousefi-Avarvand A, Najafi A, Tafaghodi M. A novel antigen of *Mycobacterium tuberculosis* and MPLA adjuvant co-entrapped into PLGA:DDA hybrid nanoparticles stimulates mucosal and systemic immunity. *Microb Pathog*. 2018;125:507–513.
35. Khademi F, Sahebkar A, Fasihi-Ramandi M, Taheri RA. Induction of strong immune response against a multicomponent antigen of *Mycobacterium tuberculosis* in BALB/c mice using PLGA and DOTAP adjuvant. *Apmis*. 2018;126(6):509–514.
36. Mansury D, Ghazvini K, Jamehdar SA, et al. Increasing cellular immune response in liposomal formulations of DOTAP encapsulated by fusion protein Hspx, PPE44, and Esxv, as a potential tuberculosis vaccine candidate. *Rep Biochem Mol Biol*. 2019;7(2):156–166.
37. Amini Y, Moradi B, Tafaghodi M, Meshkat Z, Ghazvini K, Fasihi-Ramandi M. TB trifusion antigen adsorbed on calcium phosphate nanoparticles stimulates strong cellular immunity in mice. *Biotechnol Bioprocess Eng*. 2016;21(5):653–658.
38. Niu H, Peng J, Bai C, et al. Multi-stage tuberculosis subunit vaccine candidate LT69 provides high protection against *Mycobacterium tuberculosis* infection in mice. *PLoS One*. 2015;10, e0130641.
39. Arroyo L, Rojas M, Franken KL, Ottenhoff TH, Barrera LF. Multifunctional T cell response to DosR and Rpf antigens is associated with protection in long-term *Mycobacterium tuberculosis*-infected individuals in Colombia. *Clin Vaccine Immunol*. 2016;23(10):813–824.
40. Mensah GI, Addo KK, Tetteh JA, et al. Cytokine response to selected MTB antigens in Ghanaian TB patients, before and at 2 weeks of anti-TB therapy is characterized by high expression of IFN-γ and Granzyme B and inter-individual variation. *BMC Infect Dis*. 2014;14(1):495.
41. Kassa D, Ran L, Geberemeskel W, et al. Analysis of immune responses against a wide range of *Mycobacterium tuberculosis* antigens in patients with active pulmonary tuberculosis. *Clin Vaccine Immunol*. 2012;19(12):1907–1915.
42. Commandeur S, Lin MY, van Meijgaarden KE, et al. Double- and monofunctional CD4+ and CD8+ T-cell responses to *Mycobacterium tuberculosis* DosR antigens and peptides in long-term latently infected individuals. *Eur J Immunol*. 2011;41(10):2925–2936.
43. Govender L, Abel B, Hughes EJ, et al. Higher human CD4 T cell response to novel *Mycobacterium tuberculosis* latency associated antigens Rv2660 and Rv2659 in latent infection compared with tuberculosis disease. *Vaccine*. 2010;29(1):51–57.

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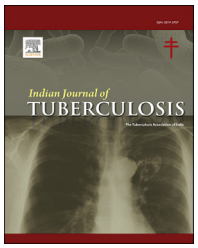

Correspondence

Building local roadmaps for TB free India

In April 2018, the journey towards a TB Free Local Roadmap was kindled by a collaboration between CETI (Collaboration for Elimination of TB among Indians-an NGO), AAPI (American Association of Physician of Indian Origin), and USAID (United States Agency for International Development). The partnerships lead to the development of a 10 city/district collaborative, with CETI leading the local effort and AAPI providing financial and logistic assistance and USAID, along with Government of India, RNTCP program, Ministry of Health and Family Welfare, WHO (World Health Organization) and a number of other agencies providing tremendous technical and organizational support.

A TB Free Local Roadmap serves as a strategic plan at a city/district level, which includes step-by-step directions, templates and metrics on creating a TB Free city/district. In the process of creating the Roadmap key local leaders learn how to build a team, develop a campaign, organize training, follow standard processes and assess overall quality.

The objective of the Local Roadmap Collaborative was to build a local roadmap in alignment with the well-crafted document *National Strategic Plan 2017–2025* for 10 "early adopter" cities and villages, Fig. 1. If successful, the Local Roadmap documents would become standardized for over 700 other districts in India.

Over the course of 7 months, from June to Dec 2018, two in-person workshops were held on June 9–10 in Indore and August 29–30, 2018 in New Delhi. Subsequently, over 10 national/international conference calls, 120 citywise team calls (approximately 15 per city) and 800 individual calls were conducted by the AAPI-CETI Team. Individual city-wide shared documents and WhatsApp message groups were created to enhance communication and collaboration between team members.

As of December 2018, seven out of 10 cities have launched a TB Free inauguration program- Indore, Bhopal, Rajkot, Varanasi, Lucknow, Nagpur and Gujrat villages-where over 150–300 community leaders gathered to commit to work for TB Free, and all had developed the Roadmap document and make a presentation to Joint Secretary of Ministry of Health and Family Welfare and other key leaders.

The Local Roadmap is a 35–40 page document which details the local strategy. The outline of the document is Fig. 2.

1. Local Epidemiology Data
2. Supporting Government Sector
3. Engaging the Private Sector
4. Empowering the Community (ACSM)
5. Emboldening the Civil Society Organizations
6. Informing the Media
7. Roles and Responsibilities

Each sector is then further detailed by a. Resources b. Achievement c. Challenges d. Strategies and e. Activity. For example, the activity section for the government sector outlines the list of innovative activities the government will take up over a period of 1–2 years. The Local Roadmap also contains a completed local Detect-Treat-Prevent Grid which aligns with local actions translated from the national strategic plan. This template was customized for each city, and individualized to local language for maximum impact.

The 10 steps to building Local Roadmap Over 3–6 months.

STEP 1: Develop Team: Develop a local team with DTO (District TB Officer) as the lead, along with WHO consultant, local opinion leader from private sector, NGOs, and representatives from other funding agencies such as JEET (Joint Effort for Elimination of TB) and social service organizations such as Rotary and Lions. If such teams exist in a given then district then engage, empower and tool up that body for an effort for TB Free locality.

STEP 2: Participate in Workshop: Attend a 2 day in-person workshop to meet other teams and learn about the steps for the TB Free Roadmap collaborative.

STEP 3: Conduct Inaugural Program: Conduct local inaugural programs with 200–300 persons in attendance at each program with key political, administration, healthcare and civil society leaders.

STEP 4: Schedule Conference Calls: Schedule twice monthly conference calls or meeting to begin drafting the Roadmap document.

STEP 5: Define Roles and Responsibilities: Have each stakeholder take responsibility for their sector eg. Rotary and Lions work on Roadmap section of social service organizations while DTO and WHO consultant take the lead on government sector.

STEP 6: Report and Compare Metrics Dashboard: Report and compare local city/district data TB Free City Comparison

Fig. 1 – The Local Roadmap is simply the local strategy for TB Free district or city in a format which parallels the National Strategic Plan.

Fig. 2 – The Local Roadmap has number of key components which include supporting the government sector, engaging the private sector, empowering the community, embracing the civil society organizations, and informing the media.

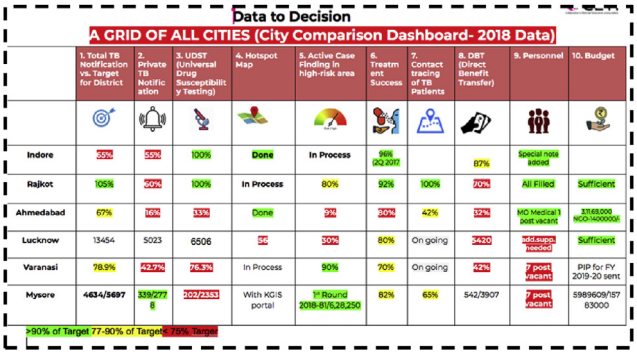

Fig. 3 – An example of th city wise comparison grid of common measures allows cities to quickly see how they are performing in comparison to others.

10 Metrics dashboard (developed by GoI, WHO, and CETI). Fig. 3. Evaluate and compare reports quarterly.

STEP 7: Work on Innovative Initiatives: Consider working on major initiatives such as active case finding with NGO on mobile app, or Continuous Quality Improvement processes or infection control initiatives through online courses from CETI.

STEP 8: Leverage AAPI Partnership: Engage and leverage AAPI partnership and communication with local private doctors with high TB patient-volume to motivate TB notification and treatment and follow up according to TB Standard TB Care.

STEP 9: Conduct Media Workshop: Conduct a media workshop at the near completion of the Roadmap document with all team members.

STEP 10: Present Local Roadmap: Present the final Local Roadmap document to State TB Officer (STO), MDNHH, Deputy Director General TB (DDGTB), Healthy Ministry's Joint Secretary, Health Minister, and Prime Minister Office.

The Local TB Free Roadmap development is a collaborative process and it does not dictate intervention strategies for local communities; rather it co-creates the Local Roadmap using quality improvement principles and sharing of best practices as established in the USAID TB CAREII June 2013 "Quality Improvement Handbook for TB and MDR-TB Programs". It' unique features include:

- Building on the existing national document, hence the document structure is already well accepted,
- Harnessing the local talent for TB elimination where by creating local urgency and impetus for TB elimination,
- Using "project based learning" approach where the development of a document serves the purpose of convening and team building and allows partners to dream about their "TB Free City/District",
- Achieving buy-in and empowering key persons who can make the necessary changes,
- Having a low-cost initiative with both standardization and customization with the help of technology such as Google Docs (editing together), Whatsapp (free voice calls), Free-conference-call (group conferences) and Skype (video calls) which enable rapid, no-cost, free flow of information and learning,
- Synergizing the national and international expertise with the tremendous local knowledge base especially in the area of local intervention
- Providing opportunity for local individuals to collaborate and interact with national and international experts by which local silos are broken down.

Throughout the Local Roadmap building process, key templates and tools were developed and tested. These tools are available to the GoI or other agencies on the website www.tbfree.org/aapi. This will obviate the need to reinvent them, rather to customize them for individual needs.

Many lessons were learned in developing the Roadmap:

1. A team approach to TB elimination at the district level is essential and of greatest need. For example, many private providers and NGOs are unaware of the high TB incidence and do not know their roles.
2. The DTO, district TB officer, should be the lead for TB elimination in a district. The DTO would greatly benefit from additional training in necessary skills for leadership development, quality improvement and engagement of other sectors. DTOs need to involve others

agencies and sectors as partners, not competitors, and as collaborators for TB elimination.
3. The DTO is often overburdened and under-resourced especially with personnel vacancies up to 30% in certain districts. This often leads to extreme discontent and poor performance from the government sector and even inaccurate data reporting to meet goals.
4. Excellent or poor performance of a district is often a reflection of DTOs' initiative and states' support.
5. Poor performing districts and states should take time and effort to learn from well performing districts and states, and create "Best Practices"
6. There is a tremendous gap between "policy" and "performance." For example policy requires contact tracing to be done yet few districts are doing it.
7. Some districts are working in mission mode and will likely be successful for reaching TB Free, while for others it is status-quo.
8. A public launch for TB Free city was a very effective event to bring all parties under common umbrella.
9. Additional agencies working on TB were initially reluctant to join the Roadmap effort stating "this does not help us," yet after engagement they found mutual value in collaboration.
10. A central collaborative coordinator is essential to engagement. Strong support from GoI, CTD, and WHO, is essential to making the collaborative successful.

Local Roadmap projects shortcomings and challenges:

1. There was difficulty engaging team members. Often it required AAPI-CETI teams 3 to 5 attempts to receive a reply from a DTO, WHO consultant or an opinion leader in a given city.
2. Crafting and writing of the Local Roadmap document felt redundant for some cities/districts since they had prepared similar document.
3. Many looked upon the exercise as "another report to be filed" rather than a working tool to help galvanize teamwork and relationships.
4. Some cities were unable to fully engage MDNHM and administrators.
5. There was a lack of understanding from all team members as to why based on TB Epidemiology, the TB incidence in their city was not declining sufficiently.
6. Outcome measures and change in them such as decline in TB incidence takes years, hence cannot be directly related to one intervention such as development of the Local Roadmap.

The development of the Local Roadmap is not a destination but rather it is a journey to have individual team members become aware of additional resources available for achieving a TB Free city/district. These steps encourage local stakeholders to co-create a common vision and mission, aligning and learning to work towards common metrics. The only way a district, city or even a village is going to become TB Free is the pooling of resources and alignment of efforts from public, private, non-profit and civil society.

In total, we believe there is an essential need for a local team building and local roadmap document to achieve TB Free locality. AAPI-CETI has offered a low-cost, successful, replicable, sustainable and scalable solution with tools which can be easily adopted within RNTCP structure.

Author's contributions

Manoj Jain – lead concept and design for project and leading the execution team.

Salil Bhargava – co lead for concept and design for project and co lead for execution team.

Monika Jain – reviewed the concept and design and prepared the manuscript development and drafting.

Sangeeta Pathak – reviewed concept and design and execution of project and day to day management.

All reviewed approved the final version.

Conflicts of interest

The authors have none to declare.

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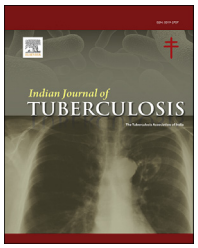

Correspondence

For drug resistant (DR) TB is there any strength in the old warriors yet?

Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis has been recently published in the Lancet.[1] This involved 50 datasets from 25 countries, with 12,030 patients treated for pulmonary multidrug-resistant tuberculosis. Of the drugs analysed, levofloxacin, moxifloxacin (MOX), linezolid (LZD), and bedaquiline were associated with greater treatment success and reduced death. Clofazimine (CLZ) and the carbapenems were associated with significantly improved treatment success but not reduced death. Pyrazinamide (PZA), streptomycin, amikacin (AMK), cycloserine and terizidone were associated with modest benefits, but only in patients with susceptible isolates, whereas the use of kanamycin (KAN), capreomycin (CAP), ethionamide (ETA), prothionamide, para-aminosalicylic acid (PAS), macrolides and amoxicillin-clavulanic acid (when used without carbapenems) were associated with no significant benefit or significantly worse outcomes.

Based primarily on the results of this meta-analysis, the shorter regime trials from Asia and Africa, the bedaquiline and delamanid trials and reports of high incidence of ototoxicity with injectable agents, the World Health Organization published a rapid advice statement suggesting a paradigm shift in the treatment of drug resistant TB.[2] The key features of this statement include a regrouping of medicines into three categories with levofloxacin/moxifloxacin/bedaquiline and linezolid in Group A, cycloserine/terizodone/clofazimine in Group B and the rest of the other drugs used for MDR TB in Group C. The principles of constructing a new longer MDR regime involve choosing all available drugs from Group A and B if susceptible and add other drugs from Group C only if Group A and B drugs cannot be used. Other factors governing choices include preference of oral over injectable agents; the results of drug-susceptibility testing (DST); the reliability of existing DST methods; population drug resistance levels; history of previous use of the medicine in a patient; drug tolerability; and potential drug–drug interactions. Finer details of these regimes are yet awaited.

However the extent of representation of Indian data in the meta-analysis is not clear. Clinicians & TB control program planners may be prompted to apply these results to govern empirical treatment choices for resistant TB in India. Furthermore this analysis applies to only pulmonary tuberculosis; extrapulmonary tuberculosis accounts for nearly 1/3 of the tuberculosis burden in any setting, more so in HIV infected and in children. This may generate important pitfalls if the resistance profiles of organisms, drug tolerability patterns, ecological, financial & logistic considerations are different from those represented in the meta-analysis.

Our reservations about the applicability of the conclusions in an endemic drug resistance TB hot spot such as India and Mumbai in particular are as follows:

1. Several of our MDR TB patients, have isolates that bear high level fluoroquinolone resistance with the *gyrA* D94G mutation that virtually precludes the addition of moxifloxacin. We have used high doses of moxifloxacin 600mg–800mg & find that it may not be tolerated well (unpublished data). There is also the concern of QT prolongation which is an additive interaction of fluoroquinolones with clofazimine and bedaquiline.
2. Despite the adverse effects of the second line injectables, dismissing drugs such as capreomycin is possibly premature, as it is difficult to 'cherry pick'drugs to garner a regimen of at least four effective drugs. Similarly scores of patients treated with kanamycin (the first line injectable agent used in MDR TB in our practice) have had good outcomes.[3,4]
3. Ethionamide has a role in patients who have isolates that are genotypically negative for *inh* A mutations and phenotypically susceptible. It is especially useful in tubercular meningitis due to its early bactericidal activity & good cerebrospinal fluid penetration. Our perception of the efficacy of ethionamide is vindicated by a recent study that used machine-learning algorithms to identify the important predictors of outcome in patients on ethionamide-containing regimens.[5] Ethionamide was an important contributor to MDR-TB treatment regimens, at Sensititre MIC <2.5 mg/L[5]. The authors propose that the drug be administered on condition of MIC <2.5 mg/L by Sensititre assay and 1.0 mg/L based on MGIT and agar dilution methods. We believe that MIC knowledge is of clinical importance not only in the use of ethionamide but also of the accompanying drugs.

Table 1 – Percentage Resistance in MDR TB 2017 = 1120

KAN	ETH	PAS	OFX	MXF 0.5	AMK	CLZ	CAP	PZA	LZD	MXF 2	EMB
0%	61.78%	8.21%	68.66%	60.57%	0.00%	0.00%	0.00%	76.82%	2.36%	11.53%	80.94%

Table 2 – Percentage Resistance in XDR TB 2017 = 310

KAN	ETH	PAS	OFX	MXF 0.5	AMK	CLZ	CAP	PZA	LZD	MXF 2	EMB
100%	80.96%	38.70%	91.60%	84.94%	74.91%	0.33%	60.86%	90.54%	12.50%	27.20%	93.44%

4. In our setting, PAS shows good in vitro susceptibility and although there are issues of the robustness of phenotypic DST, our published clinical outcome experience has been gratifying.[3,4] This is especially the case when isolates are resistant to quinolones, ethionamide and all first line agents and this drug is required to ensure that there are 4–5 effective drugs in the regime.
5. The pattern of % resistance to all other drugs in our MDR and XDR patients at our tertiary care centre in 2017 bears testimony to the points mentioned above (Tables 1 and 2).
6. The CNS penetration of bedaquiline is very limited; hence treatment of drug resistant tubercular meningitis which forms a significant and serious proportion of MDR TB in our practice will need assistance of other "old"drugs.
7. The adverse effects of linezolid including painful often irreversible peripheral neuropathy, thrombocytopenia and optic neuritis are commonly seen in practice with prolonged therapy and even with doses at 300 mg per day. This often precludes using the drug in many patients for the entire duration of treatment.
8. Using carbapenems has logistic, financial & ecological implications in our setting, notwithstanding the fallout of a build-up of carbapenem resistance in the gut flora with its inevitable consequences.
9. Promotion of cycloserine up the ladder as a result of the meta-analysis is noted; but absence of susceptibility testing makes it difficult to tease out the exact contribution of the drug in any regime. Another limitation of this drug stems from its poor lung cavitary & intracellular penetration. If used to treat tuberculous meningitis with this potentially neurotoxic drug at high doses, efficacy will be obtained at the price of severe neurotoxicity. Expense of the drug is also a limiting factor.
10. The efflux pump *Rv0678* that may confer cross resistance between clofazimine and bedaquiline is a matter of concern especially as clofazimine is being used both for MDR/XDR TB and leprosy in our part of the world.
11. Children contribute to a significant burden of MDR TB with 32,000 new cases per year. Bedaquiline is currently approved above the age of 18 (may be used in children weighing above 12 years and above weight 33 kg), while delamanid is approved in children 6 years and above.[6] Trials with delamanid in younger children are underway. This leaves out children below age three where older long MDR TB regimes based on susceptibility data of the index case or the contact may have to be used. Paradoxically, this is the group where it is most difficult to detect drug side effects including injectable associated ototoxicity or linezolid induced neuropathy/optic neuritis.

Hence careful circumspection is warranted in treating DR TB as geographic disparities in individual drug resistance & drug availability determine the exact treatment regimens. The heterogenous epidemiology of DR TB across continents is known and doling out similar TB regimens for all may not work. Local epidemiology and bacterial lineages are crucial issues that govern drug resistance. Whole Genome Sequencing will hopefully fill in this gap in future, especially if can be applied directly to clinical samples. While new drugs are a welcome addition to the therapeutic armamentarium and should be made readily available to patients who need them, there is plenty of fight left in the old warriors and their contribution to the treatment must be fully utilized. We strongly believe that individualized treatment and a personalized DST should be used to complement the programmatic approach for better control over this ancient scourge.

Conflict of Interest

The authors have none to declare.

REFERENCES

1. Ahmad N, Ahuja SD, Akkerman OW, et al. Collaborative Group for the Meta-Analysis of Individual Patient Data in MDR-TB treatment–2017.Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis. *Lancet*. 2018;392:821–834.
2. World Health Organization.Rapid Communication: Key Changes to Treatment of Multidrug- and Rifampicin-Resistant Tuberculosis (MDR/RR-TB). August 18. Available at: https://www.who.int/tb/publications/2018/rapid_communications_MDR/en/. Accessed on 8/11/2018.
3. Soman R, Pillai P, Madan S, Shetty A, Rodrigues C. Successful management of drug resistant tuberculosis using individualised DST. *J Assoc Physic India*. 2014;62:567–571.
4. Singhal T, Rodrigues C, Soman R, et al. Satisfactory Outcomes in Children with MDR Tuberculosis in Mumbai with Individualized Susceptibility Based Treatment. In: *Program and Abstracts of the 51st Annual Meeting of the Infectious Diseases Society of America*. Oct 2-6; 2013. San Francisco, California, USA, [Abstract # 1658].

5. Deshpande D, Pasipanodya JG, Mpagama SG, et al. Pharmacokinetics/pharmacodynamics derived dose, the role of MICs in clinical Outcome,and the resistance arrow of time in multidrug-resistant tuberculosis. *Clin Infect Dis*. 2018;67(S3): S317–S326.
6. Harausz EP, Garcia-Prats AJ, Seddon JA, et al. Sentinel project on pediatric drug-resistant tuberculosis. New and repurposed drugs for pediatric multidrug-resistant tuberculosis. Practice-based recommendations. *Am J Respir Crit Care Med*. 2017; 195(10):1300–1310.

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Case Report

Peritoneal tuberculosis with benign ovarian tumor

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1. Introduction

Abdominal tuberculosis should be considered when a patient presents with vague abdominal complaints, ascites and a pelvic mass, specifically in Indian subcontinent where incidence of tuberculosis is on a steady rise. But still making diagnosis is difficult. Combination of benign brenner ovarian tumor with peritoneal tuberculosis is rare and we present the case for same.

2. Case report

A 55-year-old patient presented to our department in January 2018 with complaints of gradual abdominal distention for 6 months. She also had associated pain in abdomen which was dull aching in nature. No history of fever, altered bowel or bladder habits or any other associated complaints were given by the patient. She had consulted a general practitioner for the same, where ascitic fluid was withdrawn and found to be negative for both malignant cells and AFB. Later in September 2017 she was put on ATT (anti tubercular treatment), in view of raised adenosine diaminase levels in the ascitic fluid. Our patient was a known case of type 2 diabetes mellitus and hypertension and was well controlled on insulin and antihypertensive medications respectively. She was thoroughly evaluated at our department. On examination her vitals were stable. She had tense ascites and a vague mass whose exact margins could not be assessed, was palpable in the left adnexa. Imaging studies revealed a left adnexal mass of $87 \times 84 \times 72\ cm^3$. Ascitic tap done was negative for tuberculosis and malignancy, and so was the endometrial aspiration done for CBNAAT, consequently decision for staging laparotomy was taken, which she underwent in January 2018. Per operatively 1400 cc of straw coloured ascitic fluid was drained. A mass of about 10×10 cm was present arising from the left ovary. It had irregular margins studded with areas of necrosis and increased vascularity. The uterus with right ovary and tube were inflamed and adherent to the bowel (Fig. 1). Multiple brown to yellow coloured deposits ranging from less than 0.5 cm–1 cm were present all over the abdominal cavity including the bowel, omentum and peritoneum (Fig. 2). Left salpingo ophorectomy was done and the frozen section revealed benign Brenner's tumour. Multiple biopsies were taken from abdominal lesions. Subsequently the abdomen was closed after maintaining proper haemostasis and sponge and instrument count. Postoperative phase was uneventful. Final histopathology report proven mass to be benign Brenner' s tumour (Figs. 3–5) and peritoneal deposits of tubercular origin (Fig. 6). ATT

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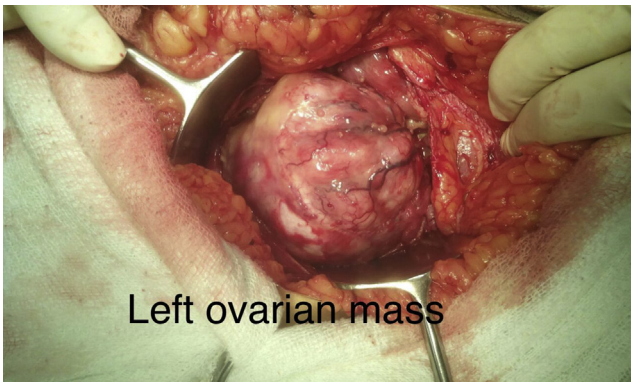


Fig. 1 – Per operative left ovarian mass.

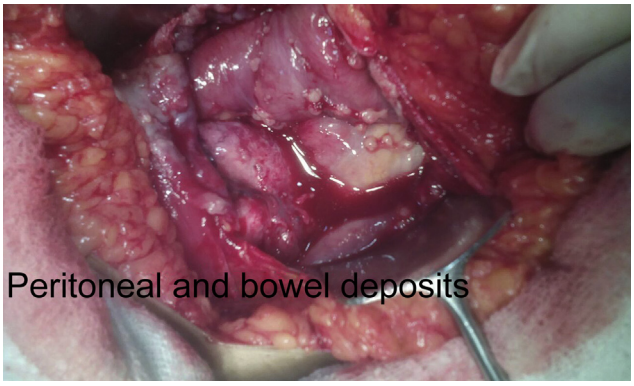


Fig. 2 – Per operative peritoneal and bowel deposits.

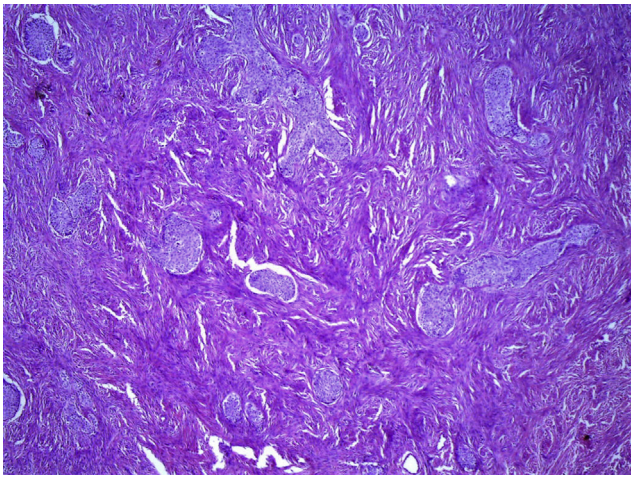


Fig. 3 – Brennar 4X: Photomicrograph of ovary showing multiple solid epithelial nests embedded within fibrous tissue (H&E stain, 4x magnification).

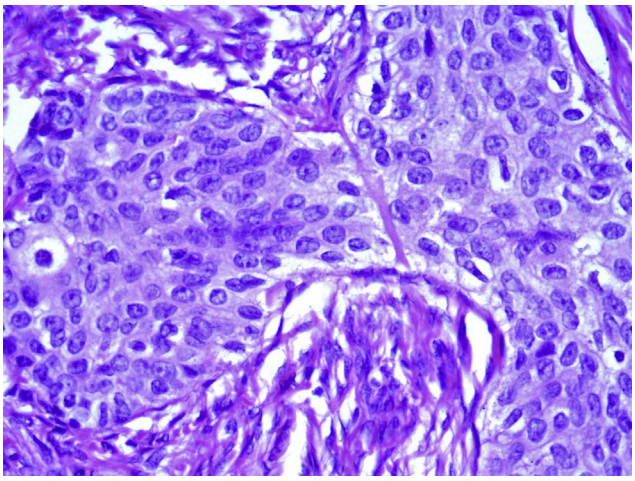


Fig. 4 – Brennar 20x: Photomicrograph showing cystic and solid areas of the epithelial cell nests with surrounding spindle cell fibrous stroma (H&E stain, 20×magnification).

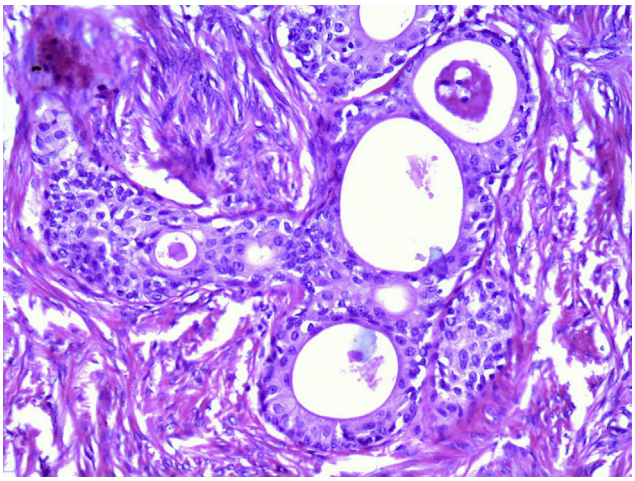


Fig. 5 – Brennar 40x: Photomicrograph of epithelial cell nests of Brenner tumor comprising of regular oval nuclei with nuclear longitudinal grooves in some cells (H&E stain, 40x magnification).

was continued in the postoperative period after histopathology confirmed the disseminated peritoneal deposits were granulomatous lesions. The patient has relief of symptoms and was in satisfactory condition till our last follow up in June 2018.

19th September 2017- ascitic fluid – ADA 47.70 IU/Lt.

22nd September 2017 ascitic fluid – DLC: predominantly lymphocytes: AFB -negative; malignant cells-negative.

7th January 2018: CA 125–43.9 IU/Lt; CA 19.9–2.16 U/Lt.

4th January 2018: CT SCAN- large sized left adnexal mildly enhancing solid hypodense lesion features suggestive of neoplasia.

24th January 2018: AFB -negative; CBNAAT: negative, malignant cells-negative.

3. Discussion

Brenner's tumour of the ovary is of a relatively uncommon occurrence. Most of them are benign and less than 5% are proliferating or borderline.[1] Most of the times these tumours are asymptomatic and when symptoms do appear they are confined to vague complaints like abdominal discomfort and bloating. The abdomen is the most common site of extrapulmonary tuberculosis, with peritoneal disease being the

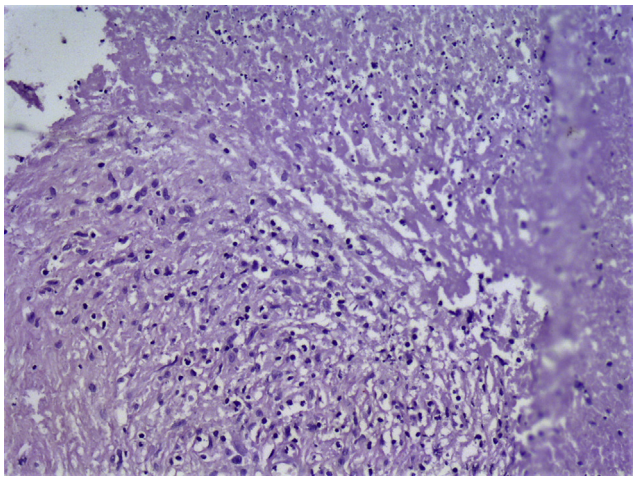


Fig. 6 – Brenner granuloma 20x: Photomicrograph shows epithelioid cell granuloma with caseous necrosis (H&E, 20x).

commonest form within the abdomen.[2] The most common differential diagnosis in a case of suspected peritoneal tuberculosis is peritoneal carcinomatosis. The presence of a tumour arising from the ovary makes the diagnosis even more elusive. In such a scenario the confirmation of the benign nature of the ovarian mass hinges the verdict. Since these are also the symptoms peritoneal tuberculosis patients predominantly have, the diagnosis of the case we present was guarded until the histopathological confirmation of the same. The histological patterns observed in Brenner's tumour are typically benign, with a few reports of borderline or malignant counterparts.[3] And so was the case with our patient. Surgical resection offers cure for most candidates of benign Brenner's tumour. Our patient was prone to disseminated form of tuberculosis not only due to the high prevalence of the infection in the Indian population but also her long standing diabetes making her status immunocompromised. Peritoneal TB is a treatable infection, but its diagnosis is often delayed due to nonspecific biological markers, long incubation times for cultures and the absence of characteristic radiographic or ultrasonographic signs. The pharmaceutical treatment of abdominal TB recommends a conventional ant tuberculous therapy for at least 6 months including an initial 2 months of rifampicin, isoniazid, pyrazinamide and ethambutol. The duration of treatment may also be extended to 12 or 18 months.[4] Our patient was put on ATT for 12 months. She is tolerating the treatment well with minimal side effects. This is a rare case not only in the difficulty of making a diagnosis of peritoneal tuberculosis in the absence of ascitic fluid results being positive but also the presence of an extremely rare benign Brenner's tumour further complicating the diagnosis.

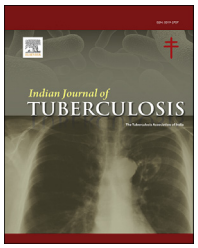
REFERENCES

1. Borah Tulon, Kumar Mahanta Ranjan, Deori Bora Bornali, Saikia Sameer. Brenner tumour of ovary: an incidental finding. *J Midlife Health*. 2011 Jan-Jun;2(1):40–41. https://doi.org/10.4103/0976-7800.83273 PMCID: PMC3156501 PMID: 21897739.
2. Uma Debi, Ravisankar Vasudevan, Prasad Kaushal Kishor, Sinha Saroj Kant, Sharma Arun Kumar. Abdominal tuberculosis of the gastrointestinal tract: revisited: World. *J Gastroenterol*. Oct 28, 2014;20(40):14831–14840. https://doi.org/10.3748/wjg.v20.i40.14831. Published online Oct 28, 2014.
3. Hemalatha AL, Konanahalli P. Bilateral malignant Brenner tumor of ovary. *J Obstet Gynaecol India*. 2005;55:81–82.
4. Blumberg HM, Leonard Jr MK, Jasmer RM. Update on the treatment of tuberculosis and latent tuberculosis infection. *J Am Med Assoc*. 2005;293:2776–2784.

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.journals.elsevier.com/indian-journal-of-tuberculosis/



Case report

Gastric tuberculosis presenting as non healing ulcer: A case report

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ABSTRACT

Tuberculosis is a major health problem in India. Gastrointestinal tuberculosis is the sixth most common causes of extrapulmonary tuberculosis and it mostly involves the ileocaecal region. Primary gastric tuberculosis in immunocompetent person is very rare. Stomach as its site is rare and is the sixth most common site of gastrointestinal tuberculosis. It mostly presents as a cases of non healing ulcer or gastric outlet obstruction. Yield of endoscopic biopsies for granuloma is low due to submucosal location of these lesions and mostly they are diagnosed after surgical intervention. We report a case of isolated gastric tuberculosis in a middle age immunocompetent female who present as a cases of non healing ulcer and responded well to standard antitubercular treatment. A high index of its suspicion should be kept in mind in any chronic infiltrative lesions of stomach like non healing ulcers and gastric outlet obstruction for its early diagnosis and treatment.

1. Introduction

Gastroduodenal tuberculosis accounts for around 1% of all cases of abdominal tuberculosis.[1] It's usually associated with pulmonary tuberculosis or in immunocompromised state. Isolated gastric tuberculosis in immunocompetent person is very rare and it usually presents as a case of peptic ulcer disease or gastric malignancy.[2]

2. Case report

A 39 year old female with no comorbidities and no addictions came to the hospital with complaints of pain in abdomen since one month. Pain was epigastric in location, intermittent, with no radiation. It increases with meals and has no effect of proton pump inhibitors. It was associated with three kilogram weight loss in a month. It was not associated with nausea, vomiting, reflux symptoms, jaundice, gastrointestinal bleeding, distension of abdomen, difficulty in passing motion or flatus or fever. There was no similar illness in past or in family. Her menstrual and obstetric history was normal. Her body mass index was 25.4 kg/m^2. General and systemic examination was unremarkable. Her complete blood counts, renal function test and liver function test were normal except for thrombocytosis. Her erythrocyte sedimentation ratio was 47 mm at one hour. She was negative for HIV and hepatitis B. Her ultrasonography of abdomen and X ray chest was normal. Then her upper gastrointestinal endoscopy was done which

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showed a large ulcer at incisura (Fig. 1). Histopathological examination of its biopsy revealed multiple granulomas with epitheloid cells and multinucleate cells (Fig. 2). Then her colonoscopy, contrast enhanced tomography of chest and abdomen was done which was unremarkable. Her montoux test was positive but serum calcium and angiotensin converting enzyme levels were normal. So it was a case of gastric ulcer granuloma. We have two options whether to start antitubercular treatment or to start immunosuppressive therapy. If we start immunosuppressive therapy, it can worsen the condition of the patient if its tuberculosis. On the contrary if we start antitubercular therapy, it can only delay the diagnosis if its crohn's disease. After discussing with the patient, empirical antitubercular treatment with standard four antitubercular drugs were started. After it her pain starts decreasing and she regains her weight. Repeat upper gastrointestinal endoscopy at end of two months of therapy shows complete healing of ulcer (Fig. 3).

3. Discussion

Tuberculosis is endemic in India. Pulmonary tuberculosis accounts for 85% cases and extrapulmonary cases accounts for 15% of cases. Abdominal tuberculosis is the sixth most common site of extrapulmonary tuberculosis. Ileocaecal region is the most common site of gastrointestinal tuberculosis followed by ascending colon, jejunum, appendix, duodenum and stomach.[3] Incidence of tuberculosis reduces as we move proximally and distally from ileocaecal region. Stomach as an isolated site of tuberculosis is rare due to bactericidal properties of gastric acid, paucity of lymphoid tissue and rapid transit of food in stomach.[4] Its route of infection is direct infection of mucosa, hematogenous spread or extension from any neighbouring tubercular lesion.[4] Most commonly it originates from adjacent celiac lymph nodes.[5] It presentation is mostly nonspecific as most common symptoms are abdominal pain followed by vomiting. Due to delay in its diagnosis, it mostly present as its sequelae in the form of gastric outlet obstruction, gastrointestinal bleed, perforation or fistulous communication. It mostly involves the antrum or prepyloric region in the lesser curvature.[6] Endoscopic biopsy has a low yield for granulomas due to submucosal location of these lesions. Due to it its diagnosed is delayed and mostly patient has to undergone surgical intervention. We were lucky to get granulomas in our endoscopic biopsy leading to its early diagnosis and treatment. Granulomas in stomach can be caused by many causes but tuberculosis and crohn's disease are the commonest. Granulomas are present in 80–100% of gastrointestinal tuberculosis compared to 30–60% in crohn's disease. Caseation is present in around 40% of cases of gastrointestinal tuberculosis. Granulomas are more in number, larger inn size and confluent in tuberculosis compared to crohn's disease.[7] Yield of culture is 10–30% and of polymerase chain reaction is 20–64% in gastrointestinal tuberculosis. Asia Pacific Association of Gastroenterology and Indian Society of

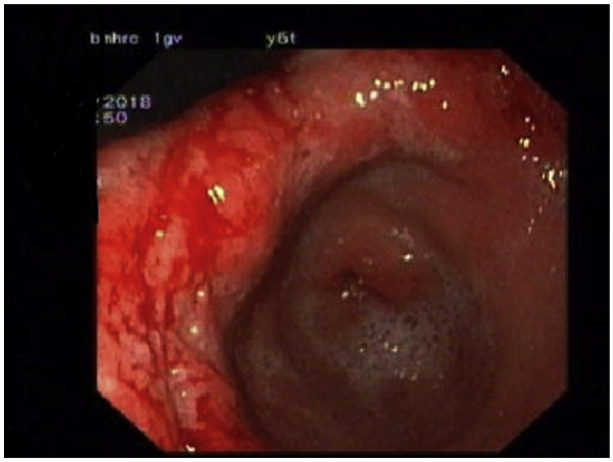

Fig. 1 – Endoscopic image showing large gastric ulcer.

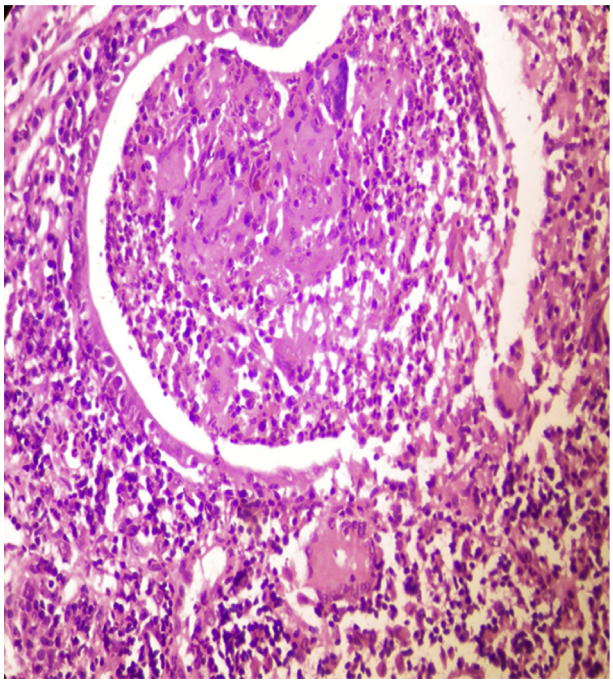

Fig. 2 – Endoscopic biopsy showing granuloma with multinucleate giant cell.

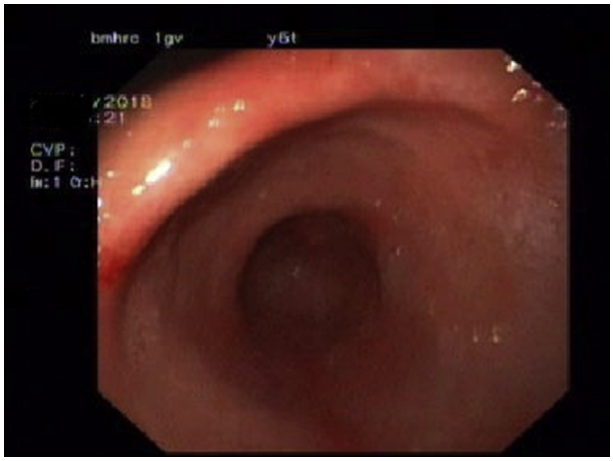

Fig. 3 – Endoscopic image showing healing of ulcer after 2 month of antitubercular treatment.

Gastroenterology consensus on crohn's disease has suggested a trial of antitubercular treatment in case where there is a doubt in its diagnosis.[8,9] Treatment of gastric tuberculosis is conventional antitubercular therapy for at least six months with initial two months of intensive therapy. Some authors has also recommended one year duration of treatment for gastric tuberculosis.[10] Surgery is often needed for gastric outlet obstruction or massive gastrointestinal bleed.

So to conclude, tuberculosis can involve any part of the gut even in immunocompetent state. Gastric tuberculosis though rare should be in the differential diagnosis of non healing ulcers and gastric outlet obstruction. In the presence of granuloma in any lesion of gut without any other definitive diagnosis, empirical antitubercular therapy is the best way out.

Conflicts of interest

The authors have none to declare.

REFERENCES

1. Sharma MP, Bhatia V. Abdominal tuberculosis. *Indian J Med Res*. 2004;120:305–315.
2. Gupta B, Mathew S, Bhalla S. Pyloric obstruction due to gastric tuberculosis: an endoscopic diagnosis. *Postgrad Med J*. 1990;66:62–65.
3. Marshall JB. Tuberculosis of the gastrointestinal tract and peritoneum. *Am J Gastroenterol*. 1993;88:989–999.
4. Tromba JL, Inglese R, Rieders B, Todaro R. Primary gastric tuberculosis presenting as pyloric outlet obstruction. *Am J Gastroenterol*. 1991;86:1820–1821.
5. Placido RD, Pietroletti R, Leardi S, Simi M. Primary gastroduodenal tuberculosis infection presenting as pyloric outlet obstruction. *Am J Gastroenterol*. 1996;91:807–808.
6. Loig JD, Vaiphei K, Tashi M, Kochar R. Isolated gastric tuberculosis presenting as massive hematemesis: report of a case. *Surg Today*. 2000;30:921–922.
7. Das K, Ghoshl UC, Dhali GK, Benjamin J, Ahuja V, Makharia GK. Crohn's disease in India: a multicentre study from a country where tuberculosis is endemic. *Dig Dis Sci*. 2009;54:1099–1107.
8. Ramakrishna BS, Makharia GK, Ahuja V, et al. ISG consensus statements on crohns disease in India. *Indian J Gastroenterol*. 2015;43:3–22.
9. Ooi CJ, Makharia GK, Hilmi I, et al. Asia pacific consensus statement on crohns disease. Part 2: management. *J Gastroenterol Hepatol*. 2016;31:56–68.
10. Rao YG, Pande GK, Sahni P, Chattopadhyay TK. Gastroduodenal tuberculosis management guidelines, based on a large experience and a review of the literature. *Can J Surg*. 2004;47:364–368.

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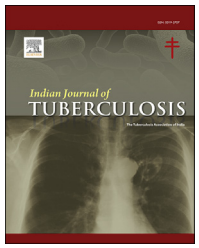

Editorial

Tuberculosis Association of India—In a torchbearers role

Tuberculosis has been a major public health problem in the country but it was only in the year 1912 that the then Government appointed Dr. A. Lankaster to undertake an in depth assessment of situation and thus the enormity of the problem was realized. However, in the absence of any effective treatment, the government efforts in combating the disease were only half hearted. It was primarily philanthropic societies and voluntary organizations who took the lead in focusing on the issues. Gradually the momentum picked up and in the year 1929, King George V Thanks giving Anti-Tuberculosis Fund was created, which primarily focused on health education, establishing a few TB clinics and training health workers.

The Establishment of Tuberculosis Association of India in the year 1939 was a great landmark in the history of Tuberculosis prevention and cure in India. With the prime objective of prevention, control, treatment and relief from Tuberculosis the Association has come a long way in its glorious existence of over 80 years.

The Association has proud tradition of having the blessings of President of India as it's Patron. The Director General of Health Services of the Government of India is ex-officio Chairman of the Association. The general management of affairs of the Association invested in and rests with the Central Committee who for purpose of Act XXI of 1960 is taken to be and acts as the Governing Body of the Association. The Central Committee includes among others the nominees of the Patron, Trustees of the Association, Honorary Treasurer, the Members of State TB Association, Members of Parliament, Director General of Armed Forces Medical Services, Director General, Railway Health Services, TB Adviser of the Government of India.

Primarily the main functions of TAI were to act as an Advisory Body on the prevention, control, treatment and relief of TB. It used to be a coordinating agency for standardizing methods for TB control, establishing model demonstration centres, undertaking research and investigation on subjects concerning TB and training health workers of the community and professionals. In the pre-chemotherapy era, when no anti TB drugs were available, the emphasis was laid on early diagnosis and prevention of the disease. Use of collapse therapy, nutritional support as the treatment and BCG vaccination for prevention of disease were practiced and advocated. TAI used to propagate these policies through workshops and conferences.

During the Chemotherapy era, it was realized that the traditional approach to the TB problem i.e. the sanatorium was beyond the means of our country with the limited resources and hence worked out the scheme of domiciliary treatment (then known as the Organized Home Treatment - OHT). This was later adopted as domiciliary treatment in National TB Control Programme. To demonstrate OHT, a model clinic, New Delhi TB Clinic was established, where in addition to treatment, patients were given advice regarding sputum hygiene, contact examination and other preventive measures.

TAI is uninterruptedly publishing IJT, the quarterly journal, for over 65 years now. This is the only renowned TB journal published at the national level. Being a highly respected journal among the medical fraternity, it is indexed in Medline of National Library of Medicine USA. The Journal incorporates original research articles on TB and respiratory diseases of international standards. It has, on its editorial board, eminent scholars and researchers and good circulation among TB workers, Institutions in India and worldwide. The journal has been given a new look from the January, 2015 issue which coincides with its publication and marketing being outsourced with M/s. Elseviers.

IJT has been publishing many review articles in recent years pertaining to recent developments in the field of TB. Noteworthing are: Journey of Tuberculosis Control in India,[1] The Dynamics of Tuberculosis Epidemiology,[2] Smear microscopy as a diagnostic tool of tuberculosis: Review of smear negative cases, frequency, risk factors, and prevention criteria,[3] Detection of drug resistance in *Mycobacterium tuberculosis*: Methods, principles and applications,[4] Standards for TB care in India: A tool for universal access to TB care,[5] Accelerating TB notification from the private health sector in Delhi, India,[6] Extensively Drug-resistant Tuberculosis (XDR-TB): A daunting challenge to the current End TB Strategy and policy recommendations,[7] Abdominal tuberculosis: A retrospective analysis of 45 cases,[8] Endobronchial tuberculosis,[9] Central Nervous System Tuberculosis[10], Vaccines against

tuberculosis: A Review,[11] Progress in Achieving Universal Access to Care for Multidrug Resistant Tuberculosis (MDR-TB),[12] Reaching all Tuberculosis Patients in India with Quality Care: Challenges, Opportunities and the Way Forward to Address the Missing Millions,[13] Improving Quality of Tuberculosis Care in India[14]

In this special issue of IJT, we are publishing all these most relevant topics related review articles at one place for benefit of our readers.

REFERENCES

1. Arora VK, Chopra KK. Journey of tuberculosis control in India. *Indian J Tuberc*. January 2019;Volume 66:178–183.
2. Rieder Hans L. The dynamics of tuberculosis epidemiology. *Indian J Tuberc*. January 2014;Volume 61:19–29.
3. Alnour Tarig MS. Smear microscopy as a diagnostic tool of tuberculosis: review of smear negative cases, frequency, risk factors, and prevention criteria. *Indian J Tuberc*. July 2018;Volume 65:190–194.
4. Gupta Anamika, Anupurba Shampa. Detection of drug resistance in mycobacterium tuberculosis: methods, principles and applications. *Indian J Tuberc*. January 2015;Volume 62:13–22.
5. Nair Sreenivas Achuthan, Sachdeva KS, Malik Parmar, et al. Standards for TB care in India: a tool for universal access to TB care. *Indian J Tuberc*. October 2015;Volume 62:200–206.
6. Kundu Debashish, Chopra Kamal, Khanna Ashwani, Babbar Neeti, Padmini TJ. Accelerating TB notification from the private health sector in Delhi, India. *Indian J Tuberc*. January 2016;Volume 63:8–12.
7. Rahman Md Arifur, Sarkar Atanu. Extensively Drug-Resistant Tuberculosis (XDR-TB): a daunting challenge to the current End TB Strategy and policy recommendations. *Indian J Tuberc*. July 2017;Volume 64:153–160.
8. Shreshtha Suruchi, Ghuliani Deepak. Abdominal tuberculosis: a retrospective analysis of 45 cases. *Indian J Tuberc*. October 2016;Volume 63:219–224.
9. Lee Pyng. *Endobronchial Tuberc*. January 2015;Volume 62:7–12.
10. Guleria Randeep, Kavitha. *Cent Nerv Syst Trauma*. July 2014;Volume 61:195–199.
11. Bhargava Salil, Choubey Satyadeo, Mishra Satyendra. Vaccines against tuberculosis: a review. *Indian J Tuberc*. January 2016;Volume 63:13–18.
12. Wares Fraser, Falzon Dennis. Progress in achieving universal access to care for multi drug resistant tuberculosis (MDR-TB). *Indian J Tuberc*. October 2014;Volume 61:298–306.
13. Sahu Suvanand. Reaching all tuberculosis patients in India with quality care: challenges, opportunities and the way forward to address the missing Millions. *Indian J Tuberc*. April 2014;Volume 61:116–120.
14. Pai Madhukar, Satyanarayana Srinath, Hopewell Phil. Improving quality of tuberculosis care in India. *Indian J Tuberc*. January 2014;Volume 61:12–18.

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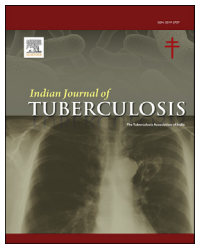

Review article

Protocol for the management of newly diagnosed cases of tuberculosis

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Keywords:
Tuberculosis
Newly diagnose TB
Rifampicin resistance
India

ABSTRACT

To achieve the targets and milestones set by the World Health Organization (3) to their 'End TB Strategy' to stop the global TB epidemic by 2035 and India's commitment to eliminate this disease from the country by 2025 (4), it will be important to improve the case finding and effectively treat cases of tuberculosis both in the public and the private sector, the latter still holding a major share. To strengthen the management of tuberculosis in the private sector and to have uniformity in the treatment, we need to have a protocol, suitable to our socio-economic conditions, which will not only provide guidance in getting better treatment outcomes, but also help to interrupt transmission of the disease in the community, besides curbing the development of drug resistance. Several guidelines on the management of tuberculosis are available, but these are considered as very good starting points for treatment but not the only treatment option, since guidelines cannot address every possible situation and substitute for good clinical judgment (5).Hence to meet these requirements and shortcomings following protocol is provided to manage cases of tuberculosis and resolve several issues related to it.

1. Introduction

Worldwide, around 10 million people still fall ill with the tuberculosis each year (more adults than children, and more men than women), and it remains to be one of the top 10 causes of death and also is the leading cause of death from a single infectious agent, ranking above HIV and AIDS[1] Tuberculosis (TB) continues to be India's severest health crisis as it kills an estimated 480,000 people every year (more than 1,400 every day), the third leading cause of years of life lost (YLLs), in the country. India continues to be the highest TB burden country in the world[2] accounting for more than one fourth (2.8 million cases) of the annual global incidence.

To achieve the targets and milestones set by the World Health Organization[3] to their 'End TB Strategy' to stop the global TB epidemic by 2035 and India's commitment to eliminate this disease from the country by 2025,[4] it will be important to improve the case finding and effectively treat cases of tuberculosis both in the public and the private sector, the latter still holding a major share. To strengthen the management of tuberculosis in the private sector and to have uniformity in the treatment, we need to have a protocol,

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suitable to our socio-economic conditions, which will not only provide guidance in getting better treatment outcomes, but also help to interrupt transmission of the disease in the community, besides curbing the development of drug resistance. Several guidelines on the management of tuberculosis are available, but these are considered as very good starting points for treatment but not the only treatment option, since guidelines cannot address every possible situation and substitute for good clinical judgment.[5] Hence to meet these requirements and shortcomings following protocol is provided to manage cases of tuberculosis and resolve several issues related to it.

2. The main objectives of tuberculosis therapy

While treating cases of tuberculosis following aims and objectives need to be considered for the benefit of the individual and the community: [6]

(1) to rapidly reduce the number of actively growing bacilli, thereby decreasing severity of the disease, minimizing the risk of death and disability; obtaining cure and halting transmission of *M. tuberculosis to other persons*;
(2) to eradicate populations of persisting bacilli in order to achieve durable cure (prevent relapse) after completion of therapy; and
(3) to prevent acquisition of drug resistance during therapy

3. Criteria for diagnosis of tuberculosis

The diagnosis of tuberculosis is based on the following criteria:

1. Clinical criteria: When the symptoms are typicalor suggestive of tuberculosis and where an alternative diagnosis is less likely; the disease is life threatening; there is an exposure risk to tuberculosis; the individual has an immuno-compromised status (HIV infection, Diabetes mellitus, Long-term corticosteroid therapy); and where there is concern for loss of follow-up and high transmission risk. In one or the more of these clinical situation's,tuberculosis is to be suspected as a strong probability, especially in areas with a high prevalence of the disease.
2. Radiological criteria: Radiographic imaging, mostly plain radiograph, and only occasionally supported by CT images and ultrasound, consistent with tuberculosis. However, radiological evidence should mostly arouse a suspicion of tuberculosis, which needs to be confirmed bacteriologically, in as many cases as possible, except in early non-bacillary cases.
3. Laboratory, bacteriological or histopathological criteria: Evidence of tubercular infection (tuberculin or Interferon Gamma Release Assay (IGRA) test positive); smear and/or culture for *Mycobacterium tuberculosis*; or rapid molecular test positive for TB; Cytology or histopathology findings consistent with tuberculosis

4. Indications for use of X-pert MTB/RIF assay

This relatively new rapid cartridge based fully automated molecular test, approved by WHO,[7,8] which simultaneously detects *M. tuberculosis* as well as mutation that confer rifampicin resistance, with a high sensitivity and specificity, making it useful in diagnosis of tuberculosis and in screening the cases for MDR-TB. It preferably should be done, if possible, in all the cases of tuberculosis, or else, at least in those cases who are contacts of MDR-TB cases; whose sputum is positive at the end of initial intensive phase of therapy; cases having clinico-radiological failure of therapy; all the cases showing relapse of disease after completion of therapy and who had defaulted from treatment. The X-pert MTB/RIF assay, however, is not suitable for monitoring response to treatment in a case of tuberculosis which requires conventional microscopy & culture.

5. Empiric treatment

In certain clinical situations, an empiric anti-tubercular treatment is sometimes started, even in the absence of a definitive diagnosis. This could be a case with a strong clinical suspicion of tuberculosis; in an area with high prevalence of tuberculosis e.g. India; with a risk of progression and dissemination of disease; who may be considered for anti-tuberculosis therapy, even in absence of some important diagnostic parameters. In above mentioned situation, persistence of a radiographic lesion despite a suitable course of antibiotic (without an anti-mycobacterial effect), to exclude possibility of a non-tubercular infection, also makes a case for empiric anti-tubercular treatment.

Clinical judgment and the index of suspicion for tuberculosis are critical in making a decision to initiate treatment in some patients who have a high likelihood of tuberculosis based on certain circumstantial evidences e.g. history of exposure to tuberculosis or who are seriously ill with a life threatening disease; empiric treatment with an optimal drug regimen needs to be initiated promptly even before the results of smear microscopy, molecular tests, and mycobacterial culture are known.

6. When to delay or not to initiate treatment

In the absence of a definitive diagnosis, patients who are clinically stable, where symptoms are not typical of tuberculosis; radiographic imaging not consistent with tuberculosis or is indicative of quiescent or healed lesions; smear positive for AFB but rapid molecular tests negative (suspicion of non-tuberculous mycobacterial infection) or both the tests are negative; the transmission risk of disease is low and an alternative diagnosis is possible; the anti-tuberculous

treatment in such situations needs to be postponed or is not given at all, till a definite lead to diagnosis becomes available.

7. Sputum smear and culture negative tuberculosis

Anti-tuberculosis treatment sometimes, even when the initial sputum smears are negative, is initiated in patients who based on their careful clinical and radiographic evaluation, are thought to have pulmonary tuberculosis. Later, If *M. tuberculosis* is isolated on culture or a rapid molecular test is positive, treatment for active disease is continued for a full course, and if possible based on drug susceptibility test results. Patients who have negative cultures but who still are presumed to have pulmonary tuberculosis should have thorough clinical and radiographic follow-up after 2–3 months of therapy. If there is clinical or radiographic improvement and no other etiological disease is identified, the anti-tuberculosis treatment should be continued.[9]

8. Detection of drug resistance before initiation of therapy

This may be done either by newer molecular techniques (X-pert MTB/RIF assay for rifampicin resistance; Line Probe Assay for the detection of resistance to fluoroquinolone, ethambutol, isoniazid and second line injectable drugs); or by conventional phenotypic drug sensitivity tests. The inability to perform these tests should not form a barrier to the start of treatment. However, it will be preferable to work up at least those cases for drug resistance who had an exposure to a resistant case of tuberculosis. It will also be important in such situations to know the resistance profile of the index case for deciding the drug regimen for better management of a case. World Health Organization recommends that drug-susceptibility testing should be performed in all these cases for at least isoniazid and rifampicin.[10]

9. Pre-treatment counselling prior to start of therapy

It is important that a prior counselling of the patient and near relatives is done on the following lines before start of therapy in all the cases of tuberculosis to achieve better outcomes:

1. Educating the patient about tuberculosis and its prolonged treatment, emphasizing on the possible adverse effects of drugs [11,12]
2. Discussing about the need for proper compliance to treatment and its expected outcomes, including the chances of obtaining cure in these patients.
3. Plans for periodic assessment of response to therapy; and how to prevent drug resistance occurring or amplification of resistance taking place during therapy
4. Discussing infectiousness and infection control measures to prevent transmission of the disease.[13]
5. Need for nutritional supplement

10. Presence of co-morbidities, alcoholism, tobacco addiction and air pollution

There is a constant interplay in a case between the environment, health status, and genetics. In tuberculosis the important host factors that play a role in this dynamic process include age, nutritional status, emotional and physical stress, concurrent co-morbid conditions, social circumstances, and possibly host genotype, including gender.[14] In the pre-chemotherapy era, treatment of tuberculosis was directed towards strengthening the host's resistance and providing nourishing diet and rest were believed to improve the patient's immune response.[15,16] Unfortunately, in the present time, India is facing, in abundance, problem of co-morbid conditions and factors like diabetes mellitus, HIV infection, malnutrition, vitamin-D deficiency, alcoholism, addiction to tobacco, ambient pollution etc., which not only predispose to tuberculosis but also adversely affect its management and outcomes.

Diabetes mellitus (DM), whose prevalence in India is high, is known to increase the risk of tuberculosis, accelerate its progression& complicate the treatment with poor outcomes.[17–19] An association between malnutrition & tuberculosis has also been found in several studies and there are several epidemiological evidences and biological basis favouring this relationship.[20] Hence, it is not only important to identify these co-morbid conditions, but also to simultaneously manage them effectively for better results.

Alcoholism, tobacco addiction and environmental pollution also are important contributory factors to the development of tuberculosis and its management and abstaining from these is important for the control of tuberculosis problem.

11. Treatment of newly diagnosed cases of tuberculosis

Treatment of newly diagnosed cases tuberculosis, having no or less than 15 days anti-tuberculosis treatment in past, is discussed below, however, it does not include cases harbouring drug-resistant bacilli. To achieve high success rates and prevent drug resistance developing or amplification of drug resistance occurring during treatment, these cases need to be treated effectively with an optimal therapy. Some basic principles and guidelines to be followed for this purpose are mentioned below:

Effective treatment of tuberculosis, though apparently simple, is one of the most challenging aspects in the management of tuberculosis. There are several problems and issues in the treatment including drug intolerance, adverse drug reactions, prolonged treatment, cost of therapy, emergence of drug resistance etc. In situations where sensitivity status is known prior to start of therapy or becomes available during therapy, the drugs are chosen or modified according to the pattern of resistance, if any, in the case. Where facilities for culture or rapid molecular based drug-susceptibility testing do

not exist, the drug regimen is formulated in such a way that it yields, high cure rates with low relapses. Keeping this in mind the choice of drugs is done based on some basic principles e.g. giving a bi-phasic therapy, combining multiple drugs, usually four in the initial intensive phase (rifampicin, isoniazid, ethambutol and pyrazinamide) and three drugs in the continuation phase (rifampicin, isoniazid and ethambutol), for a prolong edduration.[21,22]

Multiple drug therapy in tuberculosis is given to combat the problem of resistant mutants present in a wild population besides the other factors e.g. primary drug resistance in the region which is high in India;[23] tackling different populations of mycobacteria in a lesion[24] (rapid growing; slow growing; dormant bacilli with spurts of metabolism; and fully dormant bacilli); and utilizing various properties of anti-tuberculous drugs (bactericidal action; bacteriostatic action; and prevention of resistance to companion drugs. The resistant mutants in a lesion are proportionate to the size of bacillary population which is influenced by several factors including the type of lesion, solid or liquefied; cavitary or non-cavitary; size of the cavity; extent of disease; environmental pH and partial oxygen pressure; target organ; concentration of the drug at the site etc. Multiple drugs are crucial for the outcome of treatment as these are helpful in patients harbouring large bacterial populations, to put a rapid stop to bacterial multiplication killing drug-susceptible bacilli fast obtaining, an"early kill".[14] This leads to a rapid reduction in the total number of bacilli in the sputum especially within the first 2 weeks of treatment.[25]

All treatment regimens have two phases of therapy – an initial intensive phase and a continuation phase.[26,27] The initial intensive phase of treatment is designed to kill actively growing and semi-dormant bacilli and the plan should be to include a minimum of three active drugs in a case of tuberculosis to obtain cure minimizing the risk of development of drug resistance. Pyrazinamide is added as a fourth drug to shorten treatment duration since it has the capability to work in an acidic environment killing slow growing bacilli. Hence, to cover the risk of development of drug resistance in new cases, the current recommendation is for giving four drugs in the initial intensive phase of treatment, not used previously or that have a higher likelihood of being susceptible. All treatment regimens must have at their core a minimum of two very active drugs responsible for killing and sterilising *M. tuberculosis*, and two or more accompanying drugs that kill little but are responsible for protecting the core drugs from developing drug resistance. Thus, drug resistance is an important consideration while deciding a regimen; however, giving multiple drugs takes care of resistance developing and obviates the need for identifying initial drug resistance to some extent.

Injection streptomycin may often be used as a replacement drug in adults below the age of 45 years, when one of the drugs in the intensive phase, cannot be given because of intolerance or adverse reaction. On occasions moxifloxacin or levofloxacin can also be used in place of ethambutol during intensive phase in adults in whom ethambutol cannot be used, or in place of isoniazid throughout treatment in adults in whom it cannot be used.

12. Continuation phase of treatment

The continuation phase eliminates most residual bacilli and reduces failures and relapses. This is a less aggressive phase of chemotherapy started when bacterial population is much reduced as demonstrated by absence of tubercle bacilli in sputum,[28] starting after 8–12 weeks of initial intensive phase and continues till the end of therapy. Since the numbers of bacilli are low hence there is less chance of selecting drug-resistant mutants and therefore, fewer drugs are needed.[14] During this phase usually two effective drugs to which bacilli are sensitive or likely to be sensitive are given (rifampicin and isoniazid). However, WHO guidelines now recommend, in areas with high prevalence of primary isoniazid resistance (>4%), adding ethambutol as the third drug, thus making a combination of isoniazid, rifampicin and ethambutol.[10,29] This improves the success rate besides preventing the amplification of drug resistance.

13. Extension of continuation phase

Patients with cavitation on the initial chest radiograph and who have positive cultures at completion of 2 months of therapy, it is recommended to extend the continuation phase for an additional 3 months, making it 7 months plus intensive phase of 2 months.[30] Those patients who only have one of the above-mentioned features, additional factors that make a case for prolong treatment include:more than 10% below ideal body weight; an active smoker; having diabetes, HIV infection, or any other immunosuppressing condition; or having extensive disease on chest radiograph.[6,31–36]

14. Type and location of lesion

The type of tissue harbouring tubercle bacilli may affect drug action since not all drugs are able to penetrate all tissues and cells or permeate biological membranes, including the normal blood–brain barrier. The number of tubercle bacilli also varies widely with the type and location of the lesion. The disease may be pulmonary or extra-pulmonary and in the former it may be cavitary or non-cavitary and thereby having a varied bacterial population. The number of bacilli in a cavitary lesion is high and a middle size cavity with a bronchial communication has 10^8 (100 million) bacilli, whereas in an encapsulated nodular lesion of the same size with no bronchial communication, the number can be as low as 10^2 (100) bacilli. The numbers are also rather low (10^2)in extra-pulmonary lesions of the skin, lymph glands, meninges, and bones.[14] The larger the bacterial population, the higher is the probability that resistant mutant strains are present even before treatment is started [37] and this fact needs to be actively considered when deciding a therapeutic regimen in a case.

Penetration of the drugs in the affected tissue has also to be taken into consideration. Certain tissue, e.g. brain and meninges; bones and joints, have poor penetration of drugs which needs selection of such drugs which easily penetrate

the affected organ and sometimes may even have to prolong the therapy.

15. Proper therapeutic dosages

A proper therapeutic dosage of a drug is always given to generate a suitable serum inhibitory concentration essential for an effective treatment of tuberculosis. Sub-therapeutic dosage leads not only to poor outcomes but also to development of drug resistance. Drugs must be given in doses large enough to produce an inhibitory concentration at the sites where bacilli are found, but it is not necessary to keep this concentration at a constant level. Studies have shown that it is the peak serum level that is more important for the response to the drug.[38] To achieve this most of the anti-tubercular drugs, as far as possible, are given in a single dose rather than in divided dosage and are also preferably given on an empty stomach for better absorption. Overdosage is also to be avoided, which not only leads to increase in the pill counts, but also more drug intolerance and toxicities leading to interruptions in treatment, often withdrawal of the drug, poor treatment compliance and inferior results. As a basic principle a single drug should never be added to a failing regimen.[14]

16. Weight monitoring and re-adjustment of dosages

The therapeutic dose of each drug in the regimen must be calculated according to the body weight of the patient as far as possible. Monitoring of weight is also to be done in all cases preferably at monthly intervals to assess response to treatment and to make dose adjustments according to the changes.

17. Therapeutic dose of rifampicin

Currently the doses of rifampicin used in the regimens is often lower than the therapeutic doses in a subset of patients with higher weight. The standard rifampicin dose of 8–12 mg/kg body weight to a maximum of 450 or 600 mg is being used all these decades. However, it never has been the optimal dose.[39,40] The dose used since 1970 was established as the minimum that was effective—largely because of fears of side effects and the high cost of rifampicin at the time.[41] This argument eventually made its way into tuberculosis treatment guidelines and still is continuing to be there.[42,43] The USPHS tuberculosis study in 1979 also had fixed up a dose of rifampicin to a maximum of 600mg/day (10mg/Kg).[44] Recent pharmaco-dynamic studies suggest that the current dose of rifampicin is at the lower end of the dose–response curve. It has also been found that a relatively small increase in dose of rifampicin is associated with a more than proportional increase in its AUC.[39,40,45–49] Rifampicin exhibits concentration-dependent killing of *M. tuberculosis*; higher exposures potentially induce better outcomes. This property of RMP has not been exploited by the standard dose, and higher doses appear to be well tolerated. Higher rifampicin exposures potentially offer more cure, less drug-resistant mutants, and a shorter treatment duration.[48,50–53] Presently, higher doses of rifampicin, in a range of 15–35 mg/kg, have been studied in several clinical trials with good results and acceptability.[52,54–56] Jindaniin their RIFATOX Trial[56]; found that a daily dose of 20 mg/kg rifampicin for 4 months is safe and well tolerated and no significant increase in adverse events occurred when the dose was increased from 10 mg/kg to 15 mg/kg or 20 mg/kg. Similar results on the safety have been shown in several other studies. Indeed, increased serum transaminase concentrations and bilirubin levels after starting rifampicin treatment are common, but these do not appear to be dose related. Severe hepatotoxicity associated with the use of rifampicin has only rarely been reported to occur in the elderly and those with pre-existing liver disease. However, caution should be exercised in patients whose liver function tests are compromised for any reason; in those with viral hepatitis infection; and in pregnant women.[45,49,55,57,58]

Hence, till definite recommendations are available on higher doses, at least, the standard therapeutic dose of 10mg/Kg., be given according to the body weight in patients belonging to the higher weight group, exceeding 600 mg maximum dose, to improve the treatment outcomes and minimizing contribution of this factor of sub-therapeutic dosing leading to the development of drug resistance.

18. Daily regimens

The frequency of administration of anti-tubercular therapy must be daily in both, initial intensive and the continuation phases. The treatment success rates are better and relapse rates lower with the daily regimene specially considering the frequently encountered advanced lesions with high bacillary loads in India. According to WHO guidelines (2017), all patients with drug-susceptible pulmonary tuberculosis, the use of thrice-weekly dosing is not recommended in both the intensive and continuation phases of therapy, and daily dosing remains the recommended dosing frequency.

19. Fixed dose combination (FDC)

The use of fixed-dose combination (FDC) tablets is recommended over separate drug formulations in treatment of patients with drug-susceptible tuberculosis.[10] The reduced pill burden by using FDCs may be especially valuable in patients with co-morbidities. However, there are issues of bioavailability with FDC which needs to be ensured using quality drugs only. Moreover, in the event of drug intolerance, adverse drug reactions and renal or liver function impairment, there may be problems of dose adjustments with the FDC and this may only be possible with separate drug formulations.

20. Initiation of anti-retroviral treatment (ART) in tuberculosis patients infected with HIV

Anti-retroviral therapy should be started in all tuberculosis patients with HIV infection regardless of theirCD4 cell count, preferably within the first 8 weeks of start of anti-tuberculosis

treatment. However, those patients with profound immunosuppression (CD4 counts less than 50 cells/mm3) must receive ART within the first 2 weeks of initiating TB treatment.[10] No extension of the period of anti-tuberculosis therapy is needed in these patients. The potential for drug–drug interactions, especially between the rifampicin and antiretroviral agents and paradoxical reactions that may be interpreted as clinical worsening must be kept in mind and handled properly and adequately[6]

21. Use of adjuvant steroids

Use of adjuvant steroids is not indicated in cases with pulmonary tuberculosis, however, it may be specifically required in certain extra-pulmonary tuberculosis cases e.g. tuberculous meningitis and pericarditis for an initial period of 6–8 weeks. According to WHO,[10] in patients with tuberculous meningitis, an initial adjuvant corticosteroid therapy with dexamethasone or prednisolone tapered over 6–8 weeks should be used. It also recommends that an initial adjuvant corticosteroid therapy may be used in patients with tuberculous pericarditis.

22. Management of adverse drug interactions

When two or more drugs are taken simultaneously, synergistic as well as antagonistic interactions may occur between the drugs and the host, generally making it impossible to say what is due to what.[14] This sometimes may lead to adverse reactions which may be often minor but sometimes major too. Major adverse reactions to antituberculosis drugs can cause significant morbidity, and compromise treatment regimens for tuberculosis.[59] These can diminish treatment effectiveness, since they significantly contribute to non-adherence, eventually contributing to treatment failure, relapse or the emergence of drug-resistance.[60–62] Mild adverse effects, mostly gastro–intestinal reactions, are usually managed with symptomatic treatment or modifying the timing of their intake minimally affecting their absorption and peak serum concentration.[63,64] An unexplained nausea, vomiting, and abdominal pain are evaluated with liver function tests to exclude possible hepatotoxicity.[65] Drug-induced hepatitis, the most frequent serious adverse reaction caused by isoniazid, rifampicin and pyrazinamide, is suspected when the ALT/liver enzyme level is $\geq$ 3 times the upper limit of normal along with the presence of symptoms of hepatitis, or $\geq$5 times of normal in the absence of symptoms. In such events the hepatotoxic drugs must be stopped, and patient be evaluated carefully excluding other causes of abnormal enzymes;[58] Later, as the liver recovers some drugs may be re-introduced, however, the optimal approach to this is still not known.[66,67]

In other severe adverse, the offending drug may often have to be withdrawn temporarily or permanently and in the event of the latter, the drug must be replaced by another from a different group. Patients with severe tuberculosis may often require continuation of the therapy with a regimen holding offending drugs and supplementing safer alternatives.

23. Risk of relapse

Pulmonary tuberculosis, caused by drug-susceptible organisms, where the lesion initially is non-cavitary and paucibacillary,they carry a lower risk of relapse after completion of treatment. Cavitation on the initial chest radiograph has been shown to be a risk factor for relapse.[68,69] Patients having both, cavitation and a positive culture at completion of two months of therapy, have been associated with rates of relapse of approximately 20% compared with 2% among patients with neither factor after treatment completion.[68] Hence, advanced disease with cavitary lesions and high bacillary counts need to be treated more cautiously in view of the high treatment failures and relapses in this group of patients.

24. Follow-up evaluations

During treatment sputum smear for AFB and culture for *M. tuberculosis* (only If the proper facilities are available), are obtained at monthly intervals, until 2 consecutive specimens are negative. Duration of the continuation phase regimen ideally depends on the sputum test results at the end of two months of intensive phase of treatment. If it is negative the continuation phase is started. Sputum specimens at the completion of two months of intensive phase is critical if negativity has not yet been documented and in such a case this phase is extended by one month. A sputum specimen positive for AFB at two months after start of therapy has also been shown to correlate with the likelihood of relapse after completion of treatment.[31,68]

25. Self-administered verses directly observed treatment (DOT)

In the Cochrane Database Systematic Reviews,[70,71] DOT did not provide a solution to poor adherence in treatment as they did not find in the existing trials any significant differences between self-administered therapy and DOT while assessing several outcomes including mortality, treatment completion, cure and relapse. However, some authors,[6,72] found DOT to be associated with improved treatment success.

In the present time more use of modern digital technology needs to be done, as it becomes easily available, for better treatment compliance, through smart phones, digital medication monitor, video observed treatment (VOT), wherever feasible.

26. Management of treatment interruptions

Interruptions in therapy are frequently seen in the treatment of tuberculosis due to varied reasons. In such an event it needs to be decided whether to restart a complete therapy once again or simply to continue therapy as intended originally. Guidelines of ATS, CDC, and IDSA[6] have very well dealt such situations arising during treatment. In general, the earlier the break in therapy and the longer its duration, more serious are the consequences

and greater the need to restart treatment from the beginning. Continuous treatment is more important in the intensive phase of therapy when the bacillary population is highest and thus the chance of developing drug resistance greatest. During the continuation phase, the number of bacilli is much smaller, and the goal of therapy is to kill the persisting organisms.

If the interruption in the therapy has been during the intensive phase and the lapse has been of less than 14 days in duration then continue treatment as per the original plan, however, if the lapse is of more than 14 days, restart treatment from the beginning.

During the continuation phase if the interruption occurs, in a case where sputum was smear negative for AFB on initial testing, and who has received 80% or more of the treatment, further therapy may not be necessary. In the same scenario if the initial sputum examination was positive for AFB, continue same therapy until completion of treatment. In a case where the interruption has occurred when the treatment received has been less than 80%, and the accumulative lapse has been less than 3 months and consecutive lapse is not more than 2 months duration, the same treatment be continued until completion of the original therapy planned. If this treatment cannot be completed within a time frame of 9 months, restart therapy from the beginning (intensive phase to be followed by continuation phase). In a situation where the case has received less than 80% of the treatment and the lapse is 3 months or more in duration, restart therapy from the beginning, starting with new intensive phase followed by the continuation phases.

Ideally, patients who are lost while undergoing treatment and brought back to therapy, with interim treatment interruption, should have sputum resent for AFB smear, culture, and drug susceptibility testing, for the treatment to be modified according to the results when available.

27. Tuberculosis patients returning after default or having relapse from the first treatment

These patients requiring re-treatment should ideally have drug susceptibility testing before constituting a drug regimen or else a therapy comprising of primary drugs already taken may be re-prescribed. Attempt be made to find out the cause of previous default which should be rectified as far as possible.

REFERENCES

1. World Health Organization. *Global Tuberculosis Report*. Geneva, Switzerland: World Health Organization; 2018:1–4.
2. *Annual Status Report on RNTCP 2018. Central TB Division*. New Delhi, India: Directorate General of Health Services, Ministry of Health with Family Welfare; 2018.
3. World Health Organization. *The End TB Strategy-Global Strategy and Targets for Tuberculosis Prevention, Care and Control after 2015*. Geneva, Switzerland: World Health Organization; 2015:1–26.
4. National Strategic Plan for Tuberculosis Elimination 2017–2025. *Revised National Tuberculosis Control Programme, Central TB Division, Directorate General of Health Services*. New Delhi: Ministry of Health with Family Welfare; 2017:5–10.
5. Peloquin C. What is the 'right' dose of rifampin? [Editorial], 2003 *Int J Tuberc Lung Dis*. 2003;7:3–5.
6. Nahid P, Dorman SE, Alipanah N, et al. Clinical practice guidelines: treatment of drug-susceptible tuberculosis (official American thoracic society/centers for disease control and prevention/infectious diseases society of America). *Clin Infect Dis*. 2016;63(7):e147–e195.
7. World Health Organization. *Automated Real-Time Nucleic Acid Amplification Technology for Rapid and Simultaneous Detection of Tuberculosis and Rifampicin Resistance: Xpert MTB/RIF System for the Diagnosis of Pulmonary and Extrapulmonary TB in Adults and Children: Policy Update*. Geneva: World Health Organization; 2013:xi–xv.
8. World Health Organization. *Xpert MTB/RIF Implementation Manual: Technical and Operational 'how-To'; Practical Considerations*. Geneva, Switzerland: World Health Organization; 2014:1–3.
9. Gordin FM, Slutkin G, Schecter G, Goodman PC, Hopewell PC. Resumptive diagnosis and treatment of pulmonary tuberculosis based on radiographic findings. *Am Rev Respir Dis*. 1989;139:1090–1093.
10. World Health Organization. *Guidelines for Treatment of Drug-Susceptible Tuberculosis and Patient Care, 2017 Update*. Geneva, Switzerland: World Health Organization; 2017:x–xv.
11. Liefooghe R, Suetens C, Meulemans H, Moran MB, De Muynck A. A randomised trial of the impact of counselling on treatment adherence of tuberculosis patients in Sialkot, Pakistan. *Int J Tuberc Lung Dis*. 1999;3:1073–1080.
12. Clark PM, Karagoz T, Apikoglu-Rabus S, Izzettin FV. Effect of pharmacist-led patient education on adherence to tuberculosis treatment. *Am J Health Syst Pharm*. 2007;64:497–505.
13. M'Imunya JM, Kredo T, Volmink J. Patient education and counselling for promoting adherence to treatment for tuberculosis. *Cochrane Database Syst Rev*. 2012;5. CD006591.
14. Toman's Tuberculosis Case Detection. *Treatment, and Monitoring – Questions and Answers*. 2nd ed. Geneva: World Health Organization; 2004:102–152.
15. Fox W. The John Barnwell Lecture. Changing concepts in the chemotherapy of pulmonary tuberculosis. *Am Rev Respir Dis*. 1968;97(5):767–790.
16. Tyrrell WF. Bed rest in the treatment of pulmonary tuberculosis. *Lancet*. 1956;270(6927):821–823.
17. Hayashi S, Chandramohan D. Risk of active tuberculosis among people with diabetes mellitus: systematic review and meta-analysis. *Trop Med Int Health*. 2018;23(10):1058–1070.
18. Al-Rifai RH, Pearson F, Critchley JA, Abu-Raddad LJ. Association between diabetes mellitus and active tuberculosis: a systematic review and meta-analysis, 12 *PLoS One*. 2017;21(11). e0187967.
19. Jeon CY, Murray MB. Diabetes mellitus increases the risk of active tuberculosis: a systematic review of 13 observational studies. *PLoS Med*. 2008;5. e152.
20. Lönnroth K, Williams BG, Cegielski P, Dye C. A consistent log-linear relationship between tuberculosis incidence and body mass index. *Int J Epidemiol*. 2010;39:149–155.
21. Mitchison DA. Chemotherapy of tuberculosis: a bacteriologist's viewpoint. *Br Med J*. 1965;1:1333–1340.
22. Canetti G. Host factors and chemotherapy of tuberculosis. In: Barry VC, ed. *Chemotherapy of Tuberculosis*. London: Butterworths; 1964:20–38.
23. *First National Anti-tuberculosis Drug Resistance Survey, India 2014-16*. New Delhi: Ministry of Health and Family Welfare, Government of India; 2018:1–24.
24. Fox W. Short course chemotherapy for tuberculosis. In: Flenley DC, ed. *Recent Advances in Respiratory Medicine*. Edinburgh: Churchill Livingstone; 1980:183.

25. Mitchison DA. Mechanisms of the action of drugs in short-course chemotherapy. *Bull Int Union against Tuberc Lung Dis*. 1985;60:30.
26. World Health Organization. *Treatment of Tuberculosis: Guidelines for National Programmes*. 3rd ed. Geneva: World Health Organization; 2003.
27. Enarson DA, Reider H, Arnadottir T, Trebucq A. *Management of Tuberculosis: A Guide for Low Income Countries*. 5th ed. Paris: International Union Against Tuberculosis and Lung Disease; 2000.
28. Canetti G. The eradication of tuberculosis: theoretical problems and practical solutions. *Tubercle*. 1962;43:301–321.
29. World Health Organization. *Treatment of Tuberculosis: Guidelines*. 4th ed. Geneva: World Health Organization; 2010:1–14.
30. American thoracic society, center for disease control and prevention, and infectious diseases society of America. *MMWR - Treatment of Tuberculosis*. 2003;52:1–77.
31. Horne DJ, Royce SE, Gooze L, et al. Sputum monitoring during tuberculosis treatment for predicting outcome: systematic review and meta-analysis. *Lancet Infect Dis*. 2010;10:387–394.
32. Khan A, Sterling TR, Reves R, Vernon A, Horsburgh CR. Lack of weight gain and relapse risk in a large tuberculosis treatment trial. *Am J Respir Crit Care Med*. 2006;174:344–348.
33. Baker MA, Harries AD, Jeon CY, et al. The impact of diabetes on tuberculosis treatment outcomes: a systematic review. *BMC Med*. 2011;9:81.
34. Wang JY, Lee MC, Shu CC, et al. Optimal duration of anti-TB treatment in patients with diabetes: nine or six months? *Chest*. 2015;147:520–528.
35. Leung CC, Yew WW, Chan CK, et al. Smoking adversely affects treatment response, outcome and relapse in tuberculosis. *Eur Respir J*. 2015;45:738–745.
36. Ahmad Khan F, Minion J, Al - Motairi A, Benedetti A, Harries AD, Menzies D. An updated systematic review and meta-analysis on the treatment of active tuberculosis in patients with HIV infection. *Clin Infect Dis*. 2012;55:1154–1163.
37. Canetti G. *The Tubercle bacillus in Pulmonary Lesion of Man; Histobacteriology and its Bearing on the Therapy of Pulmonary Tuberculosis*. New York: Springer; 1955.
38. Tuberculosis Chemotherapy Centre, Madras. A concurrent comparison of isoniazid plus PAS with three regimens of isoniazid alone in the domiciliary treatment of pulmonary tuberculosis in South India. *Bull World Health Organ*. 1960;23:535–585.
39. van Crevel R, Alisjahbana B, de Lange WC, et al. Low plasma concentrations of rifampicin in tuberculosis patients in Indonesia. *Int J Tuberc Lung Dis*. 2002 Jun;6:497–502.
40. Weiner M, Benator D, Burman W, et al. Tuberculosis Trials Consortium. Association between acquired rifamycin resistance and the pharmacokinetics of rifabutin and isoniazid among patients with HIV and tuberculosis. *Clin Infect Dis*. 2005;40:1481–1491.
41. Jakko van Ingen, Aarnoutse Rob E, Donald Peter R. Andreas H. Diacon, Rodney Dawson, Georgette Plemper van Balen, et al.. Why Do We Use 600 mg of Rifampicin in Tuberculosis Treatment? *Clin Infect Dis*. 2011;52:e194–e199.
42. Fox W, Ellard GA, Mitchison DA. Studies on the treatment of tuberculosis undertaken by the British Medical Research Council tuberculosis units, 1946-1986, with relevant subsequent publications. *Int J Tuberc Lung Dis*. 1999;3(suppl 2):S231–S279.
43. World Health Organization, Stop TB department. *Treatment of Tuberculosis: Guidelines*. 4th ed. Geneva, Switzerland: World Health Organization; 2009.
44. Long MW, Snider Jr DE, Farer LS. U.S. Public Health Service Cooperative trial of three rifampin-isoniazid regimens in treatment of pulmonary tuberculosis. *Am Rev Respir Dis*. 1979;119(6):879–894.
45. Kreis B, Pretet S, Birenbaum J, et al. Two three-month treatment regimens for pulmonary tuberculosis. *Bull Int Union Tuberc Lung Dis*. 1976;51:71–75.
46. Jayaram Ramesh, SheshagiriGaonkar Parvinder Kaur, Suresh BL, Mahesh BN, Jayashree R, et al. Pharmacokinetics-pharmacodynamics of rifampin in an aerosol infection model of tuberculosis. *Antimicrob Agents Chemother*. 2003;47:2118–2124.
47. Mitchison DA. Role of individual drugs in the chemotherapy of tuberculosis. *Int J Tuberc Lung Dis*. 2000;4:796–806.
48. Peloquin C. What is the 'right' dose of rifampin? [Editorial]. *Int J Tuberc Lung Dis*. 2003;7:3–5.
49. Diacon AH, Patientia RF, Venter A, et al. Early bactericidal activity of high-doserifampin in patients with pulmonary tuberculosis evidenced by positive sputum smears. *Antimicrob Agents Chemother*. 2007;51:2994–2996.
50. Mitnick CD, McGee B, Peloquin CA. Tuberculosis pharmacotherapy: strategies to optimize patient care. *Expert Opin Pharmacother*. 2009;10:381–401.
51. Egelund EF, Alsultan A, Peloquin CA. Optimizing the clinical pharmacology of tuberculosis medications. *Clin Pharmacol Ther*. 2015;98:387–393.
52. Boeree MJ, Diacon AH, Dawson R, et al. PanACEA Consortium. A dose-ranging trial to optimize the dose of rifampin in the treatment of tuberculosis. *Am J Respir Crit Care Med*. 2015;191:1058–1065.
53. Boeree MJ, Diacon AH, Dawson R, et al. A step toward an optimized rifampin dose completed. *Am J Respir Crit Care Med*. 2015;192:525–526.
54. Steingart KR, Jotblad S, Robsky K, et al. Higher-dose rifampin for the treatment of pulmonary tuberculosis: a systematic review. *Int J Tuberc Lung Dis*. 2011;15:305–316.
55. Peloquin CA, Velásquez GE, Lecca L, Calderón R, Coit J, Pharmacokinetic evidence from the HIRIF trial to support increased doses of rifampin for tuberculosis. Antimicrob Agents Chemother2017; 61.
56. Jindani A, Borgulya G, de Patiño IW, Gonzales T, de Fernandes RA, Shrestha B. A randomised phase II trial to evaluate the toxicity of high-dose rifampicin to treat pulmonary tuberculosis. *Int J Tuberc Lung Dis*. 2016;20:832–838.
57. Lesobre R, Ruffino J, Teyssier L, Achard F, Brefort G. Jaundice during treatment with rifampicin (12 cases). *Rev Tuberc Pneumol (Paris)*. 1969;33:393–403.
58. Saukkonen JJ, Cohn DL, Jasmer RM, Schenker S, Jereb JA, Nolan CM, et al. An official ATS statement: hepatotoxicity of antituberculosis therapy. *Am J Respir Crit Care Med*. 2006;174:935–952.
59. Yee Daphne, Valiquette Chantal, Pelletier Marthe, Parisien Isabelle, Rocher Isabelle, Menzies Dick. Incidence of serious side effects from first-line antituberculosis drugs among patients treated for active tuberculosis. *Am J Respir Crit Care Med*. 2003;167:1472–1477.
60. Kaona FA, Tuba M, Siziya S, Sikaona L. An assessment of factors contributing to treatment adherence and knowledge of TB transmission among patients on TB treatment. *BMC Public Health*. 2004;4:68.
61. Wares DF, Singh S, Acharya AK, Dangi R. Non-adherence to tuberculosis treatment in the eastern Tarai of Nepal. *Int J Tuberc Lung Dis*. 2003;7:327–335.
62. World Health Organization. *IUATLD Global Project on Anti-tuberculous Drug Resistance Surveillance.Anti-tuberculous Drug Resistance in the World*. Geneva: World Health Organization; 2004. Third global report. WHO/HTM/TB/2004.343.

63. Centers for Disease Control and Prevention. *Core Curriculum on Tuberculosis: What the Clinician Should Know*. 6th ed. Atlanta, GA: Center for Disease Control and Prevention; 2013.
64. Lin MY, Lin SJ, Chan LC, Lu YC. Impact of food and antacids on the pharmacokinetics of anti-tuberculosis drugs: systematic review and meta-analysis. *Int J Tuberc Lung Dis*. 2010;14:806–818.
65. Navarro VJ, Senior JR. Drug-related hepatotoxicity. *N Engl J Med*. 2006;354:731–739.
66. Sharma SK, Singla R, Sarda P, et al. Safety of 3 different reintroduction regimens of antituberculosis drugs after development of antituberculosis treatment-induced hepatotoxicity. *Clin Infect Dis*. 2010;50:833–839.
67. Chang KC, Leung CC. The best approach to reintroducing tuberculosis treatment after hepatotoxicity is still open to debate. *Clin Infect Dis*. 2010;51:366–367.
68. Benator D, Bhattacharya M, Bozeman L, et al. USA and Canada of HIV-negative people with drug-susceptible pulmonary tuberculosis who…plus 900 mg isoniazid once a week or 600 mg rifampicin plus 900 mg isoniazid twice a week. Rifapentine and isoniazid once a week versus rifampicin and isoniazid twice a week for treatment of drug-susceptible pulmonary tuberculosis in HIV-negative patients: a randomised clinical trial. *Lancet*. 2002;360:528–534.
69. Chang KC, Leung CC, Yew WW, Ho SC, Tam CM. A nested case-control study on treatment-related risk factors for early relapse of tuberculosis. *Am J Respir Crit Care Med*. 2004;170:1124–1130.
70. Volmink J, Garner P. Directly observed therapy for treating tuberculosis. *Cochrane Database Syst Rev*. 2007 Oct 17;(4):CD003343.
71. Karumbi J, Garner P. Directly observed therapy for treating tuberculosis. *Cochrane Database Syst Rev*. 2015 May 29;(5):CD003343.
72. Davidson BL. A controlled comparison of directly observed therapy vs self-administered therapy for active tuberculosis in the urban United States. *Chest*. 1998;114(5):1239–1243.

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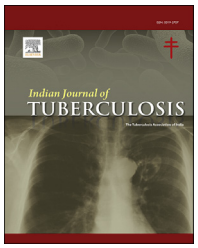

Review article

Geriatric TB: Needs focussed attention under RNTCP

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1. Introduction

Pulmonary tuberculosis in geriatric age group may cause no or mild signs and symptoms in contrast to the prolonged disease course that is common in post-primary or adult type disease. Atypical clinical manifestations of TB in older persons can result in delay in diagnosis and initiation of treatment; higher rates of morbidity and mortality from this treatable infection can occur. Underlying illnesses, age-related diminution in immune function, the increased frequency of adverse drug reactions, and institutionalization can complicate the overall outcome in elderly patients with TB. A high index of suspicion for TB in this vulnerable population is, thus, undoubtedly justifiable.[1] Acute or chronic diseases, malnutrition, and the biological changes associated with aging can disrupt protective barriers, impair microbial clearance mechanisms and contribute to the expected age-related diminution in cellular immune responses to Mycobacterium TB.[2] The diagnosis of TB can be difficult, and this treatable infection is sometimes documented only on post-mortem examination. In addition, therapy for TB in elderly individuals is challenging because of the increased incidence of adverse drug reactions. Furthermore, institutionalized elderly persons are at high risk for reactivation of latent TB and are susceptible to new TB infection.[2]

2. Clinical presentation

Tuberculosis in older patients can present atypically.[3,4] Approximately 75% of elderly persons with tuberculosis disease manifest lung involvement.[5] In addition, disseminated or miliary tuberculosis, tuberculous meningitis, and skeletal and genitourinary tuberculosis increase in frequency with advancing age.[6] Many older patients with tuberculosis disease may not exhibit the classic features of tuberculosis (i.e., cough, hemoptysis, fever, night sweats, and weight loss). Tuberculosis in this population may present clinically with changes in functional capacity (e.g., activities of daily living), chronic fatigue, cognitive impairment, anorexia, or unexplained low-grade fever.[3,4] Nonspecific symptoms and signs that range in severity from subacute to chronic and that persist for a period of weeks to months must alert clinicians to the possibility that unrecognized tuberculosis is present.

2.1. *Pulmonary tuberculosis*

Pulmonary tuberculosis is by far the most common form of tuberculosis in the elderly population.[3] Although aging patients with pulmonary tuberculosis can present with typical respiratory as well as systemic symptoms (e.g., sputum production, hemoptysis, fever, night sweats, weight loss, and anorexia), a significant number of such patients may manifest atypical complaints or may exhibit minimal pulmonary symptoms.

2.2. *Miliary tuberculosis*

Miliary, or disseminated, tuberculosis occurs with greater frequency among aging patients; many cases are detected only at autopsy.[7] Miliary tuberculosis is typically associated with an acute or subacute pattern of high, intermittent fever and clinical evidence of meningeal or serosal involvement. Overwhelming infection results in numerous caseous lesions that harbor thousands of replicating tubercle bacilli and minimal neutrophilic infiltrate with no granulomatous reaction. Clinical features include unexplained fever, weight loss,

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and hepatosplenomegaly, without other focal signs; this form of tuberculosis should be considered in the differential diagnosis of fever of unknown origin.

2.3. *Tuberculous meningitis*

Tuberculous meningitis in elderly patients results from reactivation of a primary dormant focus or is associated with miliary seeding of infection.[8] Like younger patients, older patients generally present with a subacute onset of fever, headache, and confusion, with concomitant or preceding systemic symptoms of weakness, anorexia, and fatigue. However, some older patients can also manifest unexplained dementia or obtundation without fever or nuchal rigidity; for such patients, a high index of suspicion for tuberculous meningitis must be maintained until the suspicion is disproven. Tuberculous meningitis is associated with exceedingly high mortality among elderly persons; neurological sequelae or deficits are common among survivors.

2.4. *Skeletal tuberculosis*

In elderly persons, involvement of bone in *M. tuberculosis* infection commonly affects the spine.[9,10] The thoracic and lumbar spines are commonly involved; cervical disease is unusual. Paravertebral abscesses, or cold abscesses, are often associated with spinal infection. Primary symptoms of spinal tuberculosis include pain over the involved vertebrae; neurological deficits and sinus tracts may occur with more advanced disease. Low-grade fever, weight loss, fatigue, and anorexia may be present. Tuberculous arthritis commonly involves the large, weight-bearing joints; however, in elderly persons, peripheral joints (i.e., the knees, wrists, ankles, and metatarsophalangeal joints) may be involved.[11] Pain and swelling of the involved joints and loss of range of motion can sometimes occur. Because older patients often have degenerative joint disease or other arthritides, the diagnosis of coexisting tuberculous arthritis may easily be overlooked.

2.5. *Genitourinary tuberculosis*

Although genitourinary tuberculosis occurs more often in persons in the third, fourth, and fifth decades of life, this form of disease is also seen in elderly persons.[12] The kidney is the major site of involvement, and as many as 20%–30% of patients are asymptomatic. Genitourinary tuberculosis may involve the ureters, bladder, prostate, epididymis, and seminal vesicles. Presenting symptoms may include dysuria, urinary frequency, flank pain, and hematuria. The diagnosis is often considered when an abnormal urinary sediment, pyuria without bacteruria, or hematuria is noted. Significant disease may result in pelvic or scrotal masses and draining sinuses; systemic manifestations (fever, anorexia, weight loss) may be absent.

2.6. *Other sites*

Tuberculosis in elderly patients, like that in younger patients, can involve almost any organ in the body. Tuberculosis disease involving the lymph nodes, pleura, liver, gall bladder, small and large bowel, pericardium, middle ear, and carpal tunnel has been described in older patients.[3]

3. Diagnosis

For screening purposes, the tuberculin skin test remains the diagnostic intervention of choice, despite the associated potential for false-negative results. The prevalence of decreased relative strength of reaction or lack of reaction to tuberculin increases with age and may be partly explained by anergy. Moreover, the "booster effect" of skin-test reactivity to antigen increases in prevalence in the elderly population.[13,14]

A positive tuberculin skin test reaction or clinical manifestations suggestive of tuberculosis warrant chest radiography, because (as previously stated) 75% of all tuberculosis cases in the elderly population involve the respiratory tract. Most cases of pulmonary tuberculosis in elderly patients are reactivation disease; 10%–20% of cases result from primary infection or reinfection. Although reactivation tuberculosis classically involves the upper lobes of the lung (apical and posterior segments), several studies have shown that pulmonary tuberculous infection in many elderly patients manifests in either the middle or the lower lung lobes.[5] Thus, clinicians must exercise caution when interpreting radiographic evidence of tuberculosis in older patients because of the possibility that infection may take hold in an atypical location in the lung fields.

Sputum examination for *M. tuberculosis*, using smear and culture, is indicated for all patients who have pulmonary symptoms and/or radiographic changes compatible with tuberculosis and who have not been treated with tuberculosis chemotherapy. More aggressive diagnostic intervention should be considered for elderly patients who are unable to expectorate sputum; the use of flexible fiberoptic bronchoscopy to obtain bronchial washings and bronchial biopsy specimens is clearly feasible and is a valuable diagnostic option.[15] In frail elderly patients, however, the risk of such a procedure should be carefully weighed against the benefit of potentially making a diagnosis of tuberculosis.

For suspected pulmonary tuberculosis, it is recommended that 2 sputum specimens; one obtained in the morning and one spot be used for routine mycobacteriological studies as per RNTCP guidelines. These specimens should be subjected to smear examination and then cultured for *M. tuberculosis*.

Rapid molecular tests based on nucleic acid amplification tests, such as CBNAAT and LPA for amplifying DNA may facilitate rapid detection of *M. tuberculosis* in respiratory tract specimens. The rapid diagnosis of tuberculosis is especially important in the high-risk elderly population and for HIV-infected persons and patients infected with multiple-drug–resistant *M. tuberculosis* (MDR-TB). Histologic examination of tissue from various sites, such as the liver, lymph nodes, bone marrow, pleura, and synovium, that reveals the characteristic tissue reaction (caseous necrosis with granuloma formation) is also useful for diagnosis of tuberculosis disease.

4. Therapeutic difficulties

Old people with tuberculosis present problems not only of the diagnosis but also of treatment. The key problems are a poor compliance with treatment, poor tolerance of therapy and the presence of underlying or associated diseases.[16,17] The main cause of failure of treatment in tuberculosis, whatever the age, is poor patient compliance, and in the elderly this problem is accentuated. Old people especially the very old are unreliable about taking tablets regularly, at the right time or in the right dose, particularly if several drugs are to be taken concurrently. Poor memory, poor eyesight and mental confusion may be contributory factors. Old people often become apathetic about their treatment and lack the determination required to complete a course of treatment of six months. Many countries, therefore, prefer to use supervised intermittent chemotherapy for such patients. Side effects of certain drugs may also lead to poor compliance with the treatment. A careful watch must be kept for the side effects of drug treatment because the old persons, particularly the very old, cannot be relied upon to recognize their significance. Doses of drugs must be carefully monitored and special care taken if there is evidence of hepatic or renal failure. In a retrospective review, it has been reported that elderly people were nearly three times more likely to have reactions to antituberculous drugs as compared to younger patients.[18] Various studies including those from India have definitely shown advancing age as an important predictor of hepatotoxicity due to INH and rifampicin.[18,19] Rifampicin combined with INH has an additive but not synergistic hepatotoxic effect. Monthly monitoring of serum transaminases is advisable in such patients.

Ethambutol can cause diminution of visual acuity, central scotomas and disturbance of red-green vision attributable to optic neuritis. Since some visual impairment is common in elderly, a careful examination that includes testing of visual acuity and color discrimination should be performed before initiating ethambutol therapy. In elderly patients with significant renal dysfunction associated with retinopathy, or cataracts, in whom evaluation of visual changes may be difficult, the benefits of ethambutol administration must be carefully weighed against the risks. The nephrotoxicity and ototoxicity due to streptomycin is more frequent in patients with pre-existing renal impairment and is generally irreversible. Since with normal aging, renal function declines, hearing acuity diminishes, and vestibular disturbances are more incapacitating, elderly patients have increased risks of suffering from renal toxicity and ototoxicity and of being severely impaired by them. As with ethambutol, the benefits of streptomycin therapy must be weighed against its risks in the elderly patient and dose adjusted accordingly.

Drug interactions must also be considered in old people who are likely to be on treatment for other diseases at the same time: e.g., INH can reduce the anticonvulsant action of phenytoin; rifampicin can interfere with the action of digoxin, tolbutamide and corticosteroids. In most cases, all that is needed to overcome the unwanted effects of drug interactions is an adjustment of dosage.

5. Conclusion

Tuberculosis in geriatric population is not so uncommon. It is a serious illness in this age group. Elderly people are at a high risk of developing disease and sometimes disseminated type also. Clinical presentation is usually atypical sometimes clinical features are masked by other co-existing disease. Diagnosis is difficult as tuberculin test is negative because of age related anergy; radiological features are also atypical as COPD usually co-exists. As far as treatment is concerned, dosage of drugs have to be adjusted, more chances of side effects (due to some or other concomitant therapy), difficult compliance. But if the care givers of old persons are alert, early diagnosis and ensuring treatment adherence do help in managing TB cases in this age group.

REFERENCES

1. Watkins RE, Rouse CR, Plant AJ. Tuberculosis treatment delivery in Bali: a qualitative study of clinic staff perceptions. *Int J Tuberc Lung Dis*. 2004;8:218–225.
2. Rawat J, Sindhwani G, Juyal R. Clinico-radiological profile of new smear positive pulmonary tuberculosis cases among young adult and elderly people in a tertiary care hospital at Dehradun (Uttarakhand). *Indian J Tuberc*. 2008;55:84–90.
3. Arora VK, Bedi RS. Geriatric tuberculosis in Himachal Pradesh – a clinico-radiological profile. *JAPI*. 1989;37:205–206.
4. Arora VK, Bedi RS. Immunoglobulin status of geriatric pulmonary tuberculosis patients of Himachal Pradesh. *Indian J Chest Dis Allied Sci*. 1989;31:233–236.
5. Perez-Guzman C, Vargas MH, Torres-Cruz A, et al. Does aging modify pulmonary tuberculosis? *A Meta Analytical Review. Chest*. 1999;116(961–7).
6. Dutt AK, Stead WW. Tuberculosis in the elderly. *Med Clin N Am*. 1993;77:1353–1368.
7. Sahn SA, Neff TA. Miliary tuberculosis. *Am J Med*. 1974;56:494–505.
8. Molavi A, LeFrock JL. Tuberculous meningitis. *Med Clin N Am*. 1985;69:315–331.
9. Paus B. The changed pattern of bone and joint tuberculosis in Norway. *Acta Orthop Scand*. 1977;48:277–279.
10. Tuli SM. Results of treatment of spinal tuberculosis by "middle-path" regime. *J Bone Joint Surg Br*. 1975;57(13–23).
11. Evanchick CC, Davis DE, Harrington TM. Tuberculosis of peripheral joints: an often missed diagnosis. *J Rheumatol*. 1986;13:187–189.
12. Quinn W. Genitourinary tuberculosis: a study of 1117 cases over a period of 34 years. *Br J Urol*. 1984;56:449–455.
13. Thompson NJ, Glassroth JL, Snider Jr DE, et al. The booster phenomenon in serial tuberculin testing. *Am Rev Respir Dis*. 1979;119:587–597.
14. Tort J, Pina JM, Martin Ramos A, Espaulella J, Armengol J. Booster effect in elderly patients living in geriatric institutions [in Spanish]. *Med Clínica*. 1995;105(2) (pg. 41-4).
15. Patel YR, Mehta JB, Harvill L, et al. Flexible bronchoscopy as a diagnostic tool in the evaluation of pulmonary tuberculosis in an elderly population. *J Am Geriatr Soc*. 1993;41:629–632.
16. Mackoy AD, Cole RB. The problems of tuberculosis in the elderly. *Q J Med*. 1984;212:497–510.

17. Tuberculosis in old age (Leading article). *Lancet*. 1983;64:69–71.
18. Teale C, Goldman JM, Pearson SB. The association of age with the presentation and outcome of tuberculosis: a five year survey. *Age Ageing*. 1993;22:289–293.
19. Pande JN, Singh SP, Khilnani GC, Khilnani S, et al. Risk factors for hepatotoxicity from antituberculosis drugs : a case-control study. *Thorax*. 1996;51:132–136.

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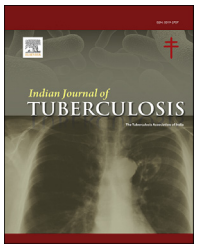

Review article

Adverse drug reactions in tuberculosis and management

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A B S T R A C T

Background: Treatment of drug susceptible tuberculosis (DS-TB) requires regimens containing first line drugs (FLDs') whereas drug resistant tuberculosis (DR-TB) are treated with regimens comprising combination of both second line drugs (SLDs') and few FLDs'. Adverse drug reactions (ADRs') to these anti-tubercular drugs are quite common as they are being used for longer duration. ADRs' may cause associated morbidity and even mortality if not recognized early. There are major concerns regarding treatment of DR-TB patients particularly with SLDs' in that they are expensive, have low efficacy and more toxic as compared to FLDs'. There may be a severe impact on adherence and higher risk of default and treatment failure affecting outcome overall if such ADRs' are not properly managed.

Methods: A search strategy was adopted involving principal electronic databases **(Pubmed, EMBASE, Google and Google scholar)** of English language articles from 1990 till now, using various terms in combination. All articles with resulting titles, abstract and full text, when available were read and kept for reference.

Results: 101 articles including 4 systematic reviews have been identified. The overall prevalence of ADRs' with FLDs' and SLDs' are estimated to vary from 8.0% to 85% and 69% to 96% respectively. Most ADRs' are observed in the intensive phase as compared to continuation phase. No difference in frequency of ADRs' was reported with intermittent or daily intake of anti-tubercular drugs. The occurrence of ADRs' may be influenced by multiple factors and may range from mild gastrointestinal disturbances to serious hepatotoxicity, ototoxicity, nephrotoxicity peripheral neuropathy, cutaneous ADRs', etc. Most of ADRs' are minor and can be managed without discontinuation of treatment. Some ADRs' can be major or severe causing life-threatening experience leading to either modification or discontinuation of regimen and even mortality if not recognized and treated promptly.

Conclusion: Early recognition by active surveillance and appropriate management of these ADRs' might improve adherence and treatment success.

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1. Introduction

India features among the 22 high tuberculosis (TB) burden countries and has accounted for an estimated one-quarter (26%) of all TB cases worldwide.[1] Treatment regimen comprising multiple first-line drugs (FLDs') such as Isoniazid (H), Rifampicin (R), Pyrazinamide (Z), Ethambutol (E) and Streptomycin (S), remains the cornerstone of treatment of drug-susceptible TB (DS-TB) whereas second line drugs (SLDs') are reserved for treatment of drug-resistant TB (DR-TB). Good bacteriological diagnosis and compliance on treatment are the two main pillars of successful treatment of TB. The World Health Organization (WHO) has defined adverse drug reactions (ADRs') as ''A response to a drug which is noxious and unintended, and which occurs at doses normally used in human for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function.''[2] Patients may experience a variety of ADRs' when managed with these anti-tubercular drugs. Treatment with these drugs can also be associated with adverse events which is defined as any untoward medical occurrence but not necessarily have a causal relationship. ADRs' to these agents are common and cause significant morbidity and even sometimes mortality if not detected early.[3–5] Most of ADRs' are minor and can be managed without discontinuation of treatment. Some can be serious or major causing life-threatening experience leading to either shorter or prolonged hospitalization, significant disability, congenital anomaly or even mortality if unrecognized and untreated promptly. Timing, the pattern of illness, the results of investigations, and re-challenge will help attribute causality to a suspected ADR.[6] Various factors such as the dose and time of day at which the medication is administered, patient age, nutritional status, the presence of pre-existing diseases or dysfunctions like impaired liver function, impaired kidney function, human immunodeficiency virus (HIV) co-infection, and alcoholism may be related to ADRs' to anti-tubercular drugs.[7] This calls for continued surveillance of ADRs' particularly in patients having DR-TB where early recognition and appropriate management of ADRs' might determine favourable outcome. This review aims to highlight the estimated burden and management strategies of various ADRs' associated with anti-tubercular drugs among patients undergoing treatment of TB.

2. Prevalence of adverse drug reactions treated with first line anti-tubercular drugs: global scenario

The data on global prevalence of ADRs' with FLDs' are scarce. The prevalence of ADRs' observed in various studies conducted worldwide ranged from 8% to 85%.[3,8–15] The reasons for the difference in the prevalence of ADRs' across these studies might be related to several possible factors such as: differences in definitions of ADRs' terminologies as adopted by physicians, whether the ADRs' were reported by patient (subjective) or detected by clinician (objective) on the basis of clinical evidence along with feasibility of monitoring with serial laboratory investigations, whether all or only the major ADRs' were studied, associated co-morbidities such as diabetes and HIV co-infection and variations in the use of specific anti-tubercular drugs including dosage and also pharmacological interactions with other group of drugs comprising anti-retroviral therapy (ART), oral hypoglycemic agents and also ancillary medications used for management of ADRs'. A study conducted in Nigeria observed that around 14% and 13% incidence of ADRs' at 6 months and 8 months, among patients receiving directly observed treatment and short-course (DOTS) respectively.[11] In another study conducted by the Hong-Kong Chest Services, ADRs' were observed in 21% of patients receiving intermittent therapy.[12] Brazilian National Ministry of Health reported the incidence of minor or mild ADRs' in patients treated with the former FLDs' to range from 5% to 20%.[13] It was also observed that major or severe ADRs' were less common (occurring in approximately 2% of the cases, reaching 8% in specialized clinics) and led to the discontinuation or alteration of the treatment. However, another study from a teaching hospital in Brazil reported that 41.1% of the patients presented with minor and 12.8% presented with major ADRs'.[14] In a study from Singapore, frequency of ADRs' was observed to be 28.7% whereas it was observed to be 29.27% from another study conducted at Hong Kong.[15,16] However, studies have revealed that there are no differential rates of ADRs' among patients having intermittent and daily intake of anti-tubercular drugs.[17] It was also observed that ADRs' were more prevalent in intensive phase than continuation phase.

3. Prevalence of adverse drug reactions treated with second line anti-tubercular drugs: global scenario

The management of MDR-TB patients has been considered to be complicated and challenging because of prolonged duration of 24–27 months of treatment and high toxicity profile of SLDs'. The prevalence of ADRs' observed in various studies conducted worldwide ranged from 69% to 96%.[18–25] Reasons for the difference in the prevalence of ADRs' across these studies is almost similar to that of FLDs'. However, diversity can also be due to the fact that regimens for DR-TB contains various combination of SLDs' including newer drugs such as Bedaquiline (Bdq) and Delamanid (Dlm). The observed frequency of specific gastrointestinal ADRs' has been reported in 0.5–100% patients.[18–25] The high prevalence of gastrointestinal ADRs' in few of the studies was probably due to frequent reporting by patients as compared to other ADRs' leading to subjective variation. Ototoxicity has been reported in 12–70% patients receiving SLDs'. Tinnitus has been reported in 5–45% patients, while that of deafness is reported in 6.7–33% patients. Ototoxicity is predominantly associated with the use of injectable aminoglycoside such as Kanamycin (Km) although there is possibility of additive effects of interaction with other concomitant and potentially ototoxic drugs that were used in the regimen such as ofloxacin (Ofx) and cycloserine (Cs). This warrants further investigation to uncover the possibility of these interactive effects. Several studies have highlighted regarding high potential of these SLDs' to cause ADRs' that has led to interruption of treatment in 19–60% of MDR-TB patients.[18–25] This high prevalence may be due to early identification and aggressive management strategies adopted by programmatic management of drug-resistant tuberculosis (PMDT). Baghaei et al reported deafness and headache/psychosis

occurring due to injectable Km and Cs respectively as major ADRs' that required frequent discontinuation and/or substitution.[24] MDR-TB patients should be managed aggressively for ADRs' during therapy, especially for ototoxicity and psychiatric disorders.

4. Prevalence of adverse drug reactions treated with first-line anti-tubercular drugs: India

The overall prevalence of ADRs' with FLDs' is estimated to vary from 2.3% to 17% in various Indian studies.[8,26–28] A study conducted by Mehrotra et al observed that the prevalence of ADRs' in the initial intensive phase was 17.39%.[26] Another study conducted at a tertiary institute in Calcutta observed that the overall toxicity was found in 35% cases in the daily regimen group, whereas it was found to be 27.9% in the intermittent regimen group.[29] Data regarding prevalence of ADRs' are still scarce and further surveys are required from different geographical areas of India in near future.

5. Prevalence of adverse drug reactions treated with second line anti-tubercular drugs: India

Very few have specifically reported frequency of ADRs' in India.[18,30–37] A study conducted in Tamil Nadu by Joseph P et al reported ADRs' associated with standardized treatment in 86.8% patients.[31] Severe ADRs' requiring either a reduction of dosage or termination of the offending drug(s) such as ethionamide (Eto), Ofx, Km and Cs were observed in 58% patients. Another study conducted in Mumbai among 67 HIV and MDR-TB co-infected patients treated with anti-TB treatment as well as ART and reported that ADRs' were more frequent in this cohort with 71%, 63% and 40% of patients experiencing one or more mild, moderate or severe ADRs' respectively.[33] ADRs' such as gastrointestinal disturbances (45%), peripheral neuropathy (38%), hypothyroidism (32%), psychiatric symptoms (29%) and hypokalemia (23%) were reported more frequently among this cohort. 11 patients required hospitalization and permanent discontinuation of one or more offending drugs were observed in 40% patients. No ADRs' led to indefinite suspension of an entire MDR-TB or ART regimen. One study conducted at Delhi reported that 40% patients experienced minor ADRs', defined as those requiring either no discontinuation of a drug or discontinuation for <1 week and manageable at peripheral level.[30] 22 (18%) patients had major ADRs' requiring treatment modification. Para-amino salicylic acid (PAS) was used in 46 patients: 6 (5%) developed simple goiter, which responded to thyroxin replacement therapy with continuation of PAS. In 15 (12%) patients, Cs had to be stopped due to major psychotic reactions varying from major depression, psychosis to violent behaviour. Km was stopped in 5 (4%) patients due to hearing loss/giddiness. Ofx and Z were stopped in one patient due to severe arthralgia and Z was stopped in another patient due to hepatotoxicity. All of these major ADRs' required referral to specialist hospitals. None of the patients required discontinuation of the entire treatment regimen, although two patients defaulted due to ADRs'. No deaths due to drug toxicity were recorded in the cohort. A study conducted at Lucknow by Prasad et al among MDR-TB patients treated with SLDs' and reported that overall 16 (41%) patients experienced ADRs'.[36] 7 patients complained of PAS associated nausea and vomiting that led to discontinuation among 3 after six to eight months of treatment whereas remaining 4 patients did not require any change of medication. 4 patients developed photosensitivity likely due to sparfloxacin (Sfx) with replacement in one of the patients by Ofx after three months of treatment. Tinnitus and vertigo developed in four patients after one to five months of treatment due to Km and it had to be stopped in two of them. 3 patients developed depression and abnormal behavior possibly due to Cs, which was replaced by a fluoroquinolone (FQ) in two patients. However, it was continued with anti-psychosis treatment in the remaining patient. A total of 21.1% patients suffered from significant ADRs', which required stoppage/change of drugs. No other ADRs', such as arthralgia or cardiotoxicity were observed in any patient. In another study, among 98 MDR-TB patients, it was observed that 46.9% patients experienced at least one ADRs'.[37] ADRs' observed most frequently were nausea/vomiting 24 (24.5%) patients, hearing disturbances 12 (12.3%) patients, dizziness/vertigo 10 (10.2%) patients and arthralgia 9 (9.2%) patients. 17 (17.4%) patients had major ADRs' requiring change or stoppage of drugs that included ototoxicity (6.1%), headache and psychosis (4.1%), gastrointestinal intolerance and hypothyroidism (3.1%) as well as arthralgia and hepatitis (4.1%).[37] Agents responsible for these ADRs' were Km (ototoxicity), Cs (headache/psychosis), Eto (gastrointestinal tolerance/hypothyroidism) and Z (arthralgia/hepatitis). There was no mortality due to occurrence of ADRs'. Further studies are required for prevalence of ADRs' in near future.

6. Gastrointestinal adverse drug reactions

Gastrointestinal symptoms are one of the most common ADRs' seen with intake of anti-tubercular drugs. Its severity can range from mild symptoms like nausea, vomiting to life-threatening complications. All the FLDs' can cause mild gastrointestinal upsets that can be managed symptomatically without change in dosage of drugs. In a study of 893 patients by Shinde et al, it was found that gastrointestinal upset with nausea, vomiting, and abdominal pain were the most common ADRs' seen in 12.5% of patients.[38] In another prospective study from China, it was found that gastrointestinal ADRs' were seen in 3.74% of 4304 patients and only 7 patients required hospital admissions.[39]

7. Hepatotoxicity

The clinical presentation of anti-tubercular drug associated hepatitis is similar to that of acute viral hepatitis. Anti-tubercular drug induced hepatotoxicity can manifest as transitory asymptomatic rise in transaminases or acute liver failure. The frequency of hepatotoxicity ranges from 2% to 39% in different countries.[40] An increased incidence of hepatotoxicity has been observed in Indian sub-population when compared to Western population.[41,42] Drug induced hepatotoxicity in Indian population was observed to be 11.5%. However, a meta-

analysis in West found the risk to be 4–28%.[43,44] The occurrence of drug induced hepatotoxicity is unpredictable though certain patients are at a relatively higher risk than other populations. The incidence has been reported to be higher in developing countries and factors such as advanced age, acute or chronic liver disease, alcoholism, HIV, indiscriminate use of drugs, malnutrition, hypoproteinemia, hypoalbuminemia, anemia, prior history of jaundice and more advanced TB have been implicated.[45–47] Isolated H administration resulted in a threefold increase in alanine aminotransferase levels over the normal in 10–20% of these patients.[43,48] A meta-analysis of six studies investigating the use of H in isolation reported the incidence of hepatitis to be 0.6%.[49] Transitory and asymptomatic increases in the serum levels of bilirubin and hepatic enzymes occurred in 5% of patients with R. When H was used in combination with R, the incidence of hepatitis was observed to be 2.7%. Cholestatic hepatitis occurred in 2.7% of the patients receiving R in combination with H and was 1.1% when R was received in combination with anti-tubercular drugs other than H.[43] Z is the most hepatotoxic drug with toxicity being either dose dependent or idiosyncratic.[47,49,50] In the study conducted in nearly 1200 patients with acute liver failure in India, anti-tubercular drug was the cause in 5.6% of cases and 76% of patients with drug associated acute liver failure died within 5 days of hospitalization.[51] Hepatotoxicity has also been reported with SLDs' but with lesser frequency as compared to FLDs'. The incidence of hepatotoxicity is 2–3% with FQs' with fulminant involvement <1% whereas it is 1–2% with Eto/prothionamide (Pto) and 0.3% with PAS.[51–54] Hepatitis has been rarely reported with Linezolid (Lzd), clofazimine (Cfz) and newer drugs such as Bdq and Dlm.[55]

8. Peripheral neuropathy

Peripheral neuropathy occurs in approximately 20% of patients treated with H.[56] This was similar to findings of a study in Pakistan where peripheral neuropathy characterized by tingling and burning sensation in the hands and feet was the most common ADR observed with H. The other anti-TB drug known to cause peripheral neuropathy is E, but very rare in comparison to H. In a study conducted by Koju et al, peripheral neuropathy was experienced by only 18.57% of the patients.[57] In the existing literatures also, occurrence of peripheral neuropathy is considered rare with the recommended doses of H used in DOTS strategy. In a study of 893 patients by Shinde et al, on patients started on FLDs', it was observed that 5.04% of patients had peripheral neuropathy and 0.22% had acute psychosis.[38] Peripheral neuropathy has also been associated with Lzd, Eto, Cs and rarely FQs.[58,59]

9. Psychiatric disorders

H-related psychiatric disorders can manifest as psychosis, obsessive-compulsive neurosis, seizure, mania, loss of memory and death.[60] The first description of psychotic symptoms due to H was by Mandel et al, who reported three such cases in 1956.[61] The mechanism of production of H-related psychiatric disorders is not clearly known, but H is known to interfere with several metabolic processes essential for the normal functioning of the neuron. H causes deficiency of vitamin B6 by causing excessive excretion of the vitamin, which in turn leads to a disturbance of normal tryptophan metabolism. There is great variability in the clinical features of H-induced psychosis in the various reported cases. Jackson, in 1957, reported five cases of H-induced psychosis that presented with excessive argumentation, mental depression, euphoria, grandiose ideas, and complex delusions; none of these patients had any previous history of mental illness.[62] A review of all cases of drug-induced seizures reported to the California Poison Control System revealed that of 386 cases, 23 (5.9%) were due to H.[63] In Turkey, out of 1149 patients with established TB who initially received therapy, neuropsychiatric manifestations were observed in 0.7% of patients.[4] Cs has been associated with diverse neuropsychiatric ADRs' most common being psychosis reported in >10% patients. Other ADRs' such as anxiety, headaches and seizures were reported in 1–10% patients and insomnia, suicidal ideation in <1% patients. Eto has reported to cause giddiness and headache in 1–10% patients and rarely mental disturbances in <1% patients. FQs' has reported to cause dizziness, headaches, insomnia in 1–10% whereas it can cause or lower threshold for seizures in <1% patients.[64]

10. Optic/retrobulbar neuritis

E is one of the important FLDs' in the treatment of TB. Carr and Henkind et al first described the ocular ADRs' of E therapy in 1962.[65] Retro-bulbar neuritis is the most important potential ADR from E. It is reversible in most cases and is related to the dose and duration of treatment, but may occasionally become irreversible resulting in permanent visual disability, especially in the older population.[66] The reported incidence of retrobulbar neuritis when E is taken for more than 2 months is 18% in subjects receiving greater than 35 mg/kg/day, 5–6% with 25 mg/kg/day, and less than 1% with 15 mg/kg/day.[67,68] Optic neuritis is observed rarely with H and SLDs' such as Lzd and capreomycin (Cm).[69,70] Lzd induced optic neuritis is usually irreversible.

11. Ototoxicity

Streptomycin (S) predominantly affects the vestibular system whereas Km and Cm affects predominantly cochlear apparatus. Audiometry data suggest that the incidence of S associated ototoxicity may be as high as 25%.[71] Prazic and Salaj et al found audiologically defined lesions in 36% of a group of 975 children treated with S sulfate for pulmonary TB.[72] Hearing loss has also been reported in infants of tuberculous mothers treated with S during pregnancy.[73] Familial occurrence of drug induced toxicity has also been reported.[74] In a large Indian study with short course chemotherapy regimes in the treatment of patients with pulmonary TB, 16.1% of the patients given S developed vertigo which was severe in 5% cases.[75] In 10% of these patients, the drug had to be stopped. Reduction of dosage was needed in about 20%. In another series of 1744 patients treated with various drugs, 10.3%

developed intolerance to S. Involvement of the VIII cranial nerve was the most common (46.8%) untoward reaction.[76] Neff et al reported intolerance to S in 12.9% of their cases. In this series, also, vestibular and auditory dysfunction was the most common.[77] A study from Ethiopia reported ototoxicity in 4.8% patients which was clinically managed by modification of treatment regimens including dose and frequency of drug administration.[78] Ototoxicity was observed in 10.12% patients within 3.8 ± 2.6 months of treatment initiation with or without audiometry assessment.[79] High prevalence of ototoxicity (27.01%) was reported in Indian patients with DR-TB treated with injectable drugs when ototoxicity was monitored regularly using pure tone audiometry.

12. Immunological and hematological adverse drug reactions

R has been associated with immune mediated thrombocytopenic purpura and haemolytic anaemia especially with intermittent dosing. In a Brazilian study, R induced thrombocytopenia, leukopenia, eosinophilia, hemolytic anemia, agranulocytosis, vasculitis, acute interstitial nephritis, and septic shock occurred in 0.1% of the patients.[43,80] However, few Asian studies reported allergic reactions with FLDs' to be between 2.02% and 2.35% and hematological ADRs' to be 0.1–0.7%. Author in his work on hematological abnormalities during therapy found that thrombocytopenia, characterized by a rapid lowering of the platelet count in sensitive individuals was observed. Generally, the most common offending agent for the causation of thrombocytopenia secondary to anti-tubercular drugs is R.[80,81] Isolated case reports showing thrombocytopenia following administration of Z, H, E are found in literature and are attributed to an immunological phenomenon.[80–83] S is very rarely implicated as a cause of thrombocytopenia. Lzd has reported to associated with hematological ADRs' most common being thrombocytopenia with reported incidence as high as 11.8%.[84] Other ADRs' like pancytopenia and myelosuppression are less common as compared to thrombocytopenia. These hematological ADRs' are dose dependent and usually reversible with clinical management.

13. Arthralgia

Z and E are two anti-tuberculous drugs that have been reported to induce hyperuricemia in non-gouty patients leading to arthralgia.[85] The metabolite pyrazinoic acid is likely responsible for the hyperuricemic effect. The mechanism is related to pyrazinoic acid, the principal metabolite of Z oxidized by xanthine oxidase, which inhibits the renal tubular secretion of uric acid.[86] Hyperuricemia has been reported in 43–100% of patients treated with Z (alone or in combination).[87] Gouty attacks have also been associated with patients taking Z. E can also cause hyperuricemia by decreasing renal uric acid clearance, but it does so less consistently and to a lesser degree than Z. In a study by Dhingra et al on patients receiving DOTS therapy general aches and pains were complained by about 35%.[88] However, in a study by Shinde et al, arthralgia was seen in 0.67%[38] which was lower in comparison to reported incidence of 2.57% in Chinese patients receiving therapy.[39] Arthralgia has been reported with FQs' particularly Lfx and Bdq containing regimens for DR-TB.[89–91]

14. Renal toxicity/nephrotoxicity

Aminoglycosides produce renal toxic effects due to their accumulation in the renal tubules. Such effects are more common in elderly individuals and in patients with a history of kidney disease. Prolonged use of aminoglycosides, hepatotoxicity, dehydration, hypotension and concurrent use of nephrotoxic drugs are other risk factors for renal toxicity. The risk of nephrotoxicity is less and range around 2% while using S.[92,93] Injectable drugs such as Km and Am as well as Cm are more nephrotoxic as compared to S making treatment for DR-TB cases challenging with reported incidence of 1.2–6.7%.[59,94] E, Z and Cs have reported to cause renal toxicity. Newer drugs such as Bdq and Dlm can be used safely in DR-TB patients with renal failure.

15. Cutaneous adverse drug reactions (CADRS)

Z has been described to cause various skin reactions like maculopapular rash, erythema multiforme, exfoliative dermatitis, and drug, rash and eosinophilia with systemic symptoms (DRESS) syndrome. Among the FLDs', Z is the commonest cause of CADRS (2.38%), followed by S (1.45%), E (1.44%), R (1.23%), and Z (0.98%).[95] It is not uncommon for exfoliative dermatitis to occur with more than one of the four drugs. It is unclear whether renal failure predisposes to increased occurrence of CADRS. So far, no definite association exists between pre-existing renal insufficiency and increased incidence of CADRS. The incidence of E induced rash is found to be 0.5%.[96] The author reported a rare occurrence of exfoliative dermatitis secondary to E and Z in a 18-year-old female.[97] Patients receiving H can develop antinuclear antibodies during the use of the drug. Less than 1% develops systemic lupus erythematosus, the incidence of which is the same in both genders. H administration can also worsen pre-existing lupus.[98] Rash has also been reported with any SLDs' including newer ones Bdq and Dlm.[99]

16. Cardiotoxicity (QTc prolongation)

QTc prolongation on electrocardiogram (ECG) has been reported with FQs' particularly moxifloxacin (Mfx), macrolides such as Clarithromycin (Clr), Cfz, Bdq and Dlm.[100,101] Risk factors for QTc prolongation include elderly, female sex, underlying cardiac disorder including congenital and acquired, electrolyte imbalance and concurrent use of ancillary medications. A systematic search showed that Bdq is a relatively well-tolerated drug, as its discontinuation occurred in only 3.4% and 0.6% of patients due to ADRs' and QTc prolongation, respectively.[100]

Table 1 – Symptoms based approach to the management of minor ADRs' to first line anti-tubercular drugs not requiring stoppage of treatment.

Symptoms	Drug	Management
Abdominal pain, nausea	- Related to rifampicin	- Reassure the patients
Burning of the Feet	- Related to isoniazid	- Continue isoniazid, and give pyridoxine 50–100 mg daily
	- Peripheral neuropathy	- Large dose of pyridoxine, may interfere the action of isoniazid
Drowsiness	- Related to isoniazid	- Reassure the patients
Gastrointestinal Upset	- Any oral medications	- Reassure patients - Give drugs with less water - Give drugs over longer period of time (e.g. 20 minutes) - Give drugs with small amount of food - If these measure fails, provide anti-emetic
Joint pains	- Related to pyrazinamide	- Continue pyrazinamide - Use aspirin or nonsteroidal anti- inflammatory drugs - Use intermittent directly observed treatment if possible
Red urine	- Related to rifampicin	- Reassure the patients
Women on rifampicin	- Rifampicin may reduce the effectiveness of oral contraceptive pills	- Alternative method of contraception should be provided

17. Other adverse drug reactions

Few case reports on H induced gynecomastia among patients treated with anti-tubercular therapy.[101,102] A rare occurrence of anaphylactic shock due to S was also reported.[103]

18. Management of adverse drug reactions

Management of ADRs' associated with anti-tubercular drugs is considered to be an essential component in order to achieve adequate adherence leading to favourable outcome. DR-TB patients with SLDs' requires special care as these drugs

Table 2 – Symptoms based approach to major ADRs' to first line anti-tubercular drugs requiring stoppage of treatment.

Symptoms	Drug	Management
Loss of hearing	- Related to streptomycin	- Otoscopy to rule out wax - Pure tone audiometry to be performed - Stop streptomycin if no other explanation
Dizziness	- If true vertigo and nystagmus, related to streptomycin	- Stop streptomycin - If just dizziness with no nystagmus, try dose reduction for one week - If there is no improvement stop streptomycin
Generalized reactions including shock and purpura	- May be due to rifampicin, pyrazinamide and/or streptomycin, thiacetazone	- Stop all medications - Use different combination of drugs
Jaundice/Hepatitis	- May be due to drug induced hepatitis (Pyrazinamide/Rifampicin/Isoniazid) - Either liver enzymes more than 5 times of upper limit of normal or more than 3 times of upper limit of normal with symptoms of hepatitis or jaundice (bilirubin >3 mg/dl)	- Stop all anti-tubercular drugs until jaundice resolves and liver enzyme revert to baseline levels or < 2 times of upper limit of normal - Rule out other causes/pre-disposing factors - Re-introduce same regimen either, gradually or all at once - If hepatitis has been life-threatening and was not of viral origin it is safer to use regimen like streptomycin, ethambutol and fluoroquinolones and cycloserine if required - Rifampicin should be re-introduced followed by isoniazid in increasing dosages under regular LFT monitoring - Pyrazinami- Continue isoniazid, and give pyridoxine 50–100 mg daily - Large dose of pyridoxine, may interfere the action of isoniazidde should not be necessarily re-introduced and regimen should be continued for atleast 9 months.
Moderate to severe skin rash	- Related to all first line anti-tubercular drugs	- Stop all anti-tubercular drugs - Re-introduce drug one by one once the rash has subsided
Visual impairment	- Related to ethambutol	- Visual examination/ophthalmologist opinion - Stop ethambutol
Vomiting/confusion	- Suspect drug induced hepatitis	- Urgent liver function test - If liver enzyme test unavailable, stop all drugs and observe

are more toxic. Principles of pharmacovigilance have been adopted by national TB control programmes all over the world. Pharmacovigilance is defined by the WHO as the "science and activities relating to the detection, assessment and prevention of ADRs or any other drug-related problem".[104] The objective is to improve patient care by assessing both risk and benefit received from the drug. Routine surveillance of ADRs' according to a framed protocol is an integral part of national programmes which should be performed by symptom based reporting followed by laboratory investigations at baseline and as when clinically indicated. Occult ADRs' should be detected timely by laboratory investigations in order to prevent unrecognised serious effects. Monitoring should be frequent and more intense particularly in high risk groups such as elderly, HIV or hepatitis co-infection, alcoholism, drug addiction, anemia, any pre-existing illnesses, diabetes mellitus, hypoalbuminemia, malnutrition, chronic kidney disease, chronic liver disease, disseminated involvement, family history of frequent ADRs' or atopy/allergy and use of ancillary medications, anti-retroviral therapy or medications for treating opportunistic infections with high probability of drug interactions. A grading system has been devised to assess severity of all types of ADRs' in order to maintain accuracy and consistency in surveillance.[105] This system includes five grades – **Grade 1:** Mild symptoms requiring only observation and no intervention; **Grade 2:** Moderate symptoms requiring medical intervention such as ancillary drugs; **Grade 3:** Severe symptoms with inability to carry social or functional activities requiring medical intervention or even hospitalization; **Grade 4:** Life-threatening symptoms with inability to perform basic health care requiring medical intervention or hospitalization in order to prevent permanent impairment, disability or death and **Grade 5:** Mortality associated with

Table 3 – Common ADRs', suspected agent(s) and management strategies of anti-tubercular drugs used in DR-TB.

Adverse drug reaction	Suspected agent	Suggested management strategies
Seizures	**CS**	- Suspend suspected agent pending resolution of seizures
	H	- Initiate anticonvulsant therapy (e.g. phenytoin, valproic acid)
	All FQs'	- Increase pyridoxine to maximum daily dose (200 mg per day)
		- Restart suspected agent or re-introduce suspected agent at lower dose, if essential to the regimen
		- Discontinue suspected agent if this can be done without compromising regimen
		- Anticonvulsant is generally continued until DR-TB treatment is completed or suspected agent discontinued
		- History of pre- Continue isoniazid, and give pyridoxine 50–100 mg daily
		- Large dose of pyridoxine, may interfere the action of isoniazidvious seizure disorder is not a contraindication to the use of agents listed here if a patient's seizures are well controlled and/or the patient is receiving anticonvulsant
		- Patients with history of previous seizures may be at increased risk for development of seizures during DR-TB treatment
Peripheral neuropathy	**Lzd**	- Increase pyridoxine to maximum da- Continue isoniazid, and give pyridoxine 50–100 mg daily
	Cs	
	H	- Large dose of- Continue isoniazid, and give pyridoxine 50–100 mg daily
	S	- Large dose of pyridoxine, may interfere the action of isoniazid pyridoxine, may interfere the action of isoniazidily dose (200 mg per day)
	Km	
	Am	- Change injectable to capreomycin if patient has documented susceptibility to capreomycin
	Cm	
	Eto/Pto	- Initiate therapy with tricyclic antidepressants such as amitriptyline 25–50 mg
	FQs'	- Nonsteroidal anti-inflammatory drugs or acetaminophen may help alleviate symptoms
		- Lower dose of suspected agent, if this can be done without compromising regimen
		- Discontinue s- Continue isoniazid, and give pyridoxine 50–100 mg daily
		- Large dose of pyridoxine, may interfere the action of isoniaziduspected agent if this can be done without compromising reg- Continue isoniazid, and give pyridoxine 50–100 mg daily
		- Large dose of py- Continue isoniazid, and give pyridoxine 50–100 mg daily
		- Large dose of pyridoxine, may interfere the action of isoniazidridoxine- Continue isoniazid, and give pyridoxine 50–100 mg daily
		- Large dose of pyridoxine, may interfere the action of isoniazid, may interfere the action of isoniazidimen
		- Patients with comorbid disease (e.g. diabetes, HIV, alcohol neuropathy (dependence) may be more likely to develop peripheral neuropathy, but these conditions are not contraindications to the use of the agents
		- Neuropathy may be irreversible; however, some patients may experience improvement when offending agents are suspended

Table 3 – (*continued*)

Adverse drug reaction	Suspected agent	Suggested management strategies
Psychotic symptoms	**Cs** **H** FQs' Eto/Pto	- Stop suspected agent for a short period of time (1–4 weeks) while psychotic symptoms are brought under control - Initiate antipsychotic therapy - Lower dose of suspected agent if this ca- Continue isoniazid, and give pyridoxine 50–100 mg daily - Large dose of pyridoxine, may interfere the action of isoniazidn be done without compromising regimen - Discontinue suspected agent if this can be done without compromising regimen - Some patients will need to continue antipsychotic treatment throughout MDR-TB therapy - Previous history of psychiatric dis- Continue isoniazid, and give pyridoxine 50–100 mg daily - Large dose of pyridoxine, may interfere the action of isoniazidease is not a contraindication to the use of agents listed here but may increase the likelihood of psychotic symptoms developing during treatment - Psychotic symptoms are generally reversible upon completion of MDR-TB treatment or cessation of the offending agent
Depression	**Cs** FQ Eto/Pto H	- Offer grou- Continue isoniazid, and give pyridoxine 50–100 mg daily - Large dose of pyridoxine, may interfere the action of isoniazidp or individual counseling - Initiate anti- Continue isoniazid, and give pyridoxine 50–100 mg daily - Large dose of pyridoxine, may interfere the action of isoniaziddepressant therapy - Lower dos- Continue isoniazid, and give pyridoxine 50–100 mg daily - Large dose of pyridoxine, may interfere the action of isoniazide of suspected agent if this can be done without compromising regimen - Discontinue s- Continue isoniazid, and give pyridoxine 50–100 mg daily - Large dose of pyridoxine, may interfere the action of isoniaziduspected agent if this can be done without compromising regimen - Socioeconomic conditions and chronic illness should not be underestimated as contributing factors to depression - Depressive symptoms may fluctuate during therapy and may improve as illness is successfully treated - History of previous depression is not a contraindication to the use of the agents listed but may increase the likelihood of depression developing during treatment
Hearing loss/Ototoxicity	**S** **Km** **Am** **Cm** Clr	- Document hearing loss and compare with baseline audiometry if available - Change parenteral treatment to capreomycin if patient has documented susceptibility to capreomycin - Decrease frequency and/or lower dose of suspected agent if this can be done without compromising the regimen (consider administration three times per week) - Discontinue suspected agent if this can be done without compromising the regimen - Patients with previous exposure to aminoglycosides may have baseline hearing loss. In such patients, audiometry may be helpful at the start of MDR-TB therapy - Hearing loss is generally not reversible - The risk of further hearing loss must be weighed against the risks of stopping the injectable in the treatment regimen - While the benefit of hearing aids is minimal to moderate in auditory toxicity, consider a trial use to determine if a patient with hearing loss can benefit from their use
Hypothyroidism	**PAS** **Eto/Pto**	- Initiate thyroxine therapy and titration according to serial thyroid function tests - Completely reversible upon discontinuation of PAS or ethionamide/prothionamide - The combination of ethionamide/prothionamide with PAS is more frequently associated with hypothyroidism than the individual use of each drug - Monitoring of TSH or complete thyroid profile if possible every three months when both PAS and Eto/Pto included in regimen or every six months when any one of them used in regimen

(*continued on next page*)

Table 3 – (*continued*)

Adverse drug reaction	Suspected agent	Suggested management strategies
Nausea and vomiting	**Eto/Pto** **PAS** H E Z Bdq Dlm	- Assess for dehydration; initiate rehydration if indicated - Initiate antiemetic therapy - Lower dose of suspected agent if this can be done without compromising regimen - Discontinue suspected agent if this can be done without compromising regimen rarely necessary - Nausea and vomiting universal in early weeks of therapy and usually abate with time on treatment and adjunctive therapy - Electrolytes should be monitored if vomiting is severe - Reversible upon discontinuation of suspected agent - Severe abdominal distress and acute abdomen have been reported with the use of clofazimine - Although these reports are rare, if this effect occurs, clofazimine should be suspended
Gastritis	**PAS** **Eto/Pto** Bdq Dlm	- H2-blockers, proton-pump inhibitors, or antacids - Stop suspected agent(s) for short periods of time (e.g. 1–7 days) - Lower dose of suspected agent, if this can be done without compromising regimen - Discontinue suspected agent if this can be done without compromising regimen - Severe gastritis, as manifested by hematemesis, melena or hematochezia, is rare - Dosing of antacids should be carefully timed so as to not interfere with the absorption of anti-tubercular drugs (take 2 hours before or 3 hours after medications) - Reversible upon discontinuation of suspected agent(s)
Hepatitis	**Z** **H** **R** Eto/Pto PAS FQs'	- Stop all therapy pending resolution of hepatitis - Eliminate other potential causes of hepatitis - Consider susp- Continue isoniazid, and give pyridoxine 50–100 mg daily - Large dose of pyridoxine, may interfere the - Continue isoniazid, and give pyridoxine 50–100 mg daily - Large dose of pyridoxine, may interfere the action of isoniazidaction of isoniazidending most likely agent permanently - Re-introduce remaining drugs, one at a time while monitoring liver function - History of previous hepatitis should be carefully analyzed to determine most likely causative agent(s); these should be avoided in future regimens - Generally reversible upon discontinuation - Continue isoniazid, and give pyridoxine 50–100 mg daily - Large dose of pyridoxine, may interfere the action of isoniazidof suspected agent
Diarrhea	**PAS** **Eto/Pto**	- Re-assurance and observation in mild cases - Maintain hydra- Continue isoniazid, and give pyridoxine 50–100 mg daily - Large dose of pyridoxine, may interfere the action of isoniazidtion in severe cases - Monitor electrolytes in severe cases - Rule out any infectious etiology or dysentery - Use of loperamide in case of non-infectious etiology
Renal toxicity/Nephrotoxicity	**S** **Km** **Am** **Cm**	- Discontinue suspected agent - Consider using capreomycin if an - Continue isoniazid, and give pyridoxine 50–100 mg daily - Large dose of pyridoxine, may interfere the action of isoniazidaminoglycoside had been the prior injectable in regimen - Consider dosing 2–3 times a week if drug is essential to the regimen and patient can tolerate (close monitoring of creatinine) - Adjust all anti-tubercular medications according to the creatinine clearance - History of diabetes or renal disease is not a contraindication to the use of the agents listed here, although patients with these comorbidities may be at increased risk for developing renal failure - Renal impairment may be permanent - Creatinine monitoring every month for first three months and then every three months when SLID continued during intensive phase - Creatinine monitoring every 1–3 weeks in case of HIV, DM and other high risk cases

Table 3 – (*continued*)

Adverse drug reaction	Suspected agent	Suggested management strategies
Electrolyte disturbances (hypokalemia and hypomagnesemia)	**Cm** **Km** **Am** S	- Check potassium - If potassium is low, also check magnesium (and calcium if hypocalcemia is suspected) - Replace electrolytes as needed - If severe hypokalemia is present, consider hospitalization - Amiloride 5–10 mg QD or spironolactone 25 mg QD may decrease potassium and magnesium wasting and is useful in refractory cases - Oral potassium replacements ca- Continue isoniazid, and give pyridoxine 50–100 mg daily - Large dose of pyridoxine, may interfere the action of isoniazidn cause significant nausea and vomiting. - Oral magnesium may cause diarrhea - Electrolyte monitoring every 1–3 weeks in case of HIV, DM and other high risk cases - Monitoring of calcium and magnesium levels in case of QTc prolongation on ECG
Optic neuritis	**E** Eto/Pto	- Stop E - Refer patient to an ophthalmologist - Usually reverses with cessation of E
Arthralgia	**Z** FQs' Bdq	- Initiate therapy with nonsteroidal anti-inflammatory drugs - Lower dose of suspected agent if this can be done without compromising regimen - Discontinue suspected agent if this can be done without compromising regimen - Symptoms of arthralgia generally diminish over time, even without intervention - Uric acid levels may be elevated in patients on Z - Allopurinol appears not to correct the uric acid levels in such cases
Tendonitis	**FQs**	- NSAIDS to be used - Provide rest to joints - Dose of FQ to be either reduced or stopped - Bdq to be considered - Care should be taken in Diabetics
Myelosuppression Thrombocytopenia	**Lzd**	- Discontinuation of offending drug in severe cases and substitution with other drugs - Exclude other causes - Blood or platelet transfusion in few cases depending on involvement of cell lineage - Dose can be reduced to either 300 mg daily or 600 mg thrice weekly if there is recovery with serial complete blood count monitoring every week for first month and then every month
Dysglycemia	**Gfx** Mfx	- Monitor blood sugars and strict control - Treat hyperglycemia or hypoglycemia - Gfx can be replaced with other FQs - Insulin based regimens should be preferred over oral hypoglycemics
Rash Itching Allergic reaction	**All FLDs and SLDs**	- Re-assurance and conservative treatment for mild dermatological reactions - Exclusion of other diagnoses - Anti-histaminics and corticosteroid ointments to be used - Oral steroids in refractory cases - Order of reintroduction will be H, R, Z, Eto, Cs, E, PAS, FQ and Km - Discontinue offending drug responsible for severe reactions such as Steven-Johnson syndrome
QTc interval prolongation	**Bdq** **Dlm** **FQs' especially Mfx** Cfz Clr	- Serial monitoring with ECG - Exclude congenital or acquired cardiac disorders - Monitor electrolytes routinely and to be more cautious when used with Cm, Am or other ancillary medications such as diuretics/macrolideantibiotics - If QTc interval <500, offending drugs should be continued under serial ECG monitoring - If QTc interval ≥500 offending drugs should be stopped temporarily - Mfx should be replaced with Lfx - Subsequently, Cfz then Bdq and Dlm if there is persistent prolongation - Avoid Bdq and Dlm combination containing regimens if there is cardiotoxicity

Abbreviations used: - H: isoniazid; R: rifampicin; E: ethambutol; Z: pyrazinamide; S: streptomycin; Km: kanamycin; Am: amikacin; Cm: capreomycin; FQ: fluoroquinolones; Eto: ethionamide; Pto: prothionamide; PAS: para-aminosalicylic acid; Cs: cycloserine; Cfz: clofazimine; Lzd: linezolid; Clr: clarithromycin; Bdq: bedaquiline; Dlm: delamanid; DR-TB: Drug resistant tuberculosis).
Note: Drugs that the strongly associated with adverse effects shown in bold.

ADR(s). Concept of active TB drug-safety monitoring and management (aDSM) has been introduced by WHO to provide active surveillance for detection of major or severe ADRs' associated with novel DR-TB regimens and newer drugs by systematic clinical and laboratory assessment.[106] Drugs have to be re-introduced in DR-TB regimens in sequence according to WHO revised grouping in case there is documented resistance or intolerance. Symptoms based approach to management of minor and major ADRs' to FLDs' are tabulated in Tables 1 and 2.

ADRs' of second line anti-tubercular drugs including management strategy of common ones are tabulated in Table 3.

19. Conclusion

The treatment of TB can cause a variety of ADRs'. ADRs' of varying severity are common during treatment of DS-TB and DR-TB, particularly in the intensive phase of therapy. Some ADRs' become more prevalent in DR-TB patients co-infected with HIV. Most ADRs' can be successfully managed on an outpatient basis through a community-based treatment program, even in a resource-limited setting. Concerns about severe ADRs' in the management of DR-TB patients are justified, however, they should not cause delays in the urgently needed rapid scale-up of SLDs'. ADRs' can be detected by clinical evidence in resource-limited settings. DR TB can be cured successfully with appropriate combination of drugs if ADRs' associated with them can be managed aggressively and timely. Newer and less toxic drugs are needed to treat DR-TB patients over large scale. Accurate diagnoses and knowledge of the pharmacological properties of the drugs involved will allow professionals to tailor their approach to each individual case in near future.

REFERENCES

1. World Health Organization. *Global Tuberculosis Report 2018*. Geneva: WHO; 2018, 2018WHO/CDS/TB/2018.20.
2. World Health Organization. *Requirements for Adverse Reaction Reporting*. Geneva, Switzerland: World Health Organization; 1975.
3. Forget EJ, Menzies D. Adverse reactions to first-line anti-tuberculosis drugs. *Expert Opin Drug Saf*. 2006;5:231–249.
4. Gülbay BE, Gürkan Ö, Yildiz Ö, et al. Side effects due to primary anti-tuberculosis drugs during the initial phase of therapy in 1149 hospitalized patients for tuberculosis. *Respir Med*. 2006;10:1834–1842.
5. Tan WC, Ong CK, Lo Kang SC, Abdul Razak M. Two years review of cutaneous adverse drug reaction from first line anti-tuberculous drugs. *Med J Malays*. 2007;62:143–146.
6. Edwards R, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. *Lancet*. 2000;356:1255–1259.
7. *Brasil. Ministério da Saúde. Fundação Nacional de Saúde. Centro de Referência Professor Hélio Fraga; Sociedade Brasileira de Pneumologia e Tisiologia. Controle da tuberculose: uma proposta de integração ensino-serviço*. Rio de Janeiro: FUNASA/CRPHF/SBPT; 2002.
8. Singh A, Prasad R, Balasubramanian V, Gupta N, Gupta P. Prevalence of adverse drug reaction with first-line drugs among patients treated for pulmonary tuberculosis. *Clin Epidemiol Glob Health*. 2015;3:s80–s90.
9. Marra F, Marra CA, Bruchet N, et al. Adverse drug reactions associated with first-line anti-tuberculosis drug regimens. *Int J Tuberc Lung Dis*. 2007;11:868–875.
10. Butov D, Kuzhko M, Stepanenko G, Butova T. Frequency of adverse reactions to first-line anti-tuberculosis chemotherapy in patients with relapse (RTB) and newly diagnosed tuberculosis (NDTB). *ERJ*. 2018;52(s62):PA2700.
11. Dosumu A. Side effects of drugs used in directly observed treatment short-course in newly diagnosed pulmonary tuberculosis subjects in Nigerian's: a controlled clinical study. *Niger Post Grad Med J*. 2002;9:34–37.
12. Hong Kong Chest Services/BMRC. Controlled trial 6-month and 8-month regimen in the treatment of pulmonary tuberculosis. 1st report. *Am Rev Respir Dis*. 1978;118:219.
13. Arbex MA, de Castro Lima Varella M, de Siqueira HR, de Mello FAF. Anti-tuberculosis drugs: drug interactions, adverse effects, and use in special situations. Part 1: first-line drugs. *J Bras Pneumol*. 2010;36:626–640.
14. Vieira DE, Gomes M. Adverse effects of tuberculosis treatment: experience at an outpatient clinic of a teaching hospital in the city of São Paulo, Brazil. *J Bras Pneumol*. 2008;34:1049–1055.
15. Breen RA, Miller RF, Gorsuch T, et al. Adverse events and treatment interruption in tuberculosis patients with and without HIV co-infection. *Thorax*. 2006;61:791–794.
16. Singapore Tuberculous Service/BMRC. Clinical trial of six month and four month regimen of chemotherapy in the TB of pulmonary tuberculosis. 1st report. *Am Rev Respir Dis*. 1979;579:119–179.
17. Mwandumba HC, Squire SB. *Fully intermittent dosing with drugs for treating tuberculosis in adults*. The Cochrane Collaboration; 2005.
18. Prasad R, Singh A, Gupta N, Giridhar BH. Epidemiology of adverse drug reaction with second line drugs among patients treated for multi-drug resistant tuberculosis. Eur J Biomed Pharm Sci; 2:553-561.
19. Wu S, Zhang Y, Sun F, et al. Adverse events associated with the treatment of multidrug-resistant tuberculosis: a systematic review and meta-analysis. *Am J Therapeut*. 2016;23:e521–e530.
20. Schnippel K, Firnhaber C, Berhanu R, Page-Shipp L, Sinanovic E. Adverse drug reactions during drug-resistant TB treatment in high HIV prevalence settings: a systematic review and meta-analysis. *J Antimicrob Chemother*. 2017;72:1871–1879.
21. Furin JJ, Mitnick CD, Shin SS, et al. Occurrence of serious adverse effects in patients receiving community-based therapy for MDR-TB. *Int J Tuberc Lung Dis*. 2001;5:648–655.
22. Nathanson E, Gupta R, Huamani P, et al. Adverse events in the treatment of MDR-TB: results from the DOTS-Plus initiative. *Int J Tuberc Lung Dis*. 2005;9:1027–1033.
23. Shin SS, Pasechnikov AD, Gelmanova IY, et al. Adverse reactions among patients being treated for MDR-TB in Tomsk, Russia. *Int J Tuberc Lung Dis*. 2007;11:1314–1320.
24. Baghaei P, Tabarsi P, Dorriz D, et al. Adverse effects of MDR-TB treatment with a standardized regimen: a report from Iran. *Am J Therapeut*. 2011;18:e29–e34.
25. Carroll MW, Lee M, Cai Y, et al. Frequency of adverse reactions to first- and second-line anti-tuberculosis chemotherapy in a Korean cohort. *Int J Tuberc Lung Dis*. 2012;167:961–966.
26. Mehrotra ML. Agra study of short course chemotherapy in pulmonary tuberculous patients. *Indian J Tuberc*. 1982;29:29–39.
27. Dedun AR, Borisagar GB, Solanki RN. Impact of adverse drug reaction of first line anti - tuberculous drugs on treatment

outcome of tuberculosis under revised national tuberculosis control programme. *Int J Adv Med*. 2017;4:645–649.
28. Naser SM, Nandy M, Banu P, et al. Adverse drug reaction monitoring through active surveillance of anti-tubercular therapy in an urban tertiary care center. *Community Acquir Infect*. 2016;3:51–54.
29. Mandal PK, Mandal A, Bhattacharyya SK. Comparing the daily versus the intermittent regimens of the anti-tubercular chemotherapy in the initial intensive phase in non-HIV, sputum positive, pulmonary tuberculosis patients. *J Clin Diagn Res*. 2013;7:292–295.
30. Singla R, Sarin R, Khalid UK, Mathuria K, Singla N. Seven-year DOTS-Plus pilot experience in India: results, constraints and issues. *Int J Tuberc Lung Dis*. 2009;13:976–981.
31. Joseph P, Desai VB, Mohan NS, Fredrick JS, Ramachandran R. Outcome of standardized treatment for patients with MDR-TB from Tamil Nadu, India. *Indian J Med Res*. 2011;133:529–534.
32. Isaakidis P, Cox HS, Varghese B, Montaldo C, Da Silva E. Ambulatory MDR-TB treatment outcomes in A cohort of HIV-infected patients in A slum setting in Mumbai, India. *PLoS One*. 2011;6, e28066.
33. Isaakidis P, Varghese B, Mansoor H, Cox HS, Ladomirska J. Adverse events among HIV/MDR-TB Co-infected patients receiving antiretroviral and second line anti-TB treatment in Mumbai, India. *PLoS One*. 2012;7, e40781.
34. Natarajan Subramanian, Subramanian Poonam. Adverse drug reactions to second line anti tuberculosis drugs: a prospective study in Mumbai, India. *ERJ*. 2013;42(S57):P2820.
35. Dela AI, Tank ND, Singh AP, Piparva KG. Adverse drug reactions and treatment outcome analysis of DOTS plus therapy of MDR-TB patients at district tuberculosis centre: a four year retrospective study. *Lung India*. 2017;34:522–526.
36. Prasad R, Verma SK, Sahai S, Kumar S, Jain A. Efficacy and safety of kanamycin, ethionamide, PAS and cycloserine in multi drug resistant pulmonary tuberculosis patients. *Indian J Chest Dis Allied Sci*. 2006;48:181–184.
37. Prasad R, Singh A, Srivastava R, et al. Adverse drug reaction in the treatment of multi drug resistant tuberculosis. *Indian J Tuberc*. 2016;63:106–114.
38. Shinde KM, Pore SM, Bapat TR. Adverse reactions to first-line anti-tuberculous agents in hospitalised patients: pattern, causality, severity and risk factors. *Indian J Med Specialities*. 2013;4:1–4.
39. Lv X, Tang S, Xia Y, et al. Adverse reactions due to directly observed treatment strategy therapy in Chinese tuberculosis patients: a prospective study. *PLoS One*. 2013;8, e65037. https://doi.org/10.1371/journal.pone.0065037.
40. Anand AC, Seth AK, Paul M, Puri P. Risk factors of hepatotoxicity during anti-tuberculosis treatment. *MJAFI (Med J Armed Forces India)*. 2006;62:45–49.
41. Parthasarathy R, Sarma GR, Janardhanam B, et al. Hepatic toxicity in south Indian patients during treatment of tuberculosis with short-course regimens containing isoniazid, rifampicin and pyrazinamide. *Tubercle*. 1986;67:99–108.
42. Purohit SD, Gupta PR, Sharma TN, Gupta DN, Chawla MP. Rifampicin and hepatic toxicity. *Indian J Tuberc*. 1983;30:107–109.
43. Blumberg HM, Burman WJ, Chaisson RE, et al. American thoracic society/centers for disease control and prevention/ infectious diseases society of America: treatment of tuberculosis. *Am J Respir Crit Care Med*. 2003;167:603–662.
44. Steele MA, Burk RF, Desprez RM. Hepatitis with isoniazid and rifampicin – a meta-analysis. *Chest*. 1971;99:465–471.
45. Gangadharan PRJ. Isoniazid, rifampicin and hepatotoxicity. *Am J Respir Dis*. 1986;133:963–965.
46. Pande JN, Singh SPN, Khilnani GC, Tandon RK. Risk factors for hepatotoxicity from anti-tuberculous drugs: a case control study. *Thorax*. 1996;51:132–136.
47. Prasad R, Verma SK, Chowdhury SR, Chandra M. Predisposing factors in hepatitis induced by anti-tuberculosis regimens containing isoniazid, rifampicin and pyrazinamide: a case control study. *JIMI*. 2006;9:73–78.
48. Baghaei P, Tabarsi P, Chitsaz E, et al. Incidence, clinical and epidemiological risk factors, and outcome of drug-induced hepatitis due to anti-tuberculous agents in new tuberculosis cases. *Am J Therapeut*. 2010;17:17–22.
49. Lee AM, Mennone JZ, Jones RC, Paul WS. Risk factors for hepatotoxicity associated with Rifampin and pyrazinamide for the treatment of latent tuberculosis infection: experience from three public health tuberculosis clinics. *Int J Tuberc Lung Dis*. 2002;6:995–1000.
50. Durand F, Bernuau J, Pessayre D, et al. Deleterious influence of pyrazinamide on the outcome of patients with fulminant or sub-fulminant liver failure during anti-tuberculous treatment including isoniazid. *Hepatology*. 1995;21:929–932.
51. Kumar R, ShalimarBhatia V, Khanal S, Sreenivas V, Gupta SD, et al. Anti-tuberculosis therapy-induced acute liver failure: magnitude, profile, prognosis, and predictors of outcome. *Hepatology*. 2010;51:1665–1674.
52. Bertino Jr J, Fish D. The safety profile of the fluoroquinolones. *Clin Ther*. 2000;22:798–817.
53. British Thoracic Association. A comparison of the toxicity of prothionamide and ethionamide: a report from the research committee of the British Tuberculosis Association. *Tubercle*. 1968;49:125–135.
54. Rossouw JE, Saunders J. Hepatic complications of anti-tuberculous therapy. *QJM*. 1975;44:1–16.
55. DR-TB STAT. *Treatment of Drug-Resistant TB with New and Re-purposed Medications: A Field Guide*. Cleveland: DR-TB STAT; 2018.
56. Chhetri AK, Saha A, Verma SC, Palaian S, Mishra P, Shankar PR. A study of adverse drug reactions caused by first line anti-tubercular drugs used in Directly Observed Treatment, Short course (DOTS) therapy in western Nepal, Pokharan. *J Pak Med Assoc*. 2008;58:531–536.
57. Koju D, Rao BS, Shrestha B, Shakya R, Makaju R. Occurrence of side effects from anti-tuberculosis drugs in urban Nepalese population under DOTS treatment. *Kathmandu Univ J Sci Eng Technol*. 2005;1.
58. Girling DJ. Adverse effects of anti-tuberculosis drugs. *Drugs*. 1982;23:56–74.
59. Philadelphia Tuberculosis Control Program. *Guidelines for the Management of Adverse Drug Effects of Anti-mycobacterial Agents*. Philadelphia: Lawrence Flick Memorial Tuberculosis Clinic, Philadelphia Tuberculosis Control Program; 1998.
60. Prasad R, Garg R, Verma SK. Isoniazid- and ethambutol-induced psychosis. *Ann Thorac Med*. 2008;3:149–151.
61. Cohn ML, Mandel W, Middlebrook G, Russell Jr WF. Serum isoniazid levels and catalase activities of tubercle bacilli from isoniazid-treated patients. *Am J Med Sci*. 1957;233:66–68.
62. Jackson SL. Psychosis due to isoniazid. *Br Med J*. 1957;28:743–745.
63. Thundiyil JG, Kearney TE, Olson KR. Evolving epidemiology of drug-induced seizures reported to a Poison control center system. *J Med Toxicol*. 2007;3:15–40.
64. Kass JS, Shandera WX. Nervous system effects of anti-tuberculosis therapy. *CNS Drugs*. 2010 Aug;24:655–667.
65. Carr RE, Henkind P. Ocular manifestations of ethambutol. *Arch Ophthalmol*. 1962;67:566–571.
66. Tsai RK, Lee YH. Reversibility of ethambutol optic neuropathy. *J Ocul Pharmacol Ther*. 1997;13:473–477.
67. Leibold JE. The ocular toxicity of ethambutol and its relation to dose. *Ann N Y Acad Sci*. 1966;135:904–909.

68. Citron KM, Thomas GO. Ocular toxicity from ethambutol (editorial). *Thorax*. 1986;41:737–739.
69. Tang S, Yao L, Hao X, et al. Efficacy, safety and tolerability of linezolid for the treatment of XDR-TB: a study in China. *Eur Respir J*. 2015;45:161–170.
70. Moore RE, Smith CR, Lietman PS. Risk factors for the development of auditory toxicity in patients receiving aminoglycosides. *J Infect Dis*. 1984;149:23–30.
71. Prrazic M, Saiaj B. Ototoxicity in children caused by streptomycin. *Audiology*. 1975;14:173–176.
72. Robinson GL, Cambon KG. Hearing loss in infants of tuberculous mothers treated with streptomycin during pregnancy. *N Engl J Med*. 1964;271:949–951.
73. Johnsonbaugh RE, Drexler HG, Light JJ, Sutherland JM. Familial occurrence of drug induced hearing loss. *Am J Dis Child*. 1974;127:245–247.
74. Indian Council of Medical Research Centre Report. Study of Chemotherapy regimens of 5 and 7 months duration and the role of corticosteroids in the treatment of Sputum-positive patients with pulmonary tuberculosis in South India. *Tubercle*. 1983;64:73–91.
75. Berte SJ, Dimase JD, Christianson CS. Isoniazid, para-aminosalicylic acid and streptomycin intolerance in 1,744 patients. *Am Rev Respir Dis*. 1964;90:598–606.
76. Neff TA, Coan BJ. Incidence of drug intolerance to anti-tuberculosis chemotherapy. *Dis Chest*. 1969;56:10–12.
77. Shibeshi W, Sheth AN, Admasu A, Berha AB, Negash Z, Yimer G. Nephrotoxicity and ototoxic symptoms of injectable second-line anti-tubercular drugs among patients treated for MDR-TB in Ethiopia: a retrospective cohort study. *BMC Pharmacol Toxicol*. 2019;20:31.
78. Sarin R, Behera D, Khanna A, Singh V, Narang P, Deepak TS. Second-line injectable induced ototoxicity in drug resistant tuberculosis: a systematic review of Indian studies. *Indian J Tuberc*. 2019;66:279–287.
79. Rybak MJ, Abate BJ, Kang SL, Ruffing MJ, Lerner SA, Drusano GL. Prospective evaluation of the effect of an aminoglycoside dosing regimen on rates of observed nephrotoxicity and ototoxicity. *Antimicrob Agents Chemother*. 1999;43:1549–1555.
80. Garg R, Gupta V, Mehra S, Singh R, Prasad R. Rifampicin induced thrombocytopenia. *Indian J Tuberc*. 2007;54:94–96.
81. Prasad R, Mukerji PK. Rifampicin induced thrombocytopenia. *Indian J Tuberc*. 1989;36:171–175.
82. Prasad R, Mukerji PK. Ethambutol induced thrombocytopenia. *Tubercle*. 1989;70:211–212.
83. Kant S, Verma SK, Gupta V, Anand SC, Prasad R. Pyrazinamide induced thrombocytopenia. *Indian J Pharmacol*. 2010;42:108–109.
84. Sotgiu G, Centis R, D'Ambrosio L, et al. Efficacy, safety and tolerability of linezolid containing regimens in treating MDR-TB and XDR-TB: systematic review and meta-analysis. *Eur Respir J*. 2012;40:1430–1442.
85. Gerdan G, Nurullah A, Ucan ES, Bulac Kir S. Paradoxical increase in uric acid level with allopurinol use in pyrazinamide-induced hyperuricemia. *Singap Med J*. 2013;54:e125–e128.
86. Gutman AB, Yu TF, Berger L. Renal function in gout. III. Estimation of tubular secretion and reabsorption of uric acid by use of pyrazinamide (pyrazinoic acid). *Am J Med*. 1969;47:575–592.
87. Postlethwaite AE, Bartel AG, Kelley WN. Hyperuricemia due to ethambutol. *N Engl J Med*. 1972;286:761–762.
88. Dhingra VK, Rajpal S, Aggarwal N, Aggarwal JK, Shadab K, Jain SK. Adverse drug reactions observed during DOTS. *J Commun Dis*. 2004;36:251–259.
89. Kang BH, Jo KW, Shim TS. Current status of fluoroquinolone use for treatment of tuberculosis in a tertiary care hospital in Korea. *Tuberc Respir Dis (Seoul)*. 2017;80:143–152. https://doi.org/10.4046/trd.2017.80.2.143.
90. Diacon A, Pym A, Grobusch M, et al. Multidrug-resistant tuberculosis and culture conversion with bedaquiline. *N Engl J Med*. 2014;371:723–732.
91. Pym AS, Diacon AH, Tang SJ, et al. Bedaquiline in the treatment of multidrug- and extensively drug-resistant tuberculosis. *Eur Respir J*. 2016;47:564–574.
92. Rougier F, Claude D, Maurin M, et al. Aminoglycoside nephrotoxicity: modelling, simulation, and control. *Antimicrob Agents Chemother*. 2003;47:1010–1016.
93. de Jager P, van Altena R. Hearing loss and nephrotoxicity in long-term aminoglycoside treatment in patients with tuberculosis. *Int J Tuberc Lung Dis*. 2002;6:622–627.
94. Yang TW, Park HO, Jang HN, et al. Side effects associated with the treatment of multidrug-resistant tuberculosis at a tuberculosis referral hospital in South Korea: a retrospective study. *Medicine (Baltimore)*. 2017;96, e7482.
95. Tawanda G. *Chemotherapy of Tuberculosis, mycobacterium Avium Complex Disease and Leprosy. Goodman and Gilman's the Pharmacological Basis of the Therapeutics*. 12th ed. McGraw Hill Med; 2011:1559.
96. Vedove CD, Del Giglio M, Schena D, Girolomoni G. Drug-induced lupus erythematosus. *Arch Dermatol Res*. 2009;301:99–105.
97. Garg R, Verma S, Mahajan V, Prasad R. Exfoliative dermatitis secondary to ethambutol and pyrazinamide. *Internet J Pulm Med*. 2008;9:1.
98. Rakotoson JL, Randriamanana D, Rakotomizao JR, Andrianasolo R, Rakotoarivelo R, Andrianarisoa AC. Severe systemic lupus erythematosus induced by isoniazid [Article in French]. *Rev Pneumol Clin*. 2009;65:361–364.
99. Potter JL, Capstick T, Ricketts WM, Whitehead N, Kon OM. A UK-based resource to support the monitoring and safe use of anti-tuberculosis drugs and second-line treatment of multidrug-resistant tuberculosis. *TB Drug Monographs*. 2015:90–96.
100. Pontali E, Sotgiu G, Tiberi S, D'Ambrosio L, Centis R, Migliori GB. Cardiac safety of bedaquiline: a systematic and critical analysis of the evidence. *Eur Respir J*. 2017;50:1701462.
101. Garg R, Mehra S, Prasad R. Isoniazid induced gynaecomastia: a case report. *Indian J Tuberc*. 2009;56:51–54.
102. Khan A, Agarwal R. Isoniazid related gynaecomastia: description of a case and systematic review of literature. *Lung India*. 2012;29:189–191.
103. Prasad R. Anaphylactic shock due to streptomycin sulphate. *J Indian Med Assoc*. 1989;82:254–255.
104. WHO. *A Practical Handbook on the Pharmacovigilance of Medicines Used in the Treatment of Tuberculosis. Enhancing the Safety of the TB Patient*. Geneva, Switzerland; 2012. www.who.int/medicines/publications/pharmacovigilance_tb/en/.
105. Division of AIDS, National Institute of Allergy and Infectious Diseases. *Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events. Corrected Version 2.1. Bethesda*. US Department of Health and Human Services, National Institutes of Health; 2017. https://rsc.tech-res.com/docs/default-source/safety/division-of-aids-(daids)-table-for-grading-the-severity-of-adult-and-pediatric-adverse-events-corrected-v-2-1.pdf.
106. World Health Organization. *WHO Consolidated Guidelines on Drug-Resistant Tuberculosis Treatment*. Geneva: WHO; 2019 (WHO/CDS/TB/2019.7); downloaded from https://www.who.int/tb/.../consolidated guidelines-drug-resistant-TB-treatment/en/.

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Review article

Diabetes and respiratory system including tuberculosis - challenges

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ABSTRACT

Diabetes mellitus is a common disorder associated with systemic inflammation and oxidative stress affecting various organ systems leading to microvascular (retinopathy, nephropathy and neuropathy) and macrovascular (myocardial infarction, stroke, peripheral vascular disease) complications. Although the impact of diabetes on lung functions has been previously reported, especially in asthma and COPD, the lung has not been described as a common target organ in diabetes and this has important medical, social and financial consequences in our already overburdened healthcare system. The underlying mechanism and pathophysiology of such an association have rarely been described in the literature. This review aims to discuss the effects of diabetes on lungs, probable mechanisms by which hyperglycemia may affect lung functions and mechanisms by which respiratory diseases can lead to onset, or worsening of pre-existing hyperglycemia with inherited challenges in the management.

1. Introduction

Diabetes represents the global epidemic of chronic non-communicable diseases. The International Diabetes Federation (IDF) estimates an increase of 55% in prevalence of diabetes by the year 2045.[1] Diabetes is not only one of the leading causes of mortality, it also contributes adversely to quality of life. It also increases the cost of the care. On the other hand, respiratory diseases are among the most common diseases that are increasing in prevalence worldwide.[2] Chronic Obstructive Pulmonary Disease (COPD), bronchial asthma, pulmonary infections including tuberculosis are some of the pulmonary disorders that are more prevalent than before.[2] Lung cancer is the leading respiratory cause of death worldwide.[3] Obstructive Sleep Apnea (OSA) is also being increasingly recognized as a major sleep related breathing disorder. OSA is often underdiagnosed and undertreated but has important metabolic consequences with major adverse effects. Many of these lung diseases have a bidirectional relationship with diabetes mellitus. The current review examines this adverse association between diabetes and respiratory diseases, their clinical implications and challenges in the management.

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2. Diabetes and lung functions

Diabetes is a systemic disorder and causes several microvascular complications (retinopathy, nephropathy and neuropathy) as well as macrovascular complications (myocardial infarction, stroke, peripheral vascular disease).[4] There is data to suggest that lungs are also the site of target organ damage because of persistent hyperglycemia.[5] Hyperglycemia can directly cause damage to the lung tissue by means of glycosylation (through advanced glycosylation end products), inflammation (through proinflammatory cytokines), fibrosis, loss of elastic recoil and impaired muscle strength as a result of neuropathy.[6] Lungs have an elastic structure and hyperglycemia influences elastic proteins of the lung. Damage to the elastic proteins of the lungs can therefore lead to the development of chronic airflow limitation and increasing the susceptibility to COPD. The lung is a site of maximal exposure to oxygen and oxidative stress. Diabetes represents a chronic inflammatory state with an increase in reactive oxygen species and impairment of antioxidant defense mechanisms. Diabetes also causes changes in the pulmonary vasculature and pulmonary microvascular angiopathy may be responsible for decrease in lung diffusion capacity for carbon monoxide and pulmonary capillary blood volume.[7] Studies have shown that there is thickening in alveolar capillaries and pulmonary arteriolar walls in patients with diabetes. Diabetes mellitus also adds to the comorbidity of Interstitial Lung Diseases (ILD) with increased breathlessness and worsening of parenchymal fibrosis. Earlier studies[7,8] examining the lung functions in diabetics showed that patients with newly diagnosed diabetes had a significant baseline reduction in their lung functions in comparison to healthy controls. The Framingham heart study,too, has shown that diabetes leads to impairment of lung functions.[8] The Fremantle diabetes study [9]showed that rate of decline of lung function as measured by spirometry was faster at the rate of 71ml/year in comparison to non-diabeticnon-smoker subjects without a prior history of lung disease (25–30ml/year).

3. Diabetes and COPD/Asthma

Diabetes and COPD have a bidirectional association and recent data suggest[10] that diabetes can worsen the progression and prognosis of COPD because of persistent hyperglycemia, inflammation, increased susceptibility to infections. Similarly, COPD too can also be a risk factor for difficulty in management of new onset diabetes as a result of persistent chronic inflammation, infections and use of high dose corticosteroids for the management of COPD.[11] COPD as an important risk factor for new onset diabetes is also reported by the Nurses' health study, which found that COPD patients had higher risk of developing diabetes than those without COPD[12] COPD is predicted to become the third leading cause of death by 2030. Approximately 10% of patients with diabetes have co-existing COPD. Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study,[13-] investigated 2164 COPD patients and 582 healthy subjects and identified that odds of dying from COPD increased significantly with diabetes. Coexistent diabetes was also associated with higher medical research council dyspnea score and reduced 6-minute walk distance. Acute exacerbation of COPD is commonly associated with frequent hyperglycemia during hospitalization, thereby leading to increased length of stay and increased mortality. It has also been reported that hyperglycemia is an independent risk factor for late failure of noninvasive ventilation.[12,13] Co-existent diabetes also increases the risk of pulmonary infections in patients with COPD. Several studies[11–14] have shown that impaired lung function is a predictor of poor control of diabetes. Although the link between COPD and diabetes is supported by the literature, the strength of such an association cannot be generalized as there can be many confounding factors. More research is required to understand the complex relationship between diabetes and COPD. Though the literature[14] suggests an independent bidirectional association between diabetes and asthma yet asthma does not significantly affect diabetes and inhaled steroids in low doses do not significantly affect glycemia.

4. Diabetes and lung cancer

Diabetes is associated with an increased risk of malignancies including breast, endometrium, colorectal, liver, pancreas and bladder. The relationship between diabetes and lung malignancy is not extensively studied. Some studies from the USA and UK reported no association between diabetes and lung cancer, however two recent studies from Sweden and Denmark reported that diabetes significantly increases the risk of lung cancer.[14,15] In a population-based study from Taiwan[16] in 2014, it was found that diabetes was significantly associated with an enhanced risk of lung cancer. The same study reported that the risk of lung cancer was particularly higher in diabetic males, smokers and those with co-existing COPD. The study[16] also concluded that it is the uncontrolled diabetes instead of insulin therapy that increases the risk of lung cancer. Diabetes can also affect the prognosis of lung malignancy and is reported to have an adverse impact on short term prognosis in surgically treated patients of non-small cell carcinoma of the lung.[17] Studies have also suggested that metformin, the most common used first line drug for the management of Type 2 Diabetes, has a protective effect on lung cancer that is postulated to be due to its antitumor properties, although the exact mechanism is unknown.[18]

5. Cystic fibrosis related diabetes

Cystic fibrosis is a monogenic autosomal inherited disorder due to mutation in cystic fibrosis transmembrane conductance regulator gene. It principally affects the functions of the exocrine glands and commonly involves respiratory and digestive systems leading to frequent pulmonary infections and pancreatic enzyme insufficiency. Bronchiectasis is one of the major complications and can have an effect in diabetics. Cystic fibrosis related diabetes (CFRD) is a distinct entity although it shares features of both type 1 and type 2 diabetes.[19] CFRD is characterized by progressive decrease in

insulin secretion from childhood and declining beta cell mass due to fibrosis and amyloidosis of the pancreas. Insulin sensitivity is usually normal but is impaired in the presence of infections and corticosteroid treatment. Basal insulin secretion is preserved in patients with CFRD and fasting blood glucose levels are often normal with lowest before meals. The glucose levels rise after meals and the highest levels are reported in the evening. CFRD was earlier thought to be mild and inconsequential however it is now clear that it can cause micro as well as macrovascular complications and adversely impacts the pulmonary functions and mortality. People with CFRD have higher mortality in comparison to people with cystic fibrosis without diabetes.[20]

6. Diabetes and Obstructive Sleep Apnea

Obstructive sleep apnea (OSA) is a common sleep disorder characterized by repetitive, partial or complete, obstruction of the upper airway during sleep. This invariably leads to intermittent cerebral hypoxia, sleep fragmentation and failure to achieve deeper stages of sleep. It has shown to cause systemic inflammation and increased oxidative stress, that often leads to insulin resistance and significant cardiovascular disease.[21] Several studies[22,23] including Sleep Heart Health Study (SHHS)[23] have shown that diabetes and OSA have a close bidirectional association, independent of age, gender and BMI, and therefore OSA patients are more likely to develop diabetes, and vice-a-versa. Diabetes may also contribute to sleep disordered breathing by affecting central control of respiration and upper airway neural reflexes due to diabetic neuropathy. Estimated prevalence of diabetes among OSA patients is 15–30%. Snoring is considered a surrogate marker for OSA but only two studies have shown an association between snoring and diabetes[24] OSA symptoms like snoring, daytime somnolence, witnessed sleep apnea are associated with elevated fasting plasma glucose levels. However, whether the treatment of OSA with CPAP improves glucose metabolism is still uncertain with many studies[24–26] giving conflicting results. Some studies have reported a robust association between OSA severity and worsening of glycemic control, which is directly proportional to the severity of OSA. International Diabetes Federation as well as American Diabetes Association also recognize OSA as an important comorbidity in patients living with diabetes.[25] It has been reported[26] that though the use of CPAP for small duration has not shown any major benefit in improving glucose metabolism and insulin resistance, long term CPAP therapy leads to better control of fasting blood glucose levels. The CPAP therapy, however, remains the mainstay of treatment in OSA, irrespective of glycemic levels, as it is proven to improve hypertension, quality of sleep and overall quality of life.

7. Diabetes and respiratory infections (non-tubercular)

Individuals with diabetes are more susceptible to respiratory tract infections and diabetes is considered as an independent risk factor for respiratory infections including community acquired pneumonia.[26] Diabetes reduces bacterial clearance from the lung and there is impaired polymorphonuclear cells phagocytic function. Hyperglycemia due to uncontrolled diabetes can promote bacterial growth by enhancing interaction of the bacteria with respiratory epithelium. The spectrum of pathogens responsible for CAP in patients with diabetes is different from non-diabetic individuals.[27] Infection with *Staphylococcus aureus* and gram-negative bacteria like klebsiella pneumoniae are far more common in patients with diabetes than in those without diabetes.[28]This may be attributed to higher skin and nasopharyngeal carriage of *Staphylococcus aureus* and increased oro-pharyngeal carriage of gram-negative bacteria in diabetics. Diabetes is also associated with increased risk of recurrent pneumococcal pneumonia. Patients with diabetes are six times more likely to be hospitalized with influenza or influenza-like-illness during epidemics.[29] These patients are also at enhanced risk of secondary staphylococcal pneumonia. Fungal infections of the lungs and sinuses (Candida, Mucor) are more common in patients with diabetes than in nondiabetic patients.[30] Some of the serious respiratory tract infections like Influenza and pneumococcal pneumonia are vaccine preventable diseases, therefore vaccination of patients with diabetes must be considered very strongly to prevent morbidity[29]

8. Diabetes and tuberculosis

In 2019, WHO estimated that 10.4 million people were diagnosed with diabetes and 1.7 million people died of it.[31] IDF projections estimate that the global burden of diabetes will rise by 55% by the year 2045 and much of this increase will happen in the geographical areas where tuberculosis is endemic.[1] A close look at epidemiology of these two diseases suggest that while tuberculosis is more prevalent in poor countries, diabetes has been traditionally considered a disease of the richer population. Historically, an association between diabetes and tuberculosis was not given much importance until only recently with shift in global epidemiology of diabetes. In 2007 and 2008, a series of papers[32] explored this association between diabetes and tuberculosis. A Medline literature search by Catherine Stevenson[33] identified 9 studies published after 1995 which reported a variable increase in risk (1.5%–7.8%) of tuberculosis with diabetes mellitus.

The association between diabetes and tuberculosis is well known and is bidirectional. There is more than threefold increase in risk of tuberculosis with diabetes but whether tuberculosis increases the risk of diabetes or not remains uncertain.[34] The possibility is raised by the fact that many patients with tuberculosis develop transient hyperglycemia during treatment for tuberculosis. It is still inconclusive if the transient hyperglycemia increases the risk of future diabetes. The studies[32–34] have been limited by many potential confounders. The same group reported that in Indians diabetes was associated with 14.8% cases of pulmonary tuberculosis and 20.2% cases of smear positive pulmonary tuberculosis. Jeon and Murray in a systematic review and meta-analysis identified 13 studies from the year 1965 and reported that in three cohort studies relative risk of tuberculosis was 3.1%

while in case-controlled studies relative risk varied from 1.16 to 7.83. Further studies[35] have confirmed that there is more than threefold increase in risk of tuberculosis with diabetes. Diabetes is associated with an overall increase in risk of all infections and the precise mechanism by which leads to increase in risk of tuberculosis is not clear. Diabetes compromises the cell mediated immunity by impairing the functions of macrophages, lymphocytes and monocytes. Patients with uncontrolled diabetes are at higher risk of developing tuberculosis than in those with good glycemic control, thus indicating that hyperglycemia may play a major role in the development of tuberculosis.[35] The pulmonary microangiopathy caused by diabetes may also be one of the contributing factors. The other risk factors include the presence of diabetic kidney disease and vitamin deficiencies.

In 2009 in an expert group meeting in Paris, it was agreed that a collaborative approach is required to deal with the duo of tuberculosis and diabetes and a framework was launched in 2011. This framework focuses on establishing the mechanisms for collaboration, detection and management of tuberculosis in patients with DM and detection of DM in patients with diabetes.

Plausible ways in which diabetes can affect tuberculosis are many. Diabetes affects the susceptibility, progression, smear positivity, latent infection, contagiousness, reactivation and mortality of patients with tuberculosis.[36] Diabetes not only increases the susceptibility to tubercular infection, but it also increases the rate of developing tuberculosis in those with latent infection. Diabetes increases the risk of reinfection with tubercle bacilli and proportion of those having sputum positive tuberculosis is more with diabetes. Diabetes also increases the contagiousness of infection with both treated and untreated cases. There is an increase in mortality in patients with tuberculosis and diabetes. Diabetes also affects the treatment of tuberculosis with treatment failure more common in patients with both diabetes and tuberculosis. There is also an increased risk of development of multi drug resistant tuberculosis, increased recovery time and susceptibility to reinfection. This means that people with diabetes not only have higher risk of tuberculosis, but they are also likely to have relatively worse outcomes. The poorer outcome may be because of many reasons which include compromised innate and adaptive immune response. Further, bactericidal activity of anti-tubercular drugs may be altered by diabetes due to changes in pharmacokinetics of anti-tubercular drugs. The rifampicin may interfere with the pharmacokinetics of oral anti diabetic drugs leading to impairment of glycemic control. A better understanding and more research with robust evidence is required to conclusively establish the possible ways in which diabetes can change the natural history of tuberculosis.

9. Challenges in the management of diabetes and tuberculosis - screening

There are only few studies which have examined the issue of screening diabetics for tuberculosis. Due to lack of evidence of any cost benefit, the routine screening of diabetics for tuberculosis, and *vice versa*, is not recommended, as of now. However, it is suggested to keep a high index of suspicion for tuberculosis in diabetic patients who present with symptoms off ever,persistent cough and weight loss. On the other hand, screening for diabetes in tuberculosis patients is widely recommended and is advocated by most of the tuberculosis control programs.[29] The screening for diabetes in patients suffering from tuberculosis poses significant challenges like timing of screening (at the time of diagnosis and before starting treatment, during the treatment, or at the end of the treatment) and the test to be used (random blood sugar, fasting blood sugar, post prandial blood sugar or HbA1c or OGTT). However, screening strategy in a community is guided by local factors, prevalence of diabetes and tuberculosis, associated cost and availability of resources.[37]

10. Challenges in the management of diabetes and tuberculosis - treatment

Adequate glycemic control is required for better treatment outcomes and prevention of vascular complications in patients with diabetes. The oxidative stress seen in many patients of diabetes is also an important risk factor in pathogenicity of tuberculosis.[38] Tuberculosis being a chronic inflammatory state can increase insulin resistance and diabetics suffering from tuberculosis may therefore require treatment modification and intensification. However, the need for a specifically tailored treatment for tuberculosis patients with diabetes is not yet recommended.[31] In general, patients with concurrent diabetes and tuberculosis are recommended standard treatment with two drugs, namely, rifampicin and isoniazid for 6 months each in addition to using ethambutol and pyrazinamide for the first two months.[31] Monitoring of drug levels or a longer treatment duration is not yet clearly defined in guidelines. In a study from Indonesia,[30] it was reported that drug concentration of rifampicin,when prescribed to patients with coexisting diabetes and tuberculosis, was about 50% lower in patients with than in those without it. In addition, lower serum levels of rifampicin were associated with increased blood glucose levels leading to worsening of diabetes. However, similar results could not be reproduced in larger study cohorts. It is important to highlight that pharmacokinetics of antitubercular drugs may be altered by diabetes and therefore, whether an increase in rifampicin dose will improve the outcomes needs further research. There are some studies[26,30,31] that support the hypothesis that a longer treatment duration of antitubercular drugs may prevent recurrence of tuberculosis in diabetic patients. However, data is not robust enough in many other studies to make general recommendations. A longer duration of treatment may lead to greater toxicity of antitubercular drugs including peripheral neuropathy and ocular side effects.[39]

Patients of tuberculosis with diabetes may require frequent self-monitoring of blood glucose although guidelines on these recommendations are lacking. The choice of drug for diabetes is guided by the same principles (glycemic efficacy, side effects, cost) as in patients without diabetes as there is no preferred drug for the management of diabetes in patients suffering from tuberculosis. Rifampicin has drug interactions

with sulfonylureas, one of the widely used class of antidiabetic drugs. Rifampicin increases the hepatic metabolism of sulfonylureas with great inter-individual variations,leading to frequent hypoglycemia or hyperglycemia, thus making dose adjustments a very difficult task. The drug-drug interaction data is sparse with other classes of anti-diabetic drugs. Some Indonesian guidelines[30,39] recommend the use of insulin routinely for management of diabetes, though this is supported by only limited data. Apart from the regular pharmacological interventions, all patients having diabetes and tuberculosis must receive education and counselling for self-management. In addition, these patients may also require more frequent monitoring of liver function and kidney functions.[40]

11. Integrating diabetes and tuberculosis service delivery

For a better tuberculosis control and treatment, integration of care for patients with both diseases seems to be the natural way forward. However, this integration may put additional strain on an already overburdened healthcare program. Lack of public awareness regarding diabetes as well as tuberculosis is a major challenge in improving healthcare outcomes for national tuberculosis control programs, especially in a developing country like India.[41] Cost effectiveness of bidirectional screening for tuberculosis and diabetes is yet to be established in large scale studies, though good glycemic control is expected to improve clinical outcomes in tuberculosis patients. The prevalence of diabetes in patients with tuberculosis is only going to rise and an effective strategy is therefore required to deal with the menace caused by the deadly duo.[42]

12. Conclusion

Diabetes mellitus is one of the most thoroughly investigated systemic diseases worldwide, and is considered a part of the metabolic syndrome epidemic. Although it has been shown to affect almost every organ in the body, the lung is one of the most overlooked target organs of diabetes, presumably because its clinical relevance is undetermined and underrecognized. Inspite of enough literature evidence of an undeniable link, the diabetes-lung association is rarely investigated. In fact, most pulmonology literature does not address diabetes as an influencing factor for lung diseases. Emerging evidence suggests that diabetes and the widely used hypoglycemic drugs may affect the pathogenesis, development, and progression of several lung diseases and their prognosis and clinical outcome, suggesting that diabetes should be considered as a relevant factor in the clinical approach to lung disease patients. The pro-inflammatory, proliferative, and oxidative properties of hyperglycemia have been shown to have an important role in affecting pulmonary vasculature, airways, and lung parenchyma. The evidence reviewed in this article supports further investigation in this field. More studies are needed to evaluate and reinforce the pathological and clinical associations between diabetes and lung disease. The convergence of two epidemics of this century, namely diabetes and tuberculosis,have a significant impact on public health programs and poses a huge social and economic challenge in a resource scarce country like India. More research should be thus promoted in the field of diabetes and respiratory diseases to further explore the unholy association of these common diseases.

REFERENCES

1. Cho N, Shaw JE, Karuranga S, et al. IDF Diabetes Atlas: global estimates of diabetes prevalence for 2017 and projections for 2045. *Diabetes Res Clin Pract*. 2018;138:271–281.
2. Burney P, Jarvis D, Perez-Padilla R. The global burden of chronic respiratory disease in adults. *Int J Tuberc Lung Dis*. 2015;19:10–20.
3. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68:394–424.
4. Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ*. 2000;321:405–412.
5. Goldman MD. Lung dysfunction in diabetes. *Diabetes Care*. 2003;26:1915–1918.
6. Kabitz HJ, Sonntag F, Walker D, et al. Diabetic polyneuropathy is associated with respiratory muscle impairment in type 2 diabetes. *Diabetologia*. 2008;51:191–197.
7. Irfan M, Jabbar A, Haque AS, Awan S, Hussain SF. Pulmonary functions in patients with diabetes mellitus. *Lung India*. 2011;28:89.
8. Walter RE, Beiser A, Givelber RJ, O'Connor GT, Gottlieb DJ. Association between glycemic state and lung function: the Framingham Heart Study. *Am J Respir Crit Care Med*. 2003;167:911–916.
9. Davis WA, Knuiman M, Kendall P, Grange V, Davis TM. Glycemic exposure is associated with reduced pulmonary function in type 2 diabetes: the Fremantle Diabetes Study. *Diabetes Care*. 2004;27:752–757.
10. Gläser S, Krüger S, Merkel M, Bramlage P, Herth FJ. Chronic obstructive pulmonary disease and diabetes mellitus: a systematic review of the literature. *Respiration*. 2015;89:253–264.
11. Divo M, Cote C, de Torres JP, et al. Comorbidities and risk of mortality in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2012;186:155–161.
12. Colditz GA, Manson JE, Hankinson SE. The Nurses' Health Study: 20-year contribution to the understanding of health among women. *J Women's Health*. 1997;6:49–62.
13. Miller J, Edwards LD, Agustí A, et al. Comorbidity, systemic inflammation and outcomes in the ECLIPSE cohort. *Respir Med*. 2013;107:1376–1384.
14. Lee CT, Mao IC, Lin CH, Lin SH, Hsieh MC. Chronic obstructive pulmonary disease: a risk factor for type 2 diabetes: a nationwide population-based study. *Eur J Clin Investig*. 2013;43:1113–1119.
15. Carstensen B, Witte DR, Friis S. Cancer occurrence in Danish diabetic patients: duration and insulin effects. *Diabetologia*. 2012;55:948–958.
16. Tseng CH. Diabetes but not insulin increases the risk of lung cancer: a Taiwanese population-based study. *PLoS One*. 2014 Jul 3;9. e101553.
17. Deng HY, Zheng X, Zha P, Peng L, Huang KL, Qiu XM. Diabetes mellitus and survival of non-small cell lung cancer patients

after surgery: a comprehensive systematic review and meta-analysis. *ThoracCancer*. 2019;10:571–578.
18. Wan G, Yu X, Chen P, et al. Metformin therapy associated with survival benefit in lung cancer patients with diabetes. *Oncotarget*. 2016;7:35437.
19. Moran A, Brunzell C, Cohen RC, et al. CFRD Guidelines Committee. Clinical care guidelines for cystic fibrosis–related diabetes: a position statement of the American Diabetes Association and a clinical practice guideline of the Cystic Fibrosis Foundation, endorsed by the Pediatric Endocrine Society. *Diabetes Care*. 2010;33:2697–2708.
20. Bridges N, Rowe R, Holt RI. Unique challenges of cystic fibrosis-related diabetes. *Diabet Med*. 2018;35:1181–1188.
21. Reutrakul S, Mokhlesi B. Obstructive sleep apnea and diabetes: a state-of-the-art review. *Chest*. 2017;152:1070–1086.
22. Aurora RN, Punjabi NM. Obstructive sleep apnea and type 2 diabetes mellitus: a bidirectional association. *Lancet Respir Med*. 2013;1:329–338.
23. Newman AB, Nieto FJ, Guidry U, et al. Sleep heart health study research group SF. Relation of sleep-disordered breathing to cardiovascular disease risk factors: the sleep heart health study. *Am J Epidemiol*. 2001;154:50–59.
24. Al-Delaimy WK, Manson JE, Willett WC, Stampfer MJ, Hu FB. Snoring as a risk factor for type II diabetes mellitus: a prospective study. *Am J Epidemiol*. 2002;155:387–393.
25. Muraki I, Wada H, Tanigawa T. Sleep apnea and type 2 diabetes. J Diabetes Investig2018; 9:991-997.
26. Peleg AY, Weerarathna T, McCarthy JS, Davis TM. Common infections in diabetes: pathogenesis, management and relationship to glycemic control. *Diabetes Metab Res Rev*. 2007;23:3–13.
27. Falguera M, Pifarre R, Martin A, Sheikh A, Moreno A. Etiology and outcome of community-acquired pneumonia in patients with diabetes mellitus. *Chest*. 2005;128:233–239.
28. Tsai SS, Huang JC, Chen ST, et al. Characteristics of Klebsiella pneumoniae bacteremia in community-acquired and nosocomial infections in diabetic patients. *Chang Gung Med J*. 2010;33:532–539.
29. Vamos EP, Pape UJ, Curcin V, et al. Effectiveness of influenza vaccine in preventing admission to hospital and death in people with type 2 diabetes. *CMAJ (Can Med Assoc J)*. 2016;188:E342–E351.
30. Alisjahbana B, van Crevel R, Sahiratmadja E, et al. Diabetes mellitus is strongly associated with tuberculosis in Indonesia. *Int J Tuberc Lung Dis*. 2006;9:696–700.
31. Global tuberculosis report 2019. *The WHO Global Task Force on TB Impact Measurement*. Geneva: World Health Organization; 2019.
32. Study on prevalence of diabetes mellitus in patients with T.B. under DOTS strategy. Chachra V, Arora VK. *Indian J Tuberc*. 2014;61:65–71.
33. Stevenson CR, Critchley JA, Forouhi NG, et al. Diabetes and the risk of tuberculosis: a neglected threat to public health? *Chronic Illness*. 2007;3:228–245.
34. Harries AD, Satyanarayana S, Kumar AM, et al. Epidemiology and interaction of diabetes mellitus and tuberculosis and challenges for care: a review. *Public Health Action*. 2013;3:S3–S9.
35. Singla R, Khan N, Al-Sharif N, Al-Sayegh MO, Shaikh MA, Osman MM. Influence of diabetes on manifestations and treatment outcome of pulmonary TB patients. *Int J Tuberc Lung Dis*. 2006;10:74–79.
36. Awad SF, Dargham SR, Omori R, Pearson F, Critchley JA, Abu-Raddad LJ. Analytical exploration of potential pathways by which diabetes mellitus impacts tuberculosis epidemiology. *Sci Rep*. 2019;9:8494.
37. TB treatment options: beyond DOTS.Arora VK, Chopra KK. *Indian J Tuberc*. 2017;64:151–152.
38. Batra J, Arora VK. Oxidative stress and tuberculosis. *Indian J Tuberc*. 2014;61:183–185.
39. Zheng C, Hu M, Gao F. Diabetes and pulmonary tuberculosis: a global overview with special focus on the situation in Asian countries with high TB-DM burden. *Glob Health Action*. 2017;10:1264–1702.
40. Riza AL, Pearson F, Ugarte-Gil C, et al. Clinical management of concurrent diabetes and tuberculosis and the implications for patient services. *Lancet Diabetes Endocrinol*. 2014;2:740–753.
41. Journey of tuberculosis control in India, Arora VK, Chopra KK. *Indian J Tuberc*. 2019;66:178–183.
42. Harries AD, Billo N, Kapur A. Links between diabetes mellitus and tuberculosis: should we integrate screening and care? *Trans RSoc Trop Med Hyg*. 2009;103:1–2.

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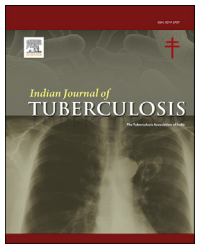

Review article

Quality improvement can revolutionize tuberculosis care in India: A review

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Quality improvement
PDSA plan-do-study-act
Quality
Quality assurance
Root cause analysis

ABSTRACT

Background/Purpose: Access, cost and quality are limiting parameters of any healthcare delivery system. RNTCP (Revised National Tuberculosis Control Program) has largely addressed the access and cost issues, however the quality of care is a major hurdle in TB care today.

Methods: We propose using an evidence based method of quality improvement principles to address many quality issues ranging from delayed turnaround time in testing, to low patient satisfaction, and slow private sector engagement.

Results: We propose a 5 step approach to learning and conducting quality improvement at the district level. Step 1: Form a team and define the problem Step 2: Develop baseline data Step 3: Create a process map Step 4: Bring a change through a PDSA Plan-Do-Study-Act cycle Step 5: Prepare run charts.

Conclusion: We cannot expect a different result by doing the same thing over and over again. This holds particularly true for the TB program in India. A major paradigm shift is necessary if we wish to achieve TB Free within our lifetimes. A shift from quality assurance to quality improvement offers this hope for change and TB elimination.

1. Why quality improvement for TB?

Rahul (name changed) is a 16-year-old boy from a "slum area" in central Madhya Pradesh who developed a fever and cough for over 1 year. Due to a lack of money, his mother treated him with home medicines, initially. Seeing no improvement, she went to a local doctor who prescribed some medicines for fever, without doing diagnostic sputum or x ray tests. Rahul continued to have a chronic cough for 8–10 months, and saw multiple other doctors in the process and still did not get sputum and x-ray test. Soon his weight declined by 10–15 kg to only 33 Kg. During this time a local NGO team doing active case finding heard about Rahul from neighbors. He had

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become so weak that he was bed-ridden and cared for by his 12-year-old sister. Having symptoms of TB (cough and fever greater than 2 weeks and weight loss), the NGO surveyor gave him an x-ray referral and sputum cup.

Three days later when the NGO team followed up on Rahul no sputum was produced and no x-ray was done. The mother was contacted at her work and an x-ray was finally done at a private facility. The mother did not want to go to the government facility because it would require a full day with the wait and she would lose her day's wages. Rahul's father had passed away when he was young and his mother worked as a servant in homes and earned Rs 5000 per month. Rahul worked by her side.

Xray at the private facility showed patchy opacification on the upper right and mid-zone lung with fibrotic shadows airspace disease consistent with TB. TB sputum was sent to a government lab and was reported as negative. The patient was started on anti-TB treatment at the local DMC and money Rs. 500 was provided by the direct benefit transaction (DBT). Within weeks Rahul's health improved, with weight gain, reduced fever and diminished cough and he was working by his mother's side. He is completing his 6-month treatment for TB.

Tuberculosis ails 2.8 million people and kills 423,000 people each year in India, even though it is a preventable and treatable disease.[1] Access, cost, and quality of care are limiting parameters of any healthcare system including the TB program in India. Over the past decades government's TB program (Revised National Tuberculosis Control Program, RNTCP) has addressed the problem of access by a comprehensive nationwide DOTS (directly observed therapy) program,[2,3] and the problem of cost by having free diagnostics, free medication and direct benefit transfer to TB patients, and yet, the number of TB cases and deaths have not dropped substantially. The reason is largely due to the poor quality of TB care in India. For example, standardized patient studies[4] show that 79% of TB cases were not managed correctly by private health providers. Some 83% of patients presenting to a health provider with a cough and fever greater than two weeks and having failed a course of antibiotics did not have sputum or x-ray ordered. The case in point is Rahul, who had multiple doctor visits with symptoms of cough and fever. Also, the quality of services at the government center, related to long wait times and possible disrespectful treatment of patients, leads to reluctance and avoidance of essential public TB facilities.

A systematic review of quality of TB care[5,6] in India of 47 studies shows that suboptimal quality of TB care with findings of only one in three providers knowing the standard regimen for drug-susceptible TB and less than one quarter ordering smears in patients with chest symptoms consistent with TB. The poor quality is not isolated to just TB yet is part of the greater health system in India.[7]

For decades the solution to the quality problem has been a "quality assurance" approach. The government system has set the benchmark for the number of sputum smears that must be tested or patients that have to be on treatment. The district TB officer and the TB health workers have to adhere to these benchmarks and those who fell below it were scrutinized for poor quality performance. This culture and strategy of "name, blame, and shame" has been successful to some extent in making sure a minimum standard was met and a central agency could monitor the output. However minimum thresholds have lead to an age-old practice of data fudging. At times numbers "are adjusted" at the local level, such as additional positive cases or repeated testing of sputum smears or dropping the defaulter cases, in order to make quarterly numbers appear better on the ledger with dismissal for genuine improvement. Such lack of buy-in and lack of responsibility on the part of some field workers can lead to poor quality and persistently high morbidity and mortality due to TB.

An alternate to quality assurance is improving the quality of care through quality improvement. Table 1 and Fig. 1. While quality assurance focuses on accountability with comparison and highlighting and changing poor performance, quality improvement is an approach for improvement with a testing of a hypothesis and small test of change recorded in run charts towards a broader goal. QI was first introduced by W. Edwards Deming and has been applied as a business manufacturing practice and is attributed to the success of companies such as Toyota and Federal Express. Over the past two decades, QI has been applied to healthcare in the United States and Europe with significant success and the approach has been adopted by the largest healthcare payer, Centers for Medicare and Medicaid Services.

In developing countries, there have been few studies on the use of QI. Several articles[8] have mentioned that the time for quality improvement is now, providing the various methodology of lean and six sigma and PDSA cycle with small steps of change and providing a structured problem-solving approach. The Quality Council of India has taken on this approach for hospitals and one study[9] has shown success with 88% decline in infection rate in the surgical unit over 12 months using a QI approach.

For tuberculosis, a QI project in Carabayllo, Peru on MDR TB has shown success.[10] There are no published studies on the use of quality improvement for TB elimination, however USAID[11] (United States Agency for International Development) has developed a handbook for TB and MDR-TB programs and IHI, Institute for Healthcare Improvement, has a detailed manual on how QI can be implemented in TB programs(12). We use these references and show how quality

Table 1 – Comparing and contrasting quality assurance and quality improvement.

Quality assurance	Quality improvement
Individual focus	System focus
Find poor performers and rejecting or reforming them	Move all towards improving them
Develop Evidence base standards and guidelines as threshold or target benchmarks	Moving all towards improvement on guidelines
Achieving a set goal or threshold	Continuous improvement

Fig. 1 – Quality assurance is taking action on the poorly performing individuals while quality improvement is targeting all to achieve better performance.

AIMS STATEMENT

In (A), we will (B) By (C) within/by (D) using (E)

A. Where will the change be implemented?
कार्य का परिवर्तन कहां से लागु होगा?

B. What are you trying to change?
आप क्या बदलाव चाहते हैं?

A. By how much will you change it?
आप इसे कैसे बदलेंगे?

B. By when do you want to see the change?
आप कब तक ये परिवर्तन देखना चाहते है?

C. How What will you do to make the change?
इस परिवर्तन करने के लिए आप क्या करेंगे?

Adopted from 5 Steps to Quality Improvement: University of Kwazulu-Natal and Institute for Healthcare Improvement

5 कार्य की गुणवत्ता में सुधार के लिए अपनाया गया: क्वाज़ुलु-नटाल विश्वविद्यालय और स्वास्थ्य सुधार संस्थान

Fig. 2 – An Aims Statement can be easily developed by answering 5 questions.

improvement can be applied in real-world setting for programmatic change in the TB program in India.

2. What is quality improvement?

"Quality Improvement is an approach aimed at systematically improving the quality of care by addressing gaps between current practices and desired standards, through management decisions, rapid cycle and team-based problem solving, process improvement and quality redesign."[11] Quality improvement is a systems-based approach that addresses the "know-do" gap through a structured continuous process.

The key components for a quality improvement system are: establishing input, process and outcomes standards, using data to identify gaps, training health providers in QI, creating improvement teams, monitoring continuous performance and documenting quality improvement.[11]

QI is a fundamental mindset change. For example, when providers do not adhere to guidelines, with the QA approach we blame them and try to change the individuals. In a QI approach, we understand that poor adherence is not a problem entirely due to the providers or individuals but rather a problem of the system, and work to change the system. It is not the "bad apples" but the "rotten bucket" within which the apples reside that requires change. Additionally, quality improvement is a universal principle and can be applied to business, healthcare as well as personal relationships as demonstrated in the article "Plan-Do-Study–Act Cycle Rejuvenates a Marriage."[13]

3. How to do quality improvement?

A number of documents describe a step by step approach that QI teams need to do to bring a change.[11,12] Most importantly, no change can occur without having full support from the leadership which includes, the TB supervisor, district TB officer, state TB officer, MD-NHM and the Central Tuberculosis Division in India. Good leaders empower teams to make changes. Tools such as a change package, checklists, aims statement, process diagram, and run-charts are essential for quality improvement. The content such as the topic of the statement of the aim may vary however the tool is essential.

3.1. *Step 1: Form a team and define the problem*

The first step on the QI journey is to form an improvement team with a designated leader. He or she does not have to be the senior-most person on the team but someone who is maintaining the momentum, scheduling regular meetings and keeping in touch with a quality improvement mentor. The team needs to include people from various sectors, a multidisciplinary team, which can meaningfully contribute to the problem, the process, and the solution. At the start, it is important for the team to mutually agree on the logistics of when, where and how long to meet.

After the team is formed it needs to reflect on the mission of the TB program at the facility, some of the problems that are under their control to improve, and the aim of how to get there using the "Develop an Aims Statement" worksheet tool (Fig. 2). By answering the question of where, what, by how much, by when, and how, one can develop the Aims statement.

3.2. *Step 2: Develop Baseline data*

The aims statement defines what one will be trying to change. More specifically it explicitly details the parameters of the change journey. It is important to choose a measure that is readily extracted from the data that is already being collected or can be collected at frequent enough intervals to be recorded with ease Fig. 3. For example, as a measure do not choose deaths due to TB due to patients missing their medicines

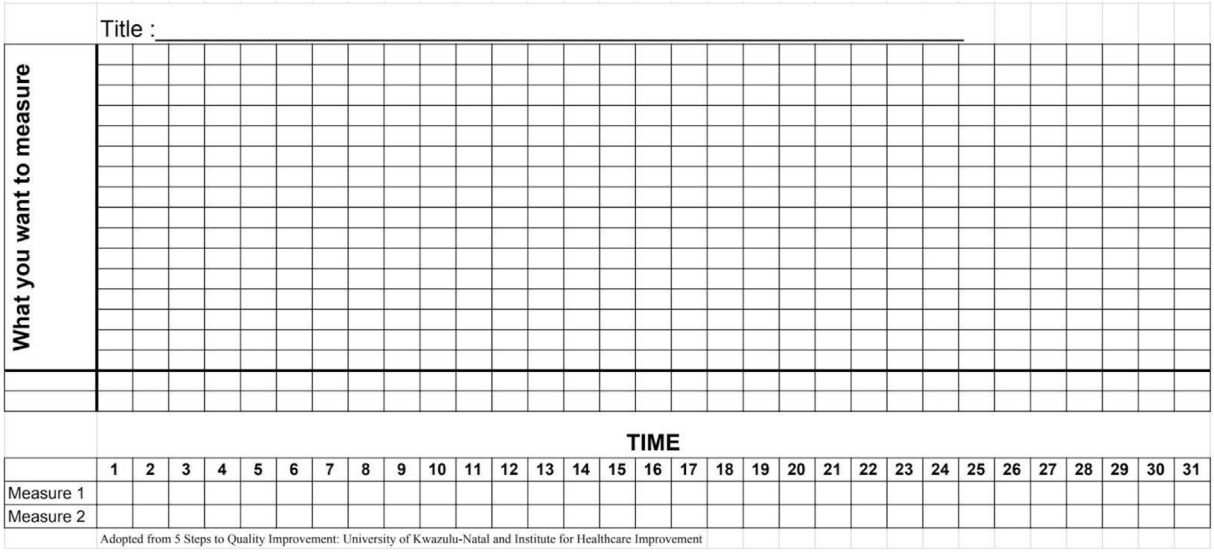

Fig. 3 – Selecting measures and collection baseline data.

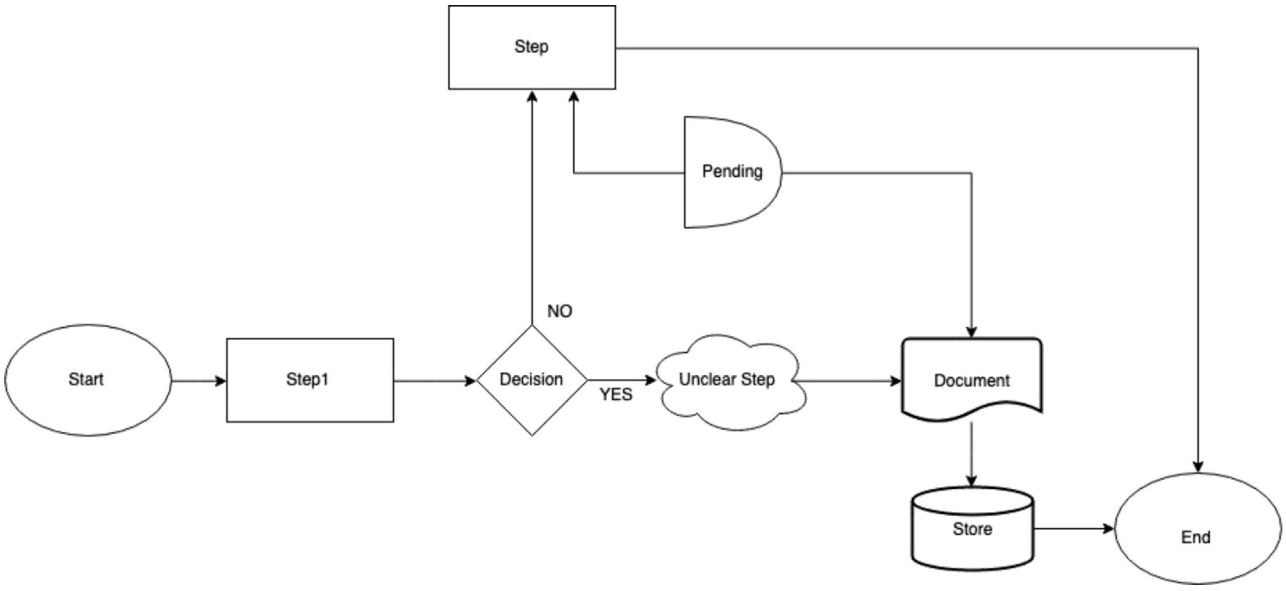

Fig. 4 – A sample process map allows one to see the "big picture" of how things are getting done.

rather choose something like percent or number of patients who have missed their TB medicine on a given day.

3.3. *Step 3: Creating a Process Map*

It is important to understand that activity and improvement happens within a larger system, not as an independent activity. So, it is critical to have the "big picture" or "30 thousand feet perspective" on the step by step process of what happens. On a flip chart as a team, it is important to draw out where the process begins and where it ends and to use standard graphics of ovals, boxes and diamonds from the patient's perspective and/or the provider's perspective (Fig. 4). The team also needs to identify the problems, bottlenecks, and delays within the process diagram.

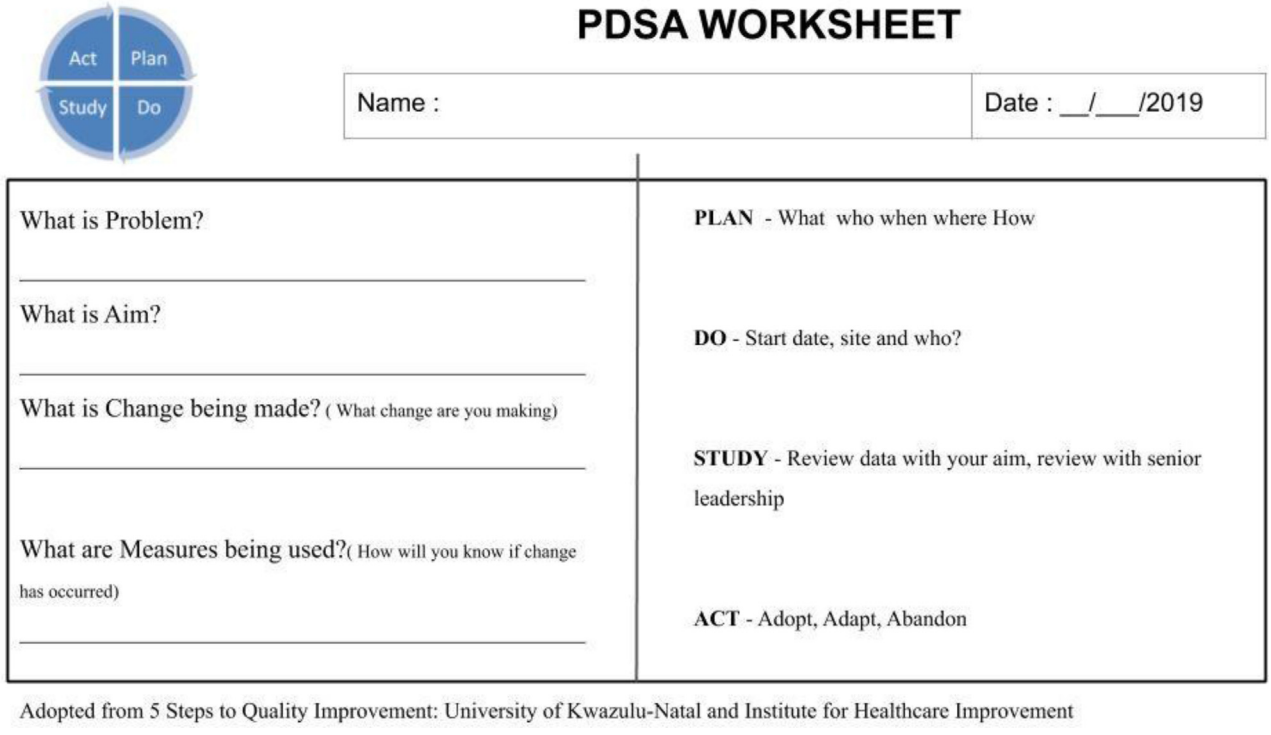

Fig. 5 – A PDSA worksheet allows improvement process.

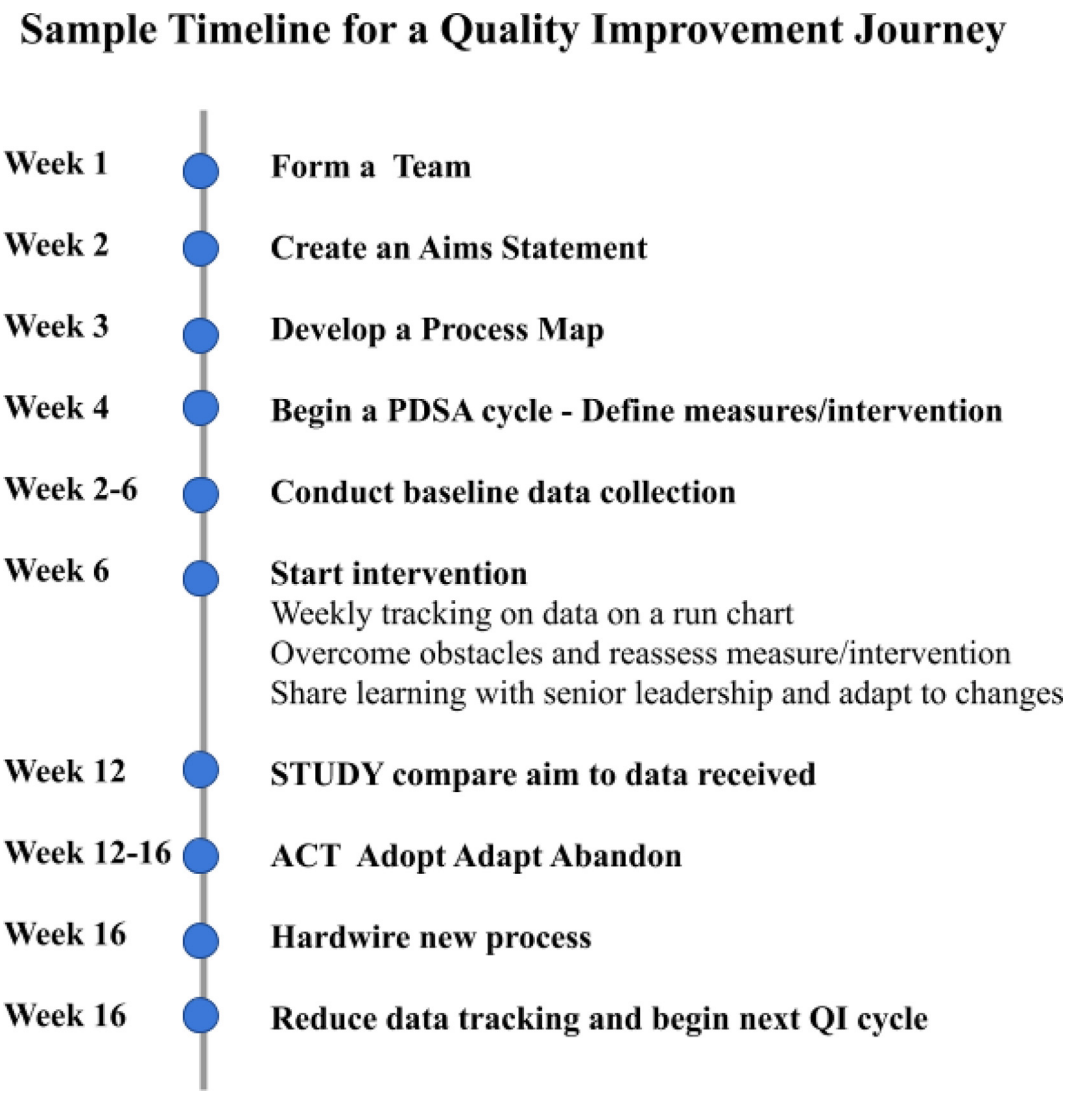

Fig. 6 – Sample Timeline shows the team's QI activity over 4 months.

3.4. *Step 4: Bring Change Through Plan-Do-Study-Act (PDSA) Cycle*

Once the process diagram is developed and an aims statement is made and baseline data that needs to be obtained is identified, the team can begin the improvement process by initiating the Plan-Do-Study–Act cycle. Fig. 5.

The PDSA worksheet synthesizes the Aims statement and intervention (change being tested) the measures, and the activity over the 3–6 month time cycle of the quality improvement initiative (Fig. 6) (see Fig. 7).

3.5. *Step 5: Run Charts*

The only way to know if a change is being made is to measure it. In order to measure we need a well defined numerator and a denominator. Once that is done, the team can track the measure over time, in the form of a run chart. The run chart helps the team visually notice if a change is occurring. The arrow notation on the run chart point to when changes are being made. The run chart needs to be reviewed at each meeting.

4. Proposal for quality improvement in India

While the QI process is a great theoretical concept, introducing it in India for the TB program will be a major challenge due to little or no familiarity with quality improvement principles. Given the RNTCP structure with Central TB Division, State TB Officer, District TB Office, and Individual Tuberculosis Units a proposed model can be the following: After buy-in from leadership at central TB division and state TB office, one can begin QI training at the district level with focus on the local district teams with the main agent of change is the district TB officer, since he or she leads a team of 30–70 persons working for TB elimination in a district.

It would be essential to do both an in-person and online course with frequent (weekly) meetings of the mentor and the district TB officers and staff. The entire staff would develop 4–5 teams with each having their own leaders and different Aims statements and PDSA cycles. Once a pilot in few centers is successful it can be piloted in 30–50 districts and then finally scaled up to over 500

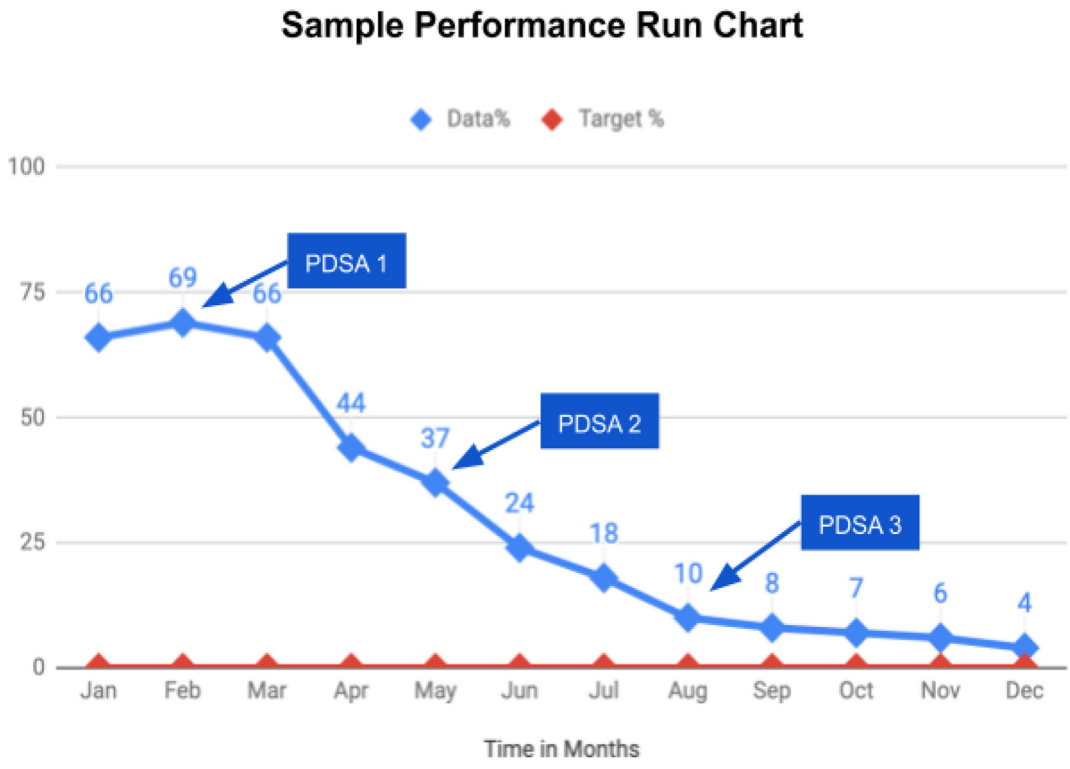

Fig. 7 – Run Chart with notation of intervention allows for easy tracking.

districts. Such a stepwise approach would be useful in learning from initial mistakes and knowing what requires greater emphasis.

5. Conclusion/summary

We cannot expect a different result by doing the same thing over and over again. This holds particularly true for the TB program in India. A major paradigm shift is necessary if we wish to achieve TB Free within our lifetimes.

A shift from quality assurance to quality improvement offers this hope for change and TB elimination. While quality assurance is setting a threshold and reforming or rejecting those below the benchmark, quality improvement is a continuous improvement for all. USAID, IHI and other agencies have handbooks on how QI can be implemented for TB and MDR-TB programs.

Among the many options, the 5 step QI process is best suited for introduction and change in India. These steps include: forming a team and defining the problem, understanding the current system with baseline data, creating the process map, introducing change through the PDSA cycle, and developing run charts. Such a disciplined process change plan can have a profound impact on making the more effective and efficient and ultimately reducing the number of people who become ill and die from tuberculosis which is a diagnosable, preventable and treatable disease.

Author contribution

Manoj Jain - lead concept and design for project and leading the execution team.

Salil Bhargava - co lead for concept and design for project and co lead for execution team.

Sangeeta Pathak - reviewed concept and design and execution of project and day to day management Edwin Rodrigues - review and graphic design and project implementation.

Monika Jain - reviewed the concept and design and prepared the manuscript development and drafting.

All reviewed approved the final version.

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Appendix 1. Example of a PDSA process

AIMS Statement

AN AIMS STATEMENT
(In English and Hindi)
By filling in the blanks.

In **(A)**, we will **(B)** By **(C)** within/by **(D)** using **(E)** _

(This is English and Hindi)

A. Where will the change be implemented? Slums of Azad Nagar, Indore

B. What are you trying to change? Increasing the testing of TB suspected patients found in ACF

C. By how much will you change it? 40% to 90%

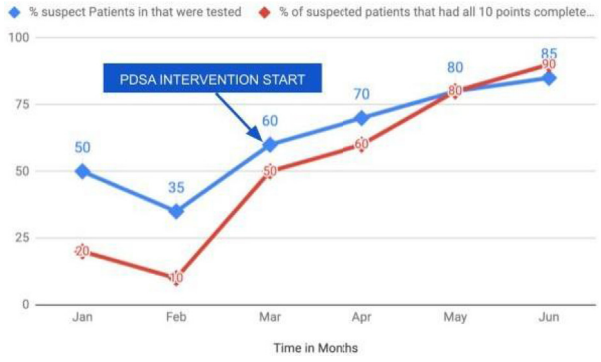
D. By when do you want to see the change? 6 months

E. What will you do to make the change? 10 point checklist on every patient

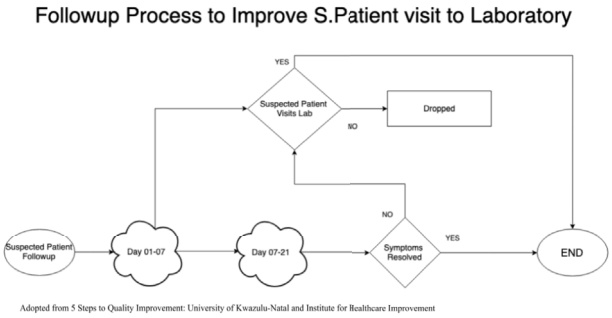
Adopted from 5 Steps to Quality Improvement: University of Kwazulu-Natal and Institute for Healthcare Improvement

Baseline Data

	Outcome Measure	Process Measure	Number of patients
	# % suspect Patients in that were tested	#/% of suspected patients that had all 10 points completed on list	Total number of suspect patients from Azad Nagar
Jan (baseline)	23 / 50%	10 / 20% (estimated)	56
Feb (baseline)	23 / 35%	6 /10% (estimated)	65
Mar (intervention start)	30 / 60%	25 / 50%	50
Apr - intervention	42 / 70%	36/60%	60
May - intervention	40/80%	40/80%	50
June - intervention	45/85%	55/90%	60



FLOW DIAGRAM



Adopted from 5 Steps to Quality Improvement: University of Kwazulu-Natal and Institute for Healthcare Improvement

PDSA WORKSHEET

What is Problem? Too many suspected TB patients are not getting xray or sputum tests

What is Aim? Increase the number of suspected TB patients getting tested for xray and sputum

What is Change being made? Do an intervention checklist

(What change are you making)

Checklist to increase testing until test is done

---- Do Counsling one day 1

____Provide sputum cup -xray slip

____Do follow up phone/visit day 3

____Do follow up phone/vist of day 7

____Do follow up on day 14

____Do follow up on day 30

____Connect with the doctor by Telemedicine

_____on Day 30 total number of intervention done on chest list (10 if symptoms resolve or testing done)

(If symptoms resolved or if testing done then and GET ALL 10 points for checklist)

What are Measures being used?

(How will you know if change has occurred)

Process Measure : What percent had checklist done by day 30.

Outcome Measure : Percent of suspected patients who are getting sputum or x ray by day 30

PLAN - What who when where How: (above in AIMS statement)

DO - start date, site and who? March, Ajad Nagar, Saraswati

STUDY - Review data with your aim, review with senior leadership:

ACT - Adopt, Adapt, Abandon: Discussed with seniors and plan is to scale up process in other areas and work better with RNTCP for better follow up

Adopted from 5 Steps to Quality Improvement: University of Kwazulu-Natal and Institute for Healthcare Improvement

REFERENCES

1. India TB Report 2018, Revised National TB control Programme Annual Status Report, Central TB Division. Directorate General of Health Services, Ministry of Health and Family Welfare, https://tbcindia.gov.in/showfile.php?lid=3314.
2. Sachdeva KS, Mase SR. The end TB Strategy for India. *Indian J Tuberc*. 2019 January;66(1):165–166.
3. Gupta D. Administrative challenges in the implementation of RNTCP. *Indian J Tuberc*. 2018;65:187–189.
4. Das J, Kwan A, Daniels B, Satyanarayana S, et al. Use of standardized patients to assess the quality of tuberculosis care: a pilot, cross-section study. *Lancet Infect Dis*. 2015:1305–1313.
5. Satyanarayana S, Subbaraman R, Shete P, et al. *Int J Tuberc Lung Dis*. 2015 July;19(7):751–763.
6. Quality of tuberculosis care in India: a Systemic review. *Indian J Tuberc*. 2015 July 62;(3):191.
7. Mohanan M, Hay K, Mor N. Quality of health care in India: challenges, priorities, and the road ahead. *Health Aff*. 2016;35(10):1753–1758.
8. Varkey A, Kollengode A. A Framework for healthcare quality improvement in India: the time is here and now. *J Postgrad Med*. 2011;57(3):237–241.
9. Anchalai MM, D'Ambruoso L. Seeking Solutions: scaling-up audit as a quality improvement tool for infection control in Gujarat, India. *Int J Qual Healthc*. 2011;23.
10. Berwick DM. Lessons from developing nations on improving health care. *BMJ*. 2004;328:1124–1129.
11. Quality Improvement Handbook for TB and MDR-TB Programs. *TB CAREII*. University Research Co. LLC. USAID.; June 2013.
12. University of Kwazulu-Natal and Institute for Healthcare Improvement. *The 5 Steps to Quality Improvement: A Facility Based Guide to Improving Clinical Outcomes*; 2009. http://qualityofcarenetwork.org/oldsite/resources/strategic-planning-documents/five-steps-quality- improvement-facility-based-guide-improving.
13. Jain M. Plan-do-study-act cycle Rejuvenates a marriage. *Ann Intern Med*. 2008;149:209–210.

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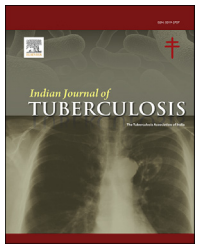

Original article

Emerging trends in microbiological diagnostics in children

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ABSTRACT

The targets of the WHO's End TB Strategy and the United Nations' (UN) Sustainable Development Goals (SDGs) have been expanded to"Find. Treat. All #EndTB" with universal access to TB diagnosis, treatment and care by 2022 in an effort to end the global TB epidemic. Trends to achieve the above targets in children have led to greater emphasis on the newer diagnostics paving way to microbiological confirmation and universal drug sensitivity in children.

1. Introduction

According to the Global TB Report 2019, out of a quarter of the world's population infected with *M. tuberculosis*, with an overall lifetime risk of developing TB disease, being 50% and 25% and 5–10% in infants, 2–5 year olds and adults respectively. In 2018, an estimated 10 million new cases (range, 9.0–million) fell ill with TB and 11% were children (aged <15 years). India accounted for about a 27% of this global burden, being the leading most cause from a single infectious agent (ranking above HIV/AIDS).[1] Further, drug-resistant TB also continues to be a major public health threat. In 2018, there were about half a million new cases of rifampicin-resistant TB (of which 78% had multidrug resistant TB), with the largest share of this global burden being in India (27%).[1] Out of the estimated 27 lakh cases in India, the Revised National Tuberculosis Control Programme (RNTCP) was able to achieve a notification of 21.5 lakh in 2018. Childhood tuberculosis (TB) continues to be one of the major causes of childhood morbidity and mortality. In India, an estimated 10 lakh children became ill with TB and 2,50,000 children died of TB in 2017 (including children with HIV associated TB).[2] Though MDR-TB and XDRTB is documented amongst the pediatric age group in India, better management strategies are being adopted by the programme with an added emphasis not only on treatment but also on prevention of pediatric TB.[3–5]

On 26 September 2018, the United Nations (UN), in its first-ever high-level meeting on TB, added four new global targets to the Sustainable Development Goals (SDGs) and WHO's End TB Strategy targets for 2030 and 2020 namely to treat 40 million people for TB disease, 30 million people with TB preventive treatment for a latent TB infection and mobilize efforts to achieve universal access to TB diagnosis, treatment, care and TB research.[1,6,7] It also recognized the far reaching negative impact of TB among women and children owing to social and health inequalities and peculiar needs of children. Hence as steps towards TB elimination, a commitment was

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made to prioritize the women and pediatric group.[6,7] However, as number of children with TB remain undiagnosed and untreated each year, the case-detection gap is maximum in children and it becomes difficult to assess actual magnitude of childhood TB epidemic resulting in greater emphasis on the newer diagnostics paving way for microbiological confirmation and universal drug sensitivity in children.[6,7]

Diagnosis of TB in children is challenging because children often have pauci-bacillary disease, both pulmonary (PTB) and extrapulmonary (EPTB) tuberculosis.[8–10] Smear positivity rate of less than 10–15% and culture positivity rate of 30–40% in PTB.[8,11] Also, it is difficult to obtain proper sample from young children, as they tend to swallow the sputum and rarely expectorate.[11] Thus traditionally, clinical and radiological findings and medical history have formed a mainstay of diagnosis of pediatric TB, especially in resource-limiting and tuberculosis-endemic countries[8,11] Recent evidence suggests that every effort needs to be made to prove microbiological diagnosis for pediatric cases as children of all age groups mostly have bacilli in their samples, especially pulmonary and advancements in diagnostics have improved the sensitivity[4,12,13] In every chest symptomatic pediatric presumptive, a chest X ray should be performed at the outset. Good-quality chest radiograph is a good supportive and screening tool for diagnosis and hilar/mediastinal lymphadenopathy, chronic fibrocavitatory disease, persistent shadows not responding to antibiotics or miliary pattern are considered suggestive.[14–16] The tuberculin skin test (TST) or mantoux test done using ≤5 tuberculin units (TU) of purified protein derivative RD 23 (equivalent) as part of the pediatric diagnostic algorithm has a limited role due to availability issues of standardized tuberculin.[4] Role of serological antibody based tests currently have been banned by World Health Organization (WHO), as they are inaccurate in sensitivity and specificity, also non-validated in –house PCR or commercial PCR based assays. Quality assured microbiological investigations on appropriate samples are essential for the diagnosis, besides clinico-radiological evidence and contact history. These investigations help in labeling a presumptive TB child as microbiologically confirmed TB[12]In cases where the sample is microbiologically negative or not available, such cases would be categorized as clinically diagnosed TB. It is imperative to rule out alternative diagnosis in cases of persistent clinico-radiological findings. Extrapulmonary TB also needs to be considered if X-ray chest is negative with a positive TST[17]

Pediatric DR-TB reflects the presence of DR-TB in the community or mismanagement of TB in that particular child. Therefore, all notified TB patients, history of family contact with DR-TB patient or death in the family due to TB, HIV, follow up positives on microscopy including treatment failures on standard first line treatment and mono/poly regimens, any clinical non-responders are considered as presumptive DR-TB patients. Like for TB diagnosis, microbiological confirmation and susceptibility testing is essential for correct diagnosis. Children with a DRTB contact having signs symptoms of active TB, even in the absence of bacteriological confirmation are considered as having 'probable MDR-TB' and started on MDR-TB treatment.[4,18,19]

All efforts must be made to get relevant good quality clinical specimens, based on the site namely sputum (2–5ml mucopurulent), pleural tap, lymph-node aspiration, cerebrospinal fluid (CSF) and excision/laparoscopic tissue biopsy. In case of insufficient sample, depending upon the age of the child, wherever facilities are available, alternate samples such as induced sputum, gastric aspirate/lavage (GA/GL) or broncho-alveolar lavage (BAL) must be collected and transported to culture & DST lab as soon as possible after collection to enhance diagnosis[,20].

Hospitalization and neutralization may not be essential for gastric aspirate and 2 fasting gastric aspirates of about 2–5 ml on consecutive days are recommended in children who are unable to produce sputum as suggested by different studies[,20,21,22] Addition of BAL to GA/GL increases sensitivity, but is highly invasive technique, hence is not recommended routinely.[21] Sputum induction has been found to be useful technique as demonstrated in literature[20,].In one study, samples from induced sputum and gastric lavage were found to be positive in 54 (87%) and 40 (65%) children, respectively (difference p = 0·018). The single sample yield from induced sputum was found to be comparable to three gastric lavages. Sputum induction is safe and helpful in microbiological confirmation of TB in young children. Technique is preferable to gastric lavage for diagnosis of pulmonary tuberculosis[22]

Evidence is being generated to detect MTB from stool samples as an alternative to sputum as it is non-invasive & convenient sample especially for very young children. In meta-analysis by Mac-lean et al of nine studies over 1681 samples, pooled sensitivity and specificity of stool Xpert were 67% (95% confidence interval [CI], 52–79%) and 99% (95% CI, 98–99%), respectively in comparison to microbiological reference standard. Sensitivity was higher among children with HIV (79% [95% CI, 68–87%] versus 60% [95% CI, 44–74%] among HIV-uninfected children). Heterogenicity was found in stool processing methodology with differences in reagents and methods of homogenization and filtering, which needs to be standardized[23]

Microbiological diagnosis of TB has been traditionally based on smear microscopy and conventional culture based on solid media till previous decade, where any diagnostic techniques have been introduced of which some have been approved by WHO. Most of WHO approved technologies have been adopted by RNTCP and PMDT for detection of TB and DR-TB. These technologies include molecular Cartridge Based Nucleic Acid Amplification Test (CBNAAT) Xpert MTB/RIF™or Gene-Xpert, Line Probe Assay, Genotype MTBDRplus and Genotype MTBDRsl and Liquid culture and Mycobacterial Growth indicator $_{\text{tubes (MGIT)}}$17–19, 24-26.

These tests have a higher sensitivity, specificity and a faster turn-around time than the conventional smear microscopy and solid (LJ) culture.

Gene-Xpert MTB/RIF assay system or CBNAAT was endorsed by WHO in December 2010 after many detailed multi-centric evaluation of the technology world-wide for providing point of care diagnostics (POC). Cepheid Gene-Xpert MTB/RIF assay is fully automated molecular assay in which real-time polymerase chain reaction technology is used to simultaneously detect *M. tuberculosis* and RIF resistant mutation in *rpo B* gene.[27] In this cartridge based system, sputum or extra-pulmonary samples require minimal laboratory expertise and results are available in less than 2 hours. Sensitivity

and specificity for detection of pulmonary TB is comparable to MGIT culture i.e. 130 bacilli per ml.

Many studies globally have been conducted to assess accuracy of Xpert for TB and RIF resistance detection. As per evidence provided in WHO policy update in 2013, in presumptive TB children, pooled sensitivity of Xpert MTB/RIF with culture as reference was 66% (95% CI, 52–77%) where either expectorated sputum or induced sputum was used; where samples from gastric lavage or aspiration were used 66% (95% CI, 51–81%). Pooled specificity of Xpert MTB/RIF compared with culture as reference standard was at least 98%, with narrow confidence intervals. The sensitivity of Xpert MTB/RIF to detect rifampicin resistance in specimens from children was 86% (95% CI, 53–98%)[27]

Evidence is available for extra-pulmonary samples, in which using lymph node aspirate samples, pooled sensitivity of 84.9% (72–92%) and specificity of 92.5% (80–97%) respectively is reported. For CSF, sensitivity and specificity is 79.5% (62–90) and 98.6% (96–100) respectively. And for other tissue samples pooled sensitivity was 81.2% (68–90) and 98.1% (87–100) respectively. Least sensitivity was seen for plural fluid at 17% (8–34) though specificity was high 99.9% (94–100%). Most of these studies were applied using culture as gold standard.[27]

In a meta-analysis comparing 15 studies which included 4768 respiratory specimens from 3640 children, pooled sensitivities and specificities of Xpert for tuberculosis detection were 62% (95% credible interval 51–73) and 98% (97–99), respectively, with use of expectorated or induced sputum samples. Pooled sensitivities and specificities of Xpert for tuberculosis detection was found to be 66% (51–81) and 98% (96–99), respectively, with use of samples from gastric lavage In these studies, Xpert was compared to culture[28]. In study from Zambia, Africa, Sensitivity of Xpert MTB/RIF assay was 68·8% (95% CI 53·6–80·9) for gastrc lavage versus 90·0% (54·1–99·5; p = 0·1649) for sputum; specificity was 99·3% (98·3–99·8) and 98·5% (94·1–99·7; p = 0·2871) for gastrc lavage and sputum samples respectively.[29] In another study from Germany, Europe, Xpert detected 100% of smear-positive cases and 66.6% of culture-positive but smear-negative cases. In absence of TB, Xpert's specificity was 100%.[30]

Hence it was suggested by WHO that Xpert MTB/RIF should be used rather than conventional phenotypic test as the initial diagnostic test in children suspected of having TB or having MDR-TB.

In a pioneering Indian study, from different centers,4,600 pediatric presumptive pulmonary TB cases were enrolled, which diagnosed 590 (12.8%, CI 11.8–13.8) pediatric PTB cases. Overall 10.4% (CI 9.5–11.2) of presumptive PTB cases were detected by Xpert MTB/RIF, in comparison to 4.8% (CI 4.2–5.4) smear-positive results. Also upfront Xpert MTB/RIF testing of presumptive PTB and presumptive DR- TB cases detected 79 and 12 rifampicin resistance cases, respectively clearly showing it's utility for programme.[24]

Usefulness of Xpert for detecting TB among infants was demonstrated in a multi-centric Indian study. 7994 presumptive infant TB cases were enrolled, among which 462 (5.7%) were TB positive on Xpert, of which of which only 89 (19.3%) were positive on smear microscopy, Only 3 cases were detected on microscopy but negative on Xpert. Overall, 26 (5.6%) of infants diagnosed with TB, were found to be rifampicin-resistant.[24]

Based on international and national evidence generated, latest RNTCP guidelines have adopted WHO based evidence and suggested Xpert MTB/RIF as diagnostic test of choice for detection of TB and RR- $_{TB}$ 18,19.

In cases where Xpert is not available, recommendations in programme is to use smear microscopy. Logistics of using smear examination at National level is driven by the simplicity of performing smear microscopy by para-medical staff, low cost and availability of result on the same day.[18,19] Although the bacteriologic yield in children is low, but adolescent children frequently develop sputum smear-positive hence sputum microscopy has definite role.[20] For smear examination, it is essential to examine at-least 2 smears, as sensitivity of detection by smear microcopy is rather low.[19] Detection of AFB in sputum samples under optimal conditions is somewhere between 10^4 and 10^5 bacilli per ml. ZN staining has a low sensitivity of 22–43% for single smear, but increases with 2 smears. Even though AFB stain of sputum is positive in up to 75% of adults with pulmonary TB, fewer than 20% of children with TB have a positive AFB smear of sputum or gastric aspirate.[8] Microscopy is highly specific for MTB, which appear as long, curved and beaded. Non-Tuberculous Mycobacteria (NTM) may appear as short, straight bacilli with no specific morphology. Smear microscopy is done by either Ziehl-Neelson (ZN) staining or light emitting based (LED based) florescent staining.[8,31] As per systematic review of 45 relevant studies, fluorescent microscopy is found to be on an average 10% more sensitive than conventional microscopy (95% CI: 5–15%) and 98% specific.[32] In an Indian study from National Reference Laboratory (NRL), New Delhi, sensitivity and specificity of LED microscopy was 83.1% and 82.4%, respectively. Mean reading time of LED was three times faster than ZN.[33] Presently, Auramine O staining-based LED has replaced conventional ZN microscopy in 200 Designated Microscopy Centers (DMC) of medical colleges operating in collaboration with India's Revised National Tuberculosis Control Programme (RNTCP).[34]

Line probe assay (LPA) is another WHO approved rapid diagnostic molecular test. It is used among smear positive presumptive DR-TB cases for diagnosing DR-TB in reference centers. Line probe assay (Genotype MTBDRplus) was introduced in the programme in 2011.[35,36] Methodology is based on nucleic acid amplification directly from specimens, permitting rapid detection of mutations in genes coding for resistance to rifampicin (RIF) and isoniazid (INH) in turnaround time of 5 days. Limit of detection of MTB by LPA is around 10,000 bacilli/ml, hence is used among smear positive pulmonary samples or cultures positive for MTB.[26] Test showed high sensitivity and specificity for detection of RIF resistance of 98.1 per cent (95% CI 95.9–99.1) and 98.7 per cent (95% CI 97.3–99.4%), in comparison with conventional susceptibility testing. However, comparably, sensitivity was low for INH at 83.3%, which is in accordance to most other studies - 84.3 per cent (95% CI 76.6–89.8), though specificity remaining above 95%.[26] In one of the initial Indian study from New Delhi, sensitivity, specificity, positive and negative predictive values for detection of RIF resistance by Genotype MTBDR plus was found to be 97.6%, 94.4%, 97.6% and 94.4% respectively. While

sensitivity and specificity for INH resistance was found to be 83.3% and 93.8% respectively.[37]

Limited studies have been done to ascertain role of LPA in pediatric cases, as they are mostly pauci-bacillary.[35,38,39] In one study from North India, 208 pediatric patients were subjected to LPA; 193 smear positive and 15 cultures. In all 15 cultures & 183 (94.8%) of smear positive sputum, MTB was detected. Test provided information about drug resistance pattern, as high MDR-TB rate of 24.7% was detected.[35] According to the current integrated aldorithm, all patients diagnosed as RS or RR on CBNAAT must be subjected to both First line LPA (FL LPA) and Second LPA (SL LPA).[19]

GenoType MTBDR*sl* was introduced in the programme in 2017, for detection of resistance to second line anti-tubercular agents, by detecting mutations within *gyrA* & *gyrB* genes, it detects resistance to FQ, while *rrs* gene detect resistance to kanamycin, capreomycin and amikacin while and *eis* gene detects low level resistance to kanamycin.[19] In an international study, sensitivity and specificity of GenoType MTBDR*sl* VER 2.0 for FQ resistance detection was found to be 100% (95% confidence interval [CI] 95.8–100%) and 98.9% (95% CI, 96.1–99.9%) respectively. For second line injectables, sensitivity and specificity reported was 89.2% (95% CI, 79.1–95.6%) and 98.5% (95% CI, 95.7–99.7%) respectively.[40]

Conventional solid culture on Lowenstein Jenson is another technique which has been used for TB diagnosis for long time, which could give positive result in 4–5 weeks or more. Detection of *Mycobacterium tuberculosis* (MTB) by culture has higher sensitivity with detection of as low as 100 bacilli per ml of sample.[19]

The BACTEC Mycobacterial Growth Indicator Tube (MGIT) 960 system is a fully automated, high capacity, non-radiometric, noninvasive instrument, which was introduced in last decade. To monitor microbial growth, the BACTEC MGIT 960 uses the oxygen-quenching fluorescent sensor technology, which facilitates early detection of the MTB growth. There is ample evidence to demonstrate that MGIT960 has better sensitivity, specificity & lesser times to detection (TTD) than conventional LJ medium[25,41–43]

In one of the initial large multi-centric study from USA, 3330 specimens were studied, which included 2210 respiratory and 1120 nonrespiratory specimens, collected from 2346 patients treated at six sites. Total of 360 MTB were isolated among which 80% were isolated in MGIT which was much more than solid LJ culture (69%). The mean time to detection (TTD) for MTB were 14.4 days for BACTEC MGIT, much lesser than 24.1 days for solid media. The contamination rate found in BACTEC MGIT 960 was 8.1% (range, 1.8–14.6%).[41] Subsequent studies also confirmed the better sensitivity & specificity & shorter time to detection for MGIT 960 as compared to solid media. In another meta-analysis of 10 studies from Italy in 2004 (1381 strains from 14,745 clinical specimens), average sensitivity and specificity in detecting Mycobacteria was found to be 81.5% and 99.6% respectively.[25]

In a latest study from China, MGIT detected MTB significantly more than L-J culture from the 565 sputum samples. Considering any positive as reference, sensitivity of MGIT960 system and L-J methods was 94%, and 74%, respectively.[42]

In an Indian study in 2005–2007, 14,597 specimens were processed using the MGIT 960 system and L.J medium. Total of 6143 (42%) isolates were positive for MTB by either method. Positivity using MGIT960 was 41%, which was almost double of LJ (24%). Mean TTTD in smear-positive specimens for MGIT 960, and LJ was 9 and 38 days whereas in smear negative specimens, it was 16 and 48 days respectively.[43]

Very few studies based on MGIT have been conducted exclusively in pediatric population. In a study from USA conducted among 118 children with presumptive TB, 8 (7%) were culture-positive from at least one specimen; Of the 8 positive cultures, isolation rate from induced sputum, GA, blood and urine was found to be 88%, 83%, 38% and 43% respectively.[44]

Therefore, MGIT culture was introduced in the National programme in last decade and subsequently many certified culture and sensitivity laboratories have been established across the country by central TB.

Division (CTD) supported by FIND, India (Foundation of Innovative Diagnostics). It was recommended to perform in cases of suspected drug resistance found to be smear negative and in follow up cases on patients on MDR-TB treatment. However, it is essential to first grow MTB followed by susceptibility testing. Besides, all drugs tested by molecular methods can be tested by culture based methods Currently culture is utilized for long-term follow-up of patients on drug resistant TB treatment and helps to detect early recurrence in both drug sensitive and drug-resistant TB also. As per the programme algorithm, any strain, found to have mutations in any of *gyrA*, *gyrB*, *rrs* or *eis* gene are considered for phenotypic susceptibility to MGIT to high dose moxifloxacin (Mfx 1.0), kanamycin (Km), Capreomycin (Cm), Linezolid (Lzd). In cases as required, additional susceptibility to ethionamide (Eth), ethambutol (E), para-amino salicylic PAS, clofazamine (Cfz) is also put in MGIT based on request.[19] Susceptibility to bedaquiline (Bdq) is being validated at various centers in the country and will be initiated soon.

Many working groups globally have been designing novel platforms for better TB detection & on varied samples. In one study, stool was evaluated as an alternative to sputum for TB detection in children using the TruTip workstation novel automated lysis and extraction platform.[45]

Cepheid has launched new cartridge of Gene Ultra. Initial studies have shown that sensitivity of Xpert Ultra and Xpert is 63% and 46%, respectively, for smear-negative and culture-positive sputum, thus difference being 17% (95% CI 10 to 24).[46] In study by Nicol et al, of 76 microbiologically-confirmed TB cases using a composite reference standard of positive sputum Xpert, Ultra, or culture, sensitivity of Ultra was 74% compared to sensitivity of Xpert (63%), thus showing an incremental benefit of 11%. Specificity of Ultra was 97% (225/233, 95%CI 93–99), slightly lower than Xpert.[47] Introduction of Xpert ultra will further increase TB detection rate in pediatric population. Another indigenous technology of TrueNAT (Molbio diagnostics) has been launched, which is very similar in accuracy and ease of performance to Xpert.[48] The validation of TrueNAT in pediatric population is already underway and awaiting result analysis.

To conclude, thus in a span of about 10 years, TB diagnostics have improved significantly with the introduction of highly sensitive, simple and rapid molecular techniques especially Xpert, which has gradually replaced the low sensitivity ZN smear microscopy for TB diagnosis. Besides

Xpert, LPA and MGIT provide susceptibility to various antitubercular drugs which have been adopted by the national TB control programme as it has moved towards universal susceptibility testing. Currently, several researches are being conducted in different countries to design better serological and molecular tests for early detection of TB and drug resistance. Future of TB diagnostics promises more affordable technologies aiming at timely early diagnosis and point of care testing at field level.

Diagnosis of pulmonary TB (PTB) in presumptive TB is based on a combination of definite symptoms and signs, contact with an infectious case, a positive mantoux/TST (tuberculin skin test), a suggestive CxR 10e12 These perlude microbiological confirmation by WHO approved Rapid Diagnostic Tests (WRDT)on sputum or alternative specimens (GA,IS,BAL) depending on age of the patient and availability in the hospital setting.13,14 Ruling out alternative diagnosis also becomes important in patients with negative WRDTs. Although disease is usually paucibacillary in children and sample collection is difficult but children of all ages do have bacilli in their biological specimens and an attempt should always be made to demonstrate the M. tb. 7e9 Advances in TB diagnostics using WHO approved Rapid Diagnostic Tests (WRDT) include Cartridge Based Nucleic Acid Amplification Test (CBNAAT) Xpert MTB/RIF™or Gene Xpert, Line Probe Assay and Liquid culture and Mycobacterial Growth indicator tubes (MGIT).14,15 These tests have a higher sensitivity, specificity and a faster turn around time than the conventional smear microscopy and solid (LJ) culture. WRDTs are used as priority in diagnosing TB children among presumptive TB cases under the programme. These tools help in labeling a presumptive TB child as either microbiologically confirmed or clinically diagnosed TB. Clinically diagnosed TB includes both probable and possible TB cases, where bacteriological confirmation fails despite using WRDTs and pediatric diagnostic algorithm followed for these presumptives. Therefore, despite these newer WRDTs, which have limited sensitivity in children, clinicians often face diagnostic dilemmas.

Conflicts of Interest

The authors have none to declare.

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REFERENCES

1. World Health Organization. *Global Tuberculosis Report*. 2019. ISBN 978-92-4-156571-4. Geneva, Switzerland.
2. *RNTCP Report*; 2019. https://www.tbcindia.gov.in/index1.php?lang=1&level=1&sublinkid=5365&lid=34502019.
3. Sharma S, R Sarin Vith Myneedu. Experiences in treating children with MDR-TB in India. *Int J Tuberc Lung Dis*. 2014;18(11):S50.
4. Sharma S. Emerging treatment trends in pediatric TB. *Indian J Tuberc*. 2019;66:214–217.
5. Harausz Elizabeth P, Garcia-Prats Anthony J, Law Stephanie, et al. HesselingTreatment and Outcomes in Children with Multidrug-Resistant Tuberculosis: a Systematic Review and Individual Patient Data Meta- Analysis. *PLoS Med*. 2018;15(7), e1002591. https://doi.org/10.1371/journal.pmed.1002591.
6. United Nations. *United to End Tuberculosis: an Urgent Global Response to a Global Epidemic*. *September 26*; 2018. https://www.un.org/pga/72/wp-content/uploads/sites/51/2018/09/Cofacilitators-Revised-text-Political-Declaraion-onthe-Fight-against-Tuberculosis.pdf. Accessed October 20, 2019.
7. World Health Organization. *Roadmap towards ending TB in children and adolescents*; 2018. Accessed http://apps.who.int/iris/bitstream/handle/10665/275422/9789241514798-eng.pdf. Accessed November 11, 2018.
8. Sharma S, Sarin R, Khalid UK, Singla N, Sharma PP, Behera D. The DOTS strategy for treatment of pediatric pulmonary tuberculosis in South Delhi, India. *Int J Tuberc Lung Dis*. 2008;12(1):74–80.
9. Sharma S, Sarin R, Khalid UK, Singla N, SharmaPP Behera D. Clinical profile and treatment outcome of tubercular pleurisy in pediatric age group using DOTS strategy. *Indian J Tuberc*. 2009;56:191–200.
10. Sharma S, Sarin R, Khalid UK, Singla N, Sharma PP, Behera D. Clinical profile and treatment outcome of tuberculous lymphadenitis in children using DOTS strategy. *Indian J Tuberc*. 2010;57(1):4–11.
11. Swaminathan S, Rekha B. Pediatric tuberculosis: global overview and challenges. *Clin Infect Dis*. 2010;50(S3). S 184-194.
12. Furin J. Advances in the diagnosis, treatment, and prevention of tuberculosis in children. *Expert Rev Respir Med*. 2019. https://doi.org/10.1080/17476348.2019.1569518.
13. Seki M, Kim C, Hayakawa S, Mitarai S. Recent advances in tuberculosis diagnostics in resource poor settings. *Eur J Clin Microbiol Infect Dis*. 2018;37(8):1405–1410.
14. Perez-Velez CM, Marais BJ. Tuberculosis in children. *N Engl J Med*. 2012 Jul 26;367(4):348–361.
15. Gie R. *Diagnostic atlas of intrathoracic tuberculosis in children: a guide for low-income countries*. Paris: International Union Against Tuberculosis and Lung Disease; 2003.
16. World Health Organization. *Chest radiography in tuberculosis detection: summary of current WHO Recommendations and guidance on programmatic approaches*; 2016. http://apps.who.int/iris/bitstream/handle/10665/252424/9789241511506-eng.pdf. Accessed November 10, 2018.
17. World Health Organization. *Guidance for National Tuberculosis Programs on the Management of Tuberculosis in Children*. Geneva. 2nd ed.; 2014. Accessed http://apps.who.int/iris/bitstream/handle/10665/112360/9789241548748_eng.pdf. Accessed November 11, 2018.
18. *Programmatic Management of Drug-Resistant TB in India. Revised National Tuberculosis Control Programme, Central TB Division, Director General of Health Services*. New Delhi: Ministry of Health & Family Welfare, Nirman Bhawan; 2017.
19. *WHO Consolidated Guidelines on Drug-Resistant Tuberculosis Treatment*. Geneva: World Health Organization; 2019. Licence: CC BY-NC-SA 3.0 IGO.
20. Marais BJ, Pai M. Specimen collection methods in the diagnosis of childhood tuberculosis. *Indian J Med Microbiol*. 2006;24:249–251.
21. Singh M, Moosa NV, Kumar L, Sharma M. Role of gastric lavage and broncho-alveolar lavage in the bacteriological diagnosis of childhood pulmonary tuberculosis. *Indian Pediatr*. 2000;37:947.

22. Zar HJ, Hanslo D, Apolles P, Swingler G, Hussey G. Induced sputum versus gastric lavage for microbiological confirmation of pulmonary tuberculosis in infants and young children: a prospective study. *Lancet*. 2005;365:130–134.
23. MacLean E, Sulis G, Denkinger CM, Johnston JC, Pai M, Khan FA. Diagnostic accuracy of stool Xpert MTB/RIF for detection of pulmonary tuberculosis in children: a systemic review and meta-analysis. *J Clin Microbiol*. 2019;57, e02057-18.
24. Raizada N, Khaparde SD, Rao R, et al. Upfront Xpert MTB/RIF testing on various specimen types for presumptive infant TB cases for early and appropriate treatment initiation. *PLoS One*. 2018;13, e0202085.
25. Cruciani M, Scarparo C, Malena M, Bosco O, Serpelloni G, Mengoli C. Meta-analysis of BACTEC MGIT 960 and BACTEC 460 TB, with or without solid media, for detection of mycobacteria. *J Clin Microbiol*. 2004;42:2321–2325.
26. Ling DI, Zwerling AA, Pai M. GenoType MTBDR assays for the diagnosis of multi-drug resistant tuberculosis. *Eur Respir J*. 2008;32:1165–1174.
27. WHO. *Automated Real-Time Nucleic Acid Amplification Technology for Rapid and Simultaneous Detection of Tuberculosis and Rifampicin Resistance: Xpert MTB/RIF Assay for the Diagnosis of Pulmonary and Extrapulmonary TB in Adults and children. Policy Update*. World Health Organization; 2013.
28. Detjen AK, DiNardo AR, Leyden J, et al. Xpert MTB/RIF assay for the diagnosis of pulmonary tuberculosis in children: a systematic review and meta- analysis. *Lancet Respir Med*. 2015;3:451–461.
29. Bates M, O'Grady J, Maeurer M, et al. Assessment of the Xpert MTB/RIF assay for diagnosis of tuberculosis with gastric lavage aspirates in children in sub-Saharan Africa: a prospective descriptive study. *Lancet Infect Dis*. 2013;13:36–42.
30. Rachow A, Clowes P, Saathoff E, et al. Increased and expedited case detection by Xpert MTB/RIF assay in childhood tuberculosis: a prospective cohort study. *Clin Infect Dis*. 2012;54:1388–1396.
31. Singhal R, Myneedu VP. Microscopy as a diagnostic tool in pulmonary tuberculosis. *International J Mycobacteriology*. 2015;4:1–6, 2015.
32. Steingart KR, Henry M, Ng V. Fluorescence versus conventional sputum smear microscopy for tuberculosis, a systematic review. *Lancet Infect Dis*. 2006;6:570–581.
33. Bhalla M, Sidiqi Z, Sharma PP, Singhal R, Myneedu VP, Sarin R. Performance of light-emitting diode fluorescence microscopy for diagnosis of tuberculosis. *Int J Mycobacteriol*. 2013;2:174–178.
34. Reza LW, Satyanarayna S, Enarson DA, et al. LED-fluorescence microscopy fordiagnosis of pulmonary tuberculosis under programmatic conditions in India. *PLoS One*. 2013;8, e75566.
35. Arora J, Singhal R, Bhalla M, et al. Drug resistance detection and mutation patterns of multidrug-resistant tuberculosis strains from children in Delhi. *J Epidemiol Glob Health*. 2017;7, 141-5.
36. Singhal R, Myneedu VP, Arora J, et al. Early detection of multi-drug resistance and common mutations in Mycobacterium tuberculosis isolates from Delhi using GenoTypeMTBDRplus assay. *Indian J Med Microbiol*. 2015;33:S46–S52.
37. Singhal R, Arora J, Lal P, Bhalla M, Behera D, Myneedu VP. Comparison of line probe assay with liquid culture for rapid detection of multi-drug resistance in Mycobacterium tuberculosis. *Indian J Med Res*. 2012:1044–1047.
38. Cuevas LE. The urgent need for new diagnostics for symptomatic tuberculosis in children. *Indian J Pediatr*. 2011;78, 449-55.
39. Shah MA, Shah I. Increasing prevalence of pediatric drug-resistant tuberculosis in Mumbai, India and its outcome. *Pediatr Infect Dis J*. 2018;37, 1261-3.
40. Gardee Y, Dreyer AW, Koornhof HJ, et al. Evaluation of the GenoTypeMTBDRsl version 2.0 assay for second-line drug resistance detection of Mycobacterium tuberculosis isolates in South Africa. *J Clin Microbiol*. 2017;55.
41. Hanna BA, Ebrahimzadeh A, Elliott LB, et al. Multicenter evaluation of the BACTEC MGIT 960 system for recovery of mycobacteria. *J Clin Microbiol*. 1999;37:748–752.
42. Zhao P, Yu Q, Zhang Y. Evaluation of a manual identification system for detection of Mycobacterium tuberculosis in a primary tuberculosis laboratory in China. *J Int Med Res*. 2019;47:2666–2673.
43. Rodrigues C, Shenai S, Sadani M, et al. Evaluation of the bactec MGIT 960 TB system for recovery and identification of Mycobacterium tuberculosis complex in a high volume tertiary care center. *Indian J Med Microbiol*. 2009;27:217–221.
44. Thomas TA, Heysell SK, Moodley P, et al. Intensified specimen collection to improve tuberculosis diagnosis in children from Rural South Africa, an observational study. *BMC Infect Dis*. 2014;14:11.
45. Mesman AW, Soto M, Coit J, et al. Detection of Mycobacterium tuberculosis in pediatric stool samples using TruTip technology. *BMC Infect Dis*. 2019;19:563.
46. Dorman SE, Schumacher SG, Alland D, et al. Xpert MTB/RIF Ultra for detection of Mycobacterium tuberculosis and rifampicin resistance: a prospective multicentre diagnostic accuracy study. *Lancet Infect Dis*. 2018;18:76–84.
47. Nicol MP, Workman L, Prins M, et al. Accuracy of xpert MTB/RIF ultra for the diagnosis of pulmonary tuberculosis in children. *Pediatr Infect Dis J*. 2018;37:e261.
48. Nikam C, Jagannath M, Narayanan MM, et al. Rapid diagnosis of Mycobacterium tuberculosis with truenat MTB: a near-care approach. *PLoS One*. 2013;8, e51121.

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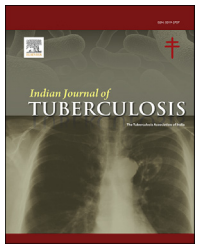

Review article

Fuelling the tuberculosis epidemic: The role of tobacco control in ending the TB emergency

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ABSTRACT

Background: Ending the TB epidemic by 2030 is among the key targets for countries to achieve Sustainable Development Goals. In current times we are grappling with dual burden of tuberculosis as well as tobacco use.

Methods: There is sufficient evidence to establish that tobacco smoking significantly spikes up the risk of acquiring, developing and death among tuberculosis patients. Active or passive exposure to tobacco smoke is significantly associated with tuberculosis infection and tuberculosis disease, independent of a large number of other potential confounders.

Results: Despite having substantial evidence about the impact of tobacco control measures, particularly tobacco cessation, on TB outcomes, the integration of TB and tobacco control still remains far-off.

Conclusion: It is high time when TB control programs must begin to address tobacco control as a potential preventive intervention to combat colliding epidemics of tobacco and tuberculosis. This white paper discusses about the role of tobacco control in reaching the ambitious goal of ending TB epidemic by 2030.

1. Executive summary

Ending the TB epidemic by 2030 is among the key targets for countries to achieve Sustainable Development Goals. In current times we are grappling with dual burden of tuberculosis as well as tobacco use and there is sufficient evidence to establish that tobacco smoking significantly spikes up the risk of acquiring, developing and death among tuberculosis patients. Despite having substantial evidence about the impact of tobacco control measures, particularly tobacco cessation, on TB outcomes, the integration of TB and tobacco control still remains far-off. This white paper discusses about the role of tobacco control in reaching the ambitious goal of ending TB epidemic by 2030.

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2. Tuberculosis

Tuberculosis is still the leading cause of death from a single infectious pathogen attributing directly to around 1.5 million deaths annually. Additionally, about a quarter of population is infected with *M. tuberculosis* and thus at risk of developing TB disease.[1] Though the disease burden caused by TB is falling in all WHO regions, but it is not fast enough to reach the first (2020) milestone of the End TB Strategy.[2] As compared to the desired (2020) fall in TB incidence rate (new cases per 100 000 population per year) at 4–5% per year, and the case fatality ratio (proportion of people with TB who die from the disease) at 10% per year, the current rate of decline are 2% and 3% per year respectively. For most countries (especially lower-middle income), however, the "end" of TB as an epidemic and major public health problem in the foreseeable future remains an aspiration rather than a reality.[2,3]

3. Tobacco use

Tobacco use kills over 8 million people each year globally, out of which, more than 7 million are the result of direct tobacco use while around 1.2 million are the result of non-smokers being exposed to second-hand smoke. It is estimated that around 100 million died prematurely by tobacco in 20th Century.[4] The total economic cost of smoking (from health expenditures and productivity losses together) globally are estimated to be around USD 1.4 trillion per year, equivalent in magnitude to 1.8% of the world's annual GDP. Almost 40% of this cost was incurred in developing countries, highlighting it's substantial burden these countries.[5,6]

4. Association betweenTB andTobacco

Systematic reviews and meta-analysis have produced significant evidence that active smoking increases the likelihood of acquiring, developing and dying from a TB infection and developing recurrent tuberculosis.[7–9] Active or passive exposure to tobacco smoke is significantly associated with tuberculosis infection and tuberculosis disease, independent of the effects of alcohol use, socioeconomic status and a large number of other potential confounders.[10] Smoking increases the risk of TB disease by more than two-and-a-half times. More than 20% of global TB incidence may be attributable to smoking, accounting for around 3 million new TB cases.[9,11] Smokers with tuberculosis had a more severe clinical and radiological presentation, more frequent sputum positivity at presentation and after 2 months of treatment, a lower rate of success, and higher relapse rate. Further, exposure to tobacco smoke increases the risk of latent TB infection, culture conversion, cavitary disease, and transmission of disease.[12] Smoking can mask TB related symptoms and thus lead to delayed diagnosis, more critical TB conditions and high mortality rates.[13,14] Further, Second Hand Smoke (SHS) also increases the risk of acquiring infection (RR-1.19) and progression to TB disease (RR-1.59), with high TB burden reported in the countries with increasing SHS exposure.[15,16]

Research has also shown that 50% of deaths from TB among Indian men were attributed to smoking,[17] which costs India's economy three times its tuberculosis budget. Also, surplus deaths occur among smokers due to tuberculosis as compared with nonsmokers, among both men (risk ratio, 2.3; 99% CI, 2.1 to 2.6) and women (risk ratio, 3.0; 99% CI, 2.4 to 3.9).[18] Smoking is predicted to cause an excess of 18 million TB cases and 40 million deaths from tuberculosis between 2010 and 2050, if the current smoking trends continue.[19–22] Smokers who quit reduce both their risk of becoming infected with TB and thereafter dying from it.[23] World Health Organization reported that TB rates could decline by as much as 20% if smoking was eliminated.[24] Vigorous tobacco control that results in a 1 percent drop annually in a country's smoking rates could substantially reduce the toll of TB deaths by almost 27 million by 2050.[22] Despite the strong evidence of the effect of tobacco control measures and tobacco cessation, the integration of TB and tobacco control remains elusive.

Exposure to tobacco smoke impairs the phagocytic function of alveolar macrophages and damages cilia in the airways, which might increase host susceptibility to TB infection. It also causes altered immune response and multiple defects in immune cells such as macrophages, monocytes and CD4 lymphocytes, which predispose the individual to high risk of TB infection (establishing biological plausibility).[37]

5. Global policies for jointTB-Tobacco activities

- In 2005, WHO Tobacco Free Initiative and WHO Stop TB program, in collaboration with The Union, developed a policy paper for successful integration of tobacco control into TB control program through a practical approach to lung health, a component of Stop TB strategy.[25]
- A WHO-The Union monograph on TB and Tobacco (2007) recommends assessment of tobacco use and tobacco cessation services routinely for all diagnosed TB patients for improving clinical outcomes.
- In 2008 and then in 2010, The Union published guidelines on "Smoking Cessation and Smoke free environments for tuberculosis patients" which addresses the association between tobacco smoke and tuberculosis and offers recommendations for health service providers who want to help their patients with TB to stop using tobacco.[17]
- In 2013, the World Health Assembly passed a resolution to approve the End TB Strategy, which was based upon three pillars, one of which calls for integrated, patient-centred care and prevention. This provides an opportune platform to align the efforts against two global epidemics simultaneously, tobacco and TB.[26]
- Pilot studies integrating brief advice for tobacco cessation in TB patients that have been implemented in Bangladesh, India and Indonesia, which demonstrated that this intervention can be effective (refer to Case Study-1 & 2). India has since developed a Joint TB-Tobacco Collaborative Framework, and is implementing the same through its NationalTB and Tobacco Control Programs.[27]
- TB and Tobacco Consortium in South Asia used "capability, opportunity, and motivation as determinants of behaviour"

(COM-B) framework to understand any issues facing health worker delivery of behaviour support, and subsequently developed a training package for health workers of LMICs for tobacco cessation support among tuberculosis patients.[28]

- South-East Asia's Regional Response Plan for Integration of TB and Tobacco 2017–2021 reiterates its Member States to implement cost-effective cessation services through TB programs and screen tobacco users for TB.[29] All 11 countries in the South- East Asia Region have a national TB program integrated into primary health care delivery systems to which a cessation service component could be added.
- Through Framework Convention on Tobacco Control (FCTC) 2030, the convention secretariat has partnered with the United Nations Development Programme (UNDP) to incorporate tobacco cessation activities into grants from The Global Fund to Fight AIDS, Tuberculosis and Malaria.[30] The partnership is based upon the successful case studies about how tobacco consumption worsens tuberculosis and HIV outcomes, and how the integration of tobacco control into these grants could increase health benefits and efficiencies.

6. Case study- 1

Health system changes for integration of tobacco cessation within routine TB services: achievements in Pakistan, Bangladesh and Nepal(TB and Tobacco Consortium, August 2019) TB and Tobacco Consortium, in close collaboration with the national TB programs (NTP) in Pakistan, Nepal and Bangladesh identified key health system barriers to the integration of behaviour support for tobacco cessation within NTP In all three countries, they found there was little mention of tobacco within policies and supervision guidelines, health workers did not see tobacco cessation as part of their job and with no training, did not feel confident to support their patients to quit. The team identified strategic health system changes to overcome the identified barriers, namely: a) policy change; b)training of NTP officers as trainers and then rolling out of a brief training for health workers using videos freely available from tbandtobacco.org along with all the tobacco cessation behaviour support materials c) revision of training manuals and supervision guidelines to include monitoring of provision of cessation and importantly, d) the inclusion of three key indicators within existing, routineTB recording and reporting forms: i) tobacco status at registration,ii) advice given andiii) stats/quit at the 6 months at the end of treatment In Pakistan, the National Guideline for the Control of Tuberculosis (August 2019) has been revised to include tobacco cessation as a core part of the service to be delivered to TB patients. They were able to train 17 trainers in a short 6-hour training session who then went on to train 115 TB health workers from 59 TB clinics and distribute the behaviour support materials. In similar fashion, a training of trainers event was held to develop a cadre of NTP officers inNepal and Bangladesh which were able to train TB health workers in their districts. NTP Nepal has now included the component of TB and Tobacco in its Basic TB Management Training Manual with revised indicators for tobacco. Following training, consortium researchers assessed the health workers' confidence to deliver cessation in each country using a validated questionnaire. They found that health worker confidence increased in all three countries to an average of 86% confident to deliver cessation behaviour support in Pakistan, 99% in Bangladesh and 81% in Nepal. The valuable lessons learnt were:

- Recording and reporting is key: including the three tobacco indicators within the existing TB forms serves two important purposes: i) it reminds health workers to ask about tobacco use and ii) allows managers to monitor implementation. Integration of the three tobacco indicators within new TB electronic patient records such as HMIS/DHIS2 will be an important step forward.
- Keep it simple: from an initial 30-minute behaviour support consultation, the Consortium has reduced the flipbook-led consultation to only 8 minutes, including key TB management messages as well as simple support for tobacco cessation.
- A brief session of a couple of hours delivered by the TB program's own staff can increase confidence to deliver cessation.
- Incorporating a tobacco cessation guide for health workers in NTP training manuals and supervision checklist helps institutionalization and scale-up of tobacco cessation practices in routine NTP services.

7. Case study- 2

Effect of a brief smoking cessation intervention on adult tobacco smokers with pulmonary tuberculosis (Goel S. et al, 2017).[38]

A 2- arm parallel cluster, randomized controlled trial with an objective to assess the effectiveness of a brief Smoking Cessation Intervention (SCI) the Ask, Brief, Cessation support (ABC) package, on treatment outcomes and smoking cessation in smear positive adult pulmonary TB patients was conducted at 17 designated microscopic centers of Chandigarh, India. These microscopic centres were randomly assigned using a computer generated randomization sequence to receive SCI within directly observed treatment, short (DOTS) services, or existing standard of care. Eligible and consenting smokers (15 + years) registered as smear positive pulmonary TB for DOTS (n = 156) between January and June 2013 were enrolled. Smoking cessation (self reported) was assessed at intervals till the end of treatment. End TB treatment outcomes were extracted from patient records. This trial concluded that smoking cessation intervention is effective in inducing smoking cessation among TB patients (adjusted incidence risk ratio = 1.56; 95% confidence interval = 1.24–1.93; $P < 0.0001$).

8. Suggestive strategies of integration

Several integration options can be considered between TB and tobacco control programs. They can be further divided into policy level and implementation level.

8.1. *Policy level*

At the level of policy development, there should be a joint effort for:

- Developing joint legislation and strategies for tacking both diseases under a broader umbrella like Universal Health Coverage.
- Developing technical and operational guidelines for TB-tobacco integration.
- Setting joint planning and monitoring indicators within both programs.
- Establishing a joint coordinating mechanism between tuberculosis control and tobacco control activities at various levels of implementation for alignment of strategies and service delivery. For example- A coordination committee consisting of TB and tobacco control program officers should be formed at each level to ensure implementation of joint collaborative activities. Similarly, TB Officer should be included as a member in the existing Coordination Committee of NTCP and vice-versa.
- Advocating for high taxation on tobacco products for financing tobacco and TB control programs

8.2. *Implementation level*

At implementation level, there should be an effective coordination for:

1. Establishing a continuum of care and support for TB patients (in TB clinics) who wish to quit smoking by providing enabling and supportive environment, where health workers and specialists record history of tobacco use (and any exposure to secondhand smoke) on routine TB reporting forms along with provision of brief customized advice on quitting and ensuring that health care facilities are strictly smoke-free. Further, pharmacological interventions may support patients to quit in settings where they are affordable. DOTS care providers should be trained on "Brief Advice" to TB patients who are tobacco users. The cured patients should be warned that starting smoking again would pose a risk of re-infection and disease[31]
2. Formulating a bi-directional screening mechanism where TB patients are screened for tobacco use and visa versa (screening tobacco users for TB symptoms) which shall be followed with appropriate referral mechanism.
3. Conduction of joint training programs for capacity building of personals under RNTCP and NTCP where, they will be sensitized through a standard common curriculum, about the importance of collective management of both TB and tobacco cessation.
4. Joint IEC activities including designing of IEC material, campaigns that support both men and women to quit all forms of tobacco should be planned.
5. Standardized common and integrated reporting mechanism for both programs should be formulated with tobacco indicators in TB report forms, and TB indicators or tobacco program forms.
6. Public private partnership through active involvement of all stakeholders should be advocated for increased penetration in the community.

9. Concluding statement

There is a huge untapped opportunity for greater integration between two national programs for mutual benefit and resource optimization.[39] Considering very few smoking cessation interventions for pulmonary TB treatment outcome globally, more research should be conducted in this area.[40] It is high time when TB control programs must begin to address tobacco control as a potential preventive intervention to combat colliding epidemics of tobacco and tuberculosis.

[32] A successful trialing of tobacco cessation treatments in conjunction with TB and respiratory health programs[33] will provide a basis for extending them to other health programs like NCD programs, oral health programs,[34] HIV/AIDS programs,[35] mental health programs, and programs addressing the needs of women's, children's and adolescents' health.[36] Incorporating brief advice into existing health care programs has the potential to reach more than 80% of all tobacco users in a country each year if delivered routinely and widely across a health care system.[36]

Given the evidence base, this integration can pave the way for ending TB emergency and attaining ambitious goal of ending TB by 2030.

REFERENCES

1. WHO. *Global Tuberculosis Report*; 2019 [Internet]. [cited 2019 Oct 20];Available from: https://www.who.int/tb/publications/global_report/en/.
2. WHO. *Global Tuberculosis Report 2018* [Internet]. WHO; 2019 [cited 2019 Sep 8]. Available from: https://www.who.int/tb/publications/global_report/en/.
3. WHO. *Fact Sheet on Tuberculosis and Tobacco* [Internet]. WHO; 2010 [cited 2019 Aug 29]. Available from: https://www.who.int/tobacco/resources/publications/fact_sheet_set09/en/.
4. World Health Organisation.Tobacco [Internet]. [cited 2019 Aug 25];Available from: https://www.who.int/news-room/fact-sheets/detail/tobacco.
5. World Health Organization.Tobacco [Internet]. [cited 2019 Aug 27];Available from: https://www.who.int/health-topics/tobacco.
6. World Health Organization. *Tobacco* [Internet]; 9 March 2018 [cited 2018 Oct 14]. Available from: http://www.who.int/news-room/fact-sheets/detail/tobacco.
7. Bates MN, Khalakdina A, Pai M, Chang L, Lessa F, Smith KR. Risk of tuberculosis from exposure to tobacco smoke. *Arch Intern Med*. 2007;167(4):335 [Internet], [cited 2019 Sep 8], Available from: http://www.ncbi.nlm.nih.gov/pubmed/17325294.
8. Lin H-H, Ezzati M, Murray M. Tobacco smoke, indoor air pollution and tuberculosis: a systematic review and meta-analysis. *PLoS Med*. 2007;4(1):e20 [Internet], [cited 2019 Sep 8], Available from: http://dx.plos.org/10.1371/journal.pmed.0040020.
9. Zellweger J-P, Cattamanchi A, Sotgiu G. Tobacco and tuberculosis: could we improve tuberculosis outcomes by helping patients to stop smoking? *Eur Respir J*.

2015;45(3):583–585 [Internet] [cited 2019 Sep 8], Available from: http://www.ncbi.nlm.nih.gov/pubmed/25726531.
10. Bothamley GH. Smoking and tuberculosis: a chance or causal association? *Thorax*. 2005;60(7):527–528 [Internet], [cited 2019 Aug 29]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15994256.
11. Siddiqi K, Khan A, Ahmad M, et al. Action to stop smoking in SuspectedTuberculosis (ASSIST) in Pakistan. *Ann Intern Med*. 2013;158(9):667 [Internet], [cited 2019 Sep 8], Available from: http://annals.org/article.aspx?doi=10.7326/0003-4819-158-9-201305070-00006.
12. Slama K, Chiang C-Y, Enarson DA, et al. Tobacco and tuberculosis: a qualitative systematic review and meta-analysis. *Int J Tuberc Lung Dis*. 2007;11(10):1049–1061 [Internet], [cited 2019 Sep 8], Available from: http://www.ncbi.nlm.nih.gov/pubmed/17945060.
13. Anderson RH, Sy FS, Thompson S, Addy C. Cigarette smoking and tuberculin skin test conversion among incarcerated adults. *Am J Prev Med*. 1997;13(3):175–181 [Internet], [cited 2019 Oct 15], Available from: http://www.ncbi.nlm.nih.gov/pubmed/9181204.
14. Gupta B, … NM-E, 1997 Undefined. A Study of Household Environmental Risk Factors Pertaining to Respiratory Diseases. For Gov INDIA [Internet] [cited 2019 Oct 15]; Available from: https://scholar.google.co.in/scholar?hl=en&as_sdt=0%2C5&q=+A+study+of+household+environmental+risk+factors+pertaining+to+respiratory+diseases+Energy+Environment+Monitor+13%3A+61–67&btnG=.
15. Patra J, Bhatia M, Suraweera W, et al. Exposure to second-hand smoke and the risk of tuberculosis in children and adults: a systematic review and meta-analysis of 18 observational studies. *PLoS Med*. 2015;12(6), e1001835 [Internet], [cited 2019 Sep 8], Available from: https://dx.plos.org/10.1371/journal.pmed.1001835.
16. DOGAR OF, PILLAI N, SAFDAR N, SHAH SK, ZAHID R, SIDDIQI K. Second-hand smoke and the risk of tuberculosis: a systematic review and a meta-analysis. *Epidemiol Infect*. 2015;143(15):3158–3172 [Internet], [cited 2019 Sep 8], Available from: http://www.ncbi.nlm.nih.gov/pubmed/26118887.
17. Bissell K, Fraser T, Chen-Yuan C, Enarson DA. *Smoking Cessation and Smokefree Environments for Tuberculosis Patients*. 2nd ed. International Union Against Tuberculosis and Lung Disease; 2010.
18. Jha P, Jacob B, Gajalakshmi V, et al. A nationally representative case–control study of smoking and death in India. *N Engl J Med*. 2008;358(11):1137–1147 [Internet], [cited 2019 Oct 15]. Available from: http://www.nejm.org/doi/abs/10.1056/NEJMsa0707719.
19. Indian Council of Medical Reserach. India: Health of the Nation's States [Internet]. [cited 2018 Oct 14]. Available from : https://www.healthdata.org/sites/default/files/files/policy_report/2017/India_Health_of_the_Nation%27s_States_Report_2017.pdf.
20. Peto R, Lopez AD, Boreham J, Thun M, Heath C. Mortality from tobacco in developed countries: indirect estimation from national vital statistics. *Lancet (London, England)*. 1992;339(8804):1268–1278 [Internet], [cited 2019 Oct 15], Available from: http://www.ncbi.nlm.nih.gov/pubmed/1349675.
21. Zhang H, Xin H, Li X, et al. A dose-response relationship of smoking with tuberculosis infection: a cross-sectional study among 21008 rural residents in China. *PLoS One*. 2017;12(4), e0175183 [Internet], [cited 2019 Aug 29] Available from: https://dx.plos.org/10.1371/journal.pone.0175183.
22. Basu S, Stuckler D, Bitton A, Glantz SA. Projected effects of tobacco smoking on worldwide tuberculosis control: mathematical modelling analysis. *BMJ*. 2011;343. d5506. [Internet], [cited 2019 Aug 29], Available from: http://www.ncbi.nlm.nih.gov/pubmed/21972295.
23. Gajalakshmi V, Peto R, Kanaka TS, Jha P. Smoking and mortality from tuberculosis and other diseases in India: retrospective study of 43?000 adult male deaths and 35?000 controls. *Lancet*. 2003;362(9383):507–515 [Internet], [cited 2019 Aug 27], Available from: http://www.ncbi.nlm.nih.gov/pubmed/12932381.
24. World Health Organization, Geneva. *Global Tuberculosis Report 2017* [Internet]; 2017 [cited 2019 Aug 27]. Available from: https://extranet.who.int/tme.
25. WHO. *Library Cataloguing-In-Publication Data: A WHO/The Union Monograph on TB and Tobacco Control: Joining Efforts to Control Two Related Global Epidemics* [Internet]; 2007 [cited 2019 Sep 8]. Available from: www.ekze.ch.
26. WHO. *The End TB Strategy* [Internet]. WHO; 2017 [cited 2019 Sep 8], Available from: https://www.who.int/tb/strategy/end-tb/en/.
27. World Health Organization. *WHO Report on the Global Tobacco Epidemic, 2019* [Internet]; 2019 [cited 2019 Aug 27]. Available from: https://apps.who.int/iris/bitstream/handle/10665/325968/WHO-NMH-PND-2019.5-eng.pdf?ua=1.
28. Warsi S, Elsey H, Boeckmann M, et al. Using behaviour change theory to train health workers on tobacco cessation support for tuberculosis patients: a mixed-methods study in Bangladesh, Nepal and Pakistan. *BMC Health Serv Res*. 2019;19(1):71 [Internet], [cited 2019 Aug 27], Available from: http://www.ncbi.nlm.nih.gov/pubmed/30683087.
29. World Health Organization S-EA. *South-East Asia Regional Response Plan for Integration of TB and Tobacco 2017–2021* [Internet]; 2017 [cited 2019 Aug 27]. Available from: http://apps.searo.who.int/PDS_DOCS/B5371.pdf.
30. Issue brief integrating tobacco control into tuberculosis and hiv responses Implementing the WHO Framework Convention on Tobacco Control to address co-morbidities [Internet]. [cited 2019 Aug 27]. Available from: https://www.who.int/fctc/publications/WHO-FCTC-HIV-TB.pdf?ua=1.
31. Pai M, Pai M. Tobacco and tb?: what clinicians can and must do? [Internet]. [cited 2019 Aug 27]. Available from: http://medind.nic.in/jaw/t09/i2/jawt09i2p1.pdf.
32. Pai M, Mohan A, Dheda K, et al. Lethal interaction: the colliding epidemics of tobacco and tuberculosis. *Expert Rev Anti Infect Ther*. 2007;5(3):385–391 [Internet], [cited 2019 Aug 27], Available from: http://www.ncbi.nlm.nih.gov/pubmed/17547503.
33. Chapter 5 Improving health care: individual interventions [Internet]. [cited 2019 Aug 27]. Available from: https://www.who.int/nmh/publications/ncd_report_chapter5.pdf.
34. Creswell J, Raviglione M, Ottmani S, et al. Tuberculosis and noncommunicable diseases: neglected links and missed opportunities. *Eur Respir J*. 2011;37(5):1269–1282 [Internet], [cited 2019 Aug 27], Available from: http://www.ncbi.nlm.nih.gov/pubmed/20947679.
35. Bertozzi S, Padian NS, Wegbreit J, et al. *HIV/AIDS Prevention and Treatment* [Internet]. The International Bank for Reconstruction and Development/The World Bank; 2006 [cited 2019 Aug 27]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21250356.
36. WHO/The Union. *A WHO/The Union Monograph on TB and Tobacco Control: Joining Efforts to Control Two Related Global Epidemics*; 2007 [cited 2019 Aug 27], Available from: https://www.who.int/tobacco/resources/publications/tb_tobac_monograph.pdf.

37. Strzelak A, Ratajczak A, Adamiec A, Feleszko W. Tobacco smoke induces and alters immune responses in the lung triggering inflammation, allergy, asthma and other lung diseases: A Mechanistic review. *Int J Environ Res Public Health*. 2018;15(5) [Internet], [cited 2019 Sep 8], Available from: http://www.ncbi.nlm.nih.gov/pubmed/29883409.
38. Goel S, Kathiresan J, Singh P, Singh RJ. Effect of a brief smoking cessation intervention on adult tobacco smokers with pulmonary tuberculosis: a cluster randomized controlled trial from North India. *Indian J Public Health*. 2017;61(5):47–53.
39. Goel S, Verma M, Singh RJ, Bhardwaj AK. Integrating tobacco and tuberculosis control programs in India. *A Win–win Situat*. 2018;3(5):9–15.
40. Jeyashree K, Kathirvel S, Shewade HD, Kaur H, Goel S. Smoking cessation interventions for pulmonary tuberculosis treatment outcomes. *Cochrane Database Syst Rev*. 2016:1465–1858. https://doi.org/10.1002/14651858.CD011125.pub2.