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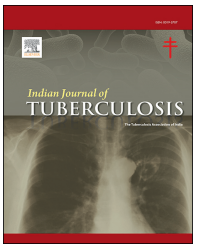

Editorial

NATCON virtual 2020 – Challenges and way ahead

TB Association of India (TAI) conducts a yearly conference - National TB and Chest Diseases Conference (NATCON), in rotation in different zones of India in association with State TB Association. In the year 2020, it was planned to celebrate Platinum Jubilee of the Conference in a big way. Due to ongoing COVID pandemic, the state association as well as TB Association was apprehensive about conducting the event. During the discussions, it was coming out that this year the NATCON should be a Hybrid one - combination of physical and virtual discussions, but at the end consensus was to conduct virtual conference, which was for the first time in history of TAI.

In spite of growing prevalence, virtual meetings are often still seen as inferior to in-person meetings – a temporary solution until people can meet up again, or a fast fix to a slow problem. But is it time to reassess the value of virtual meetings? While they might not materially solve the productive problems of meeting culture itself, they hold several advantages.

With virtual meetings, the amount of scheduling and logistical staff tends to be significantly reduced. You don't have to think about booking a room, or worry whether it's big enough for all invitees, should they turn up.

It's not smooth sailing with everything related to virtual events. However, a recent survey found that nearly one-third of all event planners did not try hosting online conferences because they felt that a virtual environment cannot deliver the value that event attendees typically look for. Availability of the right technological infrastructure is also a factor, as is the task of keeping attendees uniformly engaged with the event. We will look at the main challenges that event organisers face while planning a virtual event.

Fully online or a hybrid event has several components to take care of – right from creating an optimum content flow and planning an effective attendee engagement strategy, to selecting the best event tech platform/streaming tool and quick troubleshooting. Organisers who try to plan virtual events for the first time ever are likely to face even more problems – with the lack of experience being a serious bottleneck. Ideally, an event planner should participate in a few online conferences to understand how things are handled, learn from them, and then start planning their own event.

An organiser who is working on their very first remote conference is not likely to find everything intuitive – and what's more, they might not be the best person to answer technological queries from participants. With little or no support coming from the event tech vendor, it does not take long for the overall attendee experience to go southwards – which automatically leads to bad publicity.

Not everyone is likely to be equally technically savvy – so the entire on boarding process has to be made as simple as possible. The point to remember here is that, there are no physical check-ins and guidance available in a virtual setting and if people face difficulties, they will get flustered and angry.

Breakout sessions, coffee breaks, scheduled meetings, Q&A sessions – there are many ways in which the audience can actually participate in an in-person event. These opportunities are absent when the same event goes virtual. Many online event platforms host events that have typically one-way communication – with the live/recorded videos playing, and the viewers having precious little to do. In order to avoid such boring scenarios, it is imperative to "make people talk" – through live Q&A sessions, session feedback and opinion sections, polls, virtual breakout rooms, social community and more. It is also a good idea to track and record user activity logs (provided that the event tech vendor has that option) – to understand audience behaviour.

Peuler and McCallister (2019)[1] reviewed an inaugural virtual conference and found that a successful virtual conference tripled the number of attendees. Erickson, Kellogg, Shami, and Levine (2020)[2] showed similar findings when examining two virtual conferences held in 2009. Over half of the participants in their study agreed that the virtual meeting was a good experience and reported that they would use this virtual format again in the future. However, compared with in-person conferences, virtual conferences have been questioned on their quality of engagement and communication. Erickson et al (2020) surveyed conference attendees to draw comparisons between the experiences of traditional in-person conferences and virtual conferences in facilitating information sharing, social engagement, and producing work results. Most respondents rated both web conferencing and in-person conferencing as "satisfactory" (96.3 and 98.2%, respectively) in their ability to share information.

If a virtual event is coming up in a month, and a fully live version is scheduled next year (when, hopefully, the Covid situation would improve significantly), people can simply skip the virtual edition.

All the challenges were there in our conference also. But with cooperation of event management company (which had experience of hosting such type of scientific virtual conferences) and hard working coordination committee has been able to put up a good show.

The virtual conference has given us the chance to invite the faculties across the globe, which we could not thought of inviting them physically in the conferences, they simply logged in to our virtual platform and were with us for few hours, with their knowledge, skills and expertise for this conference. So we think it to be the most advantageous of inviting the stalwarts into these conferences, otherwise physically would not have been possible.

A post conference discussion among organisers and feedback of participants showed significant satisfaction over the conduct of conference. The encouragement has been so much that, it is felt at TAI to hold Hybrid conferences in future to rope in benefits of both virtual and physical events.

Hybrid events are the best of both worlds. Some of the participants are able to attend face-to-face while others are "brought in virtually", thus adding to the benefit of the overall interaction. Hybrid meetings can also be used as a method for cost reduction since we don't have time and travel expenses for the entire attendee pool. Allowing attendees to participate from wherever they sit in the world – either in-person or online - offers everyone flexibility and convenience and allows us to expand the impact regardless of geography.

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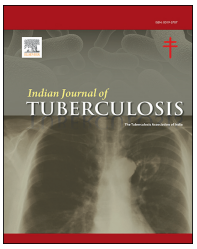

Original article

Effectiveness of m-learning on knowledge and attitude of nurses about the prevention and control of MDR TB: A quasi-randomized study

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ABSTRACT

Background: Multidrug-Resistant Tuberculosis is a fatal form because of high morbidity and poor recovery. Improper use of first line medicines and default treatment are the prime reasons of developing resistance of mycobacterium towards conventional anti- TB drugs. Nurses with refined knowledge, current evidence and positive attitude can prevent arising of MDR TB cases by ensuring adequate treatment, promoting treatment adherence and real time case monitoring. Because of paucity of data, present study was aimed to assess efficacy of m-learning in improving knowledge and attitude of nurses about the prevention and control of MDR-TB.

Methods: In this Quasi-randomized study, nurses working in the unit of pulmonary, emergency, respiratory ICU, general medicine of AIIMS Rishikesh during the months of August–October 2019 were involved. The number of participation was 190 (95 in each group; experimental and control) where m-learning intervention was available only for experimental group. There were structured questionnaire to measure knowledge and dichotomous checklist to evaluate attitude of nurses of both group before and one week after the provision of m-learning module.

Results: Both the group was homogeneous and m-learning intervention was effective to improve knowledge, when compared post-test knowledge score between experimental and control group (18.2 ± 5.4 vs 12.4 ± 4.4; $P < 0.001$); however, this one-time social media based intervention could not improve attitude of participants (10.3 ± 1.8 vs. 9.9 ± 1.8; $P = 0.175$).

Conclusion: Hence, m-learning is useful for knowledge development among large number of nurses within limited resource setting but frequent provision of technology based module is recommended to acquire positive attitude among nurses.

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1. Introduction

Multidrug-resistant tuberculosis (MDR-TB) is a rapidly emerging health problem globally,[1] which is primarily contributed by the poor drug compliance, inadequate treatment and delayed treatment initiation for tuberculosis.[2] The treatment for the MDR-TB is very challenging because of length (up to 2-years), and significantly lower cure rate (55–67%) in comparison with a-standard 6-months treatment for tuberculosis, which has cure rate as high as 95%.[3] The longer length of treatment, higher incidence of severe adverse drug effects and higher cost of second-line drugs for the treatment of MDR-TB brings serious challenges for the patients, families, and government, as in many countries, treatment of MDR-TB consumes more than half of the national TB control program budget and threatens the effectiveness of national TB control programs[4] The prevention and control of rapidly emerging MDR-TB depend on timely diagnosis, initiation of treatment for tuberculosis, quality drugs and improved treatment adherence among tuberculosis patients.

Nurses are the largest health care human resource, who can play a vital role in early diagnosis, education and follow-up of tuberculosis patients to ensure good treatment adherence and thereby high cure rate of patients with tuberculosis and prevention and control of MDR-TB.[5] However, studies highlighted there are a serious knowledge gap and poor attitude about tuberculosis among health care workers[6] especially nurses and they recommended acute need of multifaceted interventions to boost knowledge and improve their attitude about tuberculosis.[7,8] Conventionally, nurses are trained through in-service education programs, institutional, regional or national focused training program, but these programs can only educate a limited number of participants and it may not be a cost-effective solution to train a large number of nurses working in health care delivery system. The virtual teaching tools are believed to facilitate learner engagement, stimulate higher order of thinking, improve retention and are more suitable for working groups.[9] Thus m-learning modules can be considered as powerful teaching-learning tools, which can be used to educate and train a large number of nurses in a very short time with minimal efforts and cost. However, there is a paucity of data about their efficacy on knowledge and attitude of nurses. Therefore, the present quasi-randomized study was planned to assess the effectiveness of m-learning on knowledge and attitude of nurses regarding the prevention and control of MDR-TB.

2. Methods

The present study was conducted by using quasi-randomized design at a tertiary care teaching hospital in Rishikesh, Uttarakhand, India during August–October 2019 to evaluate the effect of m-learning on knowledge and attitude of nurses about prevention and control of MDR-TB.

The study was conducted on nurses working in pulmonary, emergency, medicine wards and respiratory ICU as typically tuberculosis patient getting treatment from these units. A sampling frame of nurses working in selected wards was obtained from the nursing superintendent and then nurses who were willing to participate and ready to cooperate in the study were recruited. However, nurses who were on long leave, not having smart phone and had any previous in-service education or short term training in MDR-TB were excused.

The sample size was estimated by using formula P_1 (1-P_1) + P_2 (1-P_2)/(P_1-P_2) × C[10] with an absolute error of 1%, power 90% and reference of knowledge difference from 58.27% to 85.87% in one of the similar research study.[11] The estimated sample size was 152 nurses; 76 each in the experimental and control group; while considering 25% non-response rate or loss to follow-up, total 190 sample size was considered for the present study. Thus, 95 nurses each in experimental and control groups were selected by using the quasi-random allocation technique.

The research project was approved by the institutional ethics committee of All India Institute of Medical Sciences, Rishikesh vides letter No. 52/IEC/EM/2019. Informed written consent was obtained from each participant and confidentiality of information and anonymity of participants was maintained.

Following self-structured, pre-validated tools were used for data collection:

- Socio-demographic proforma was used to assess the socio–demographic profile of participants.
- Structured questionnaire for measuring knowledge of the participants of MDR-TB, which contained 25 multiple choice questions with four options where each correct answer score one mark, so total marks ranged between 0 and 25.
- Dichotomous checklist to assess the attitude of participants about MDR-TB was used. This checklist contained 15 items, marked as yes or no by participants; where correct answer also scores one mark; thus total attitude score was ranged between 0 and 15.

Contact validity of tools was established with inputs from ten experts in the field of pulmonary medicine, tuberculosis care and nursing. Stability and internal validity of the component of a structured questionnaire were measured and calculated by the test-retest method ($r = 0.6$; Karl Pearson's). For dichotomous checklist Kunder- Richardson formula 20 (KR-20) was used to measure split-half reliability and value of r was 0.8 which showed both of the tools was reliable.

Virtual learning is a Web-based educational platform which is flexible, participant-centre, works in a self-paced format, applicable for a large group, economize on the time of teaching staff and the cost of instruction.[12] In the present study m-learning module was prepared for intervention group regarding multidrug-resistant tuberculosis which include causative factors of MDR TB, mode of transmission, warning sign and symptoms of the disease, investigating procedure and final diagnosis through CB-NAAT or gene expert, treatment regimen and its duration (DOTs Plus), follow up schedule, precautions and safety measures along with infection control policies. The learning module was short term, readable for 15 minutes duration in an attractive graphic pdf

Table 1 – Socio-demographic and clinical profile of the clinical nurses N = 190.

Socio-demographic variables	Experimental Group f (%)	Control Group f (%)	p-value
Age (in Years)			
Below 25	29 (30.5)	20 (21.1)	.218
25–30	54 (56.8)	65 (68.4)	
More than 30	12 (12.6)	10 (10.5)	
Mean ± SD (in years)	26.7 ± 2.70	26.7 ± 2.51	
Gender			
Male	70 (73.7)	59 (62.1)	.308
Female	25 (26.3)	36 (37.9)	
Marital Status			
Unmarried	53 (55.8)	57 (60.0)	.595
Married	41 (43.2)	38 (40.0)	
Widow	1 (1.1)		
Educational Status			
General Nursing & Midwifery	9 (9.5)	11 (11.6)	.544
Post Basic B.Sc. Nursing	8 (8.4)	3 (3.2)	
B.Sc. Nursing	69 (72.6)	77 (81.1)	
M.Sc. Nursing	9 (9.5)	4 (4.2)	
Institute of receiving a professional degree			
Government	28 (29.5)	48 (50.5)	.701
Private	67 (70.5)	47 (49.5)	
Occupational Status			
Nursing Officer	90 (94.7)	91 (95.8)	.630
Senior Nursing Officer	5 (5.3)	4 (4.2)	
Duration of Nursing Experience			
Less than 1 year	31 (32.6)	15 (15.8)	.544
1–3 years	34 (35.8)	39 (41.1)	
3–5 years	14 (14.7)	24 (25.3)	
More than 5 years	16 (16.8)	17 (17.9)	
Working experience in TB Unit			
Yes	30 (31.6)	14 (14.7)	.376
No	65 (68.4)	81 (85.3)	
Experience to take care of TB patient			
Yes	63 (66.3)	41 (43.2)	.722
No	32 (33.7)	54 (56.8)	

format which can be transferred and opened by any smart portable technology.

A pre-test was conducted from participants in both experimental and control group during their availability after working shift. Agreed participants had provided their written consent after go through the study details. It was taken 15–20 minutes to complete a structured questionnaire and dichotomous checklist during the pre-test. Thereafter, nurses only in the experimental group were provided m-learning module through social media (Whatsapp) by project investigator and they were asked not to share with anyone to prevent information contamination in control group. Participants were comfortable to learn from virtual module during their free time without any forced structured classroom teaching. Then after the gap of one-week post-test was conducted for participants both in the experimental and control group.

Data were coded and then entered to excel sheets and Statistical Package for the Social Sciences (SPSS 21.0) was used for statistical analysis. Data were analyzed using descriptive (frequency, percentage, measures of central tendency & measures of dispersion) and inferential statistics (unpaired t-test, chi-square).

3. Results

Socio-demographic and clinical profile of staff nurses was illustrated in Table 1; where it was identified that both groups were homogeneous. Most of the participants were within the age of 25–30 years, male, unmarried graduate nurse and having 1–3 years of nursing experience.

Table 2 – Effect of m-learning on knowledge and attitude regarding prevention & management of MDR TB among clinical nurses N = 190.

Variables Mean ± SD	Experimental Group (n = 95)	Control Group (n = 95)	p-value
Pre-test knowledge	11.7 ± 3.2	10.7 ± 3.1	0.230
Post-test Knowledge	18.2 ± 5.4	12.4 ± 4.4	**0.000***
Pretest Attitude	9.3 ± 1.8	9.8 ± 1.8	0.099
Post-test Attitude	10.3 ± 1.8	9.9 ± 1.8	0.175

*p value ≤ 0.05 considered significant.

Table 2 presented data about the effect of m-learning on knowledge and attitude of nurses regarding MDR-TB. It was found that m-learning significantly improved the knowledge of nurses, as there was significant post-test knowledge score difference between experiential and control group (18.2 ± 5.4 vs. 12.4 ± 4.4; $P < 0.001$). However, the post-test attitude score of nurses was not significantly different in the experimental and control group (10.3 ± 1.8 vs. 9.9 ± 1.8; $P = 0.175$).

4. Discussion

Tuberculosis had declared as a global emergency since 1993.[13] 'Stop TB strategies' by WHO, interventional process (DOTs) and control activities (RNTCP) are already ongoing in all over the country.[14] Though, there is incidence of default treatment, poor adherence, and missed medicine which can cause gene mutation, gene transfer and phenotypic change followed by presence of drug-resistant dominant strain among patients infected with primary TB.[15] The resistance of the causative bacterium to the most potent anti-tubercular drugs such as rifampicin, isoniazid, streptomycin, pyrazinamide, ethambutol, fluroquinolones and second-line injectable antibiotics leave limited treating options against the infection.[16,17] Treatment plan of multi drug resistant TB are expensive, need longer course, have weaker potency, adverse reaction[18] and toxic side-effects. India, China, Russian Federation, Philippines, Pakistan and South Africa had accounted for the highest digit of MDR-TB cases which indicate failure of global TB control agenda.[14]

Nurses are one of the core member in health care structure who can reach to the vulnerable populations,[19] maximize drug adherence, educate MDR- TB patients, ensure better treatment outcomes,[20] and apply infection control policies with preventive measures followed by control of drug resistant tuberculosis. All the mentioned approaches and practice requires refined and evidenced based knowledge regarding causative factor, pathogenesis, clinical sign, treatment plan, follow-up schedule and preventive strategies of MDR TB along with positive professional attitude among nurses involved in patient care.

However there are studies which pointed gap of knowledge and poor attitude among clinical nurses and other health care providers regarding multidrug-resistant tuberculosis and that usually affect cure and control of the ailment. Alotaibi B et al (2016) assessed tuberculosis knowledge, attitude and practice among physicians, nurses and non-administrative healthcare workers during Hajj.[6] Results of the study identified knowledge gaps in defining MDR-/XDR TB and latent tuberculosis infection (LTBI), smear microscopy results, length of standard TB treatment for drug-sensitive TB, 2nd line anti-TB drugs, BCG vaccination, and appropriate PPE to be used. Poor attitudes were found concerning willingness to practice in TB clinic/ward and commencing anti-TB treatment on suspected TB cases before laboratory confirmation. Malangu et al (2015) had specified a poor level of knowledge about diagnosis and duration of treatment of MDR-TB among young nurses.[21] Shreshtha et al (2017) also did not found satisfactory assessment on knowledge and practices of HCWs on TB infection control.[22] Yükseltürk N et al (2013) found less knowledge among nurses working in TB clinic about the effect and side effects of anti-TB drugs.[23] Knowledge about MDR-TB and XDR-TB was significantly lower when compared to knowledge regarding primary tuberculosis among health care professionals which indicates ignorance or less priority.[24] The insufficient knowledge was associated with a negative attitude towards patients,[6] unsafe practices, such as not wearing protective masks, as well as not referring to the MDR-TB treatment guidelines.[22] An in-service or nationalized educational intervention, regular skill-based training, structured teaching session, orientation on infection control, purchasing required protective equipment, clinical practice manual for all cadres of health care workers has been recommended in previous research.[6,22,23]

But the implementation of above-suggested activities is a costly process and couldn't train large of nurses or other health care workers at a time. Nowadays, Web technologies and virtual learning environment (e-learning/I- learning/m-learning) offer the potential for inexpensive training and learning opportunities which is flexible, easily accessible, user-centred, self-paced, quickly updated along with lower time commitment,[25] especially beneficial for health care personnel who share different work shifts and don't have a fixed work schedule.[26]

Learners need to have access to portable technology, internet browser, software communication (email, social media like Whatsapp, Messenger) and handling skills of those programs which is now very familiar to everyone.[27,28] Learning content must be understandable, attractive with an adequate script, is to be delivered via text-based web pages, video-assisted module or as interactive session.[29]

Numerous studies have already claimed that virtual learning can help in continued professional development (CPD), boost digital learning against various challenges in health care and to adopt the new changes needed for patient-centred and workplace oriented context.[30–33] Researchers have used webcast, CD-ROM, email, internet-telecommunication, Adobe system, YouTube channel to improve knowledge and attitude of participants followed by application in the practical field. Though, some of the study findings have generated mixed results in comparing V-learning programs and traditional teaching methods because the efficacy of V- learning varies from context to context, retaining the benefits of traditional face-to-face instruction and interactive motivational experience.[34]

The present study has used social media-based m-learning module to improve the knowledge and attitude of nurses for quality care of MDR TB patients. The result has shown the onetime learning module made them aware and improved their knowledge about drug-resistant tuberculosis. But for bringing change in attitude, stimulus should be sent for more times. Therefore, it has recommended to deliver multi-media based learning module, again and again, to acquire a more positive attitude among nurses in taking care of patients infected with MDR TB.

5. Conclusion

In resource-limited settings, virtual learning is feasible, and may address logistic, economic, geographic barriers and time constraints with the provision of high-quality education, boost digital learning and help to stay update with current evidence but sometimes multicomponent learning module is needed frequently in bringing change in attitude and pattern of practice.

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Conflicts of interest

The authors have none to declare.

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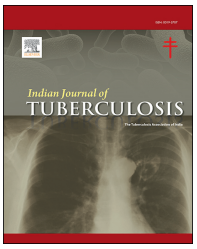

Original article

TB patient support systems in Kerala: A qualitative analysis

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ABSTRACT

Introduction: Tuberculosis (TB) is one of the leading causes of death due to infectious diseases in the world. Kerala a southern state in India aims to eliminate TB in the near future. In order to achieve its goal Kerala is providing various social support services to TB patients to ensure their smooth transition as they pass through the treatment cascade. Therefore, the objective of the current study was to qualitatively analyse the support systems provided for TB patients in Kerala and to assess the enablers and challenges faced during the provision of these services.

Methodology: A qualitative study using grounded theory approach was carried out among TB survivors, current TB patients and healthcare workers from all 14 districts of Kerala along with district health officials. A total of 14 in depth interviews were conducted among healthcare workers from all the districts of Kerala. Three FGDs were conducted, out of which two were among TB survivors and another one among current TB patients. The data was collected till data saturation was reached. The audio recorded data was transcribed, translated, manually coded and emerging themes and sub themes were identified. Using data triangulation, conclusions were made.

Results: It was observed that different TB support services were being provided across all the 14 districts of Kerala. Each of these initiatives were found to be unique in their own way for bridging the gaps in the in the continuum of care provided for TB patients. The main domains identified were grouped as support services provided for getting diagnosis, services provided after diagnosis of TB, prevention of TB and support provided to the patients reaching private sector. Under each of these domains a wide range of TB support initiatives that facilitated early diagnosis, good adherence to treatment, minimising patient inconveniences, stigma reduction, prevention out of pocket expenditure and emotional support were identified. Majority of these supportive measures were found not to be uniform throughout. Those are locally customised initiatives, evolved at different time periods

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with common objective of patient support. Community ownership, proactive health care system and political commitment contributed to these patient support systems.
Conclusion: These support services offered to TB patients were found to be very effective in paving the way towards the goal of TB elimination in Kerala.

1. Introduction

Tuberculosis (TB) is one of the leading causes of death due to infectious diseases in the world.[1] In order to reduce the morbidity and mortality due to TB, WHO has developed the End TB strategy. It highlights the need to provide "patient-centred care for all people with TB".[2] As India is striving towards the vision of achieving a "TB free" status, the National strategic plan 2017–25 has emphasised the need for identifying and closing the gaps in the continuum of care provided for TB patients.[3]

Kerala a southern state is committed to achieve the Sustainable Development Goals related to TB. Kerala's TB incidence rate is 67 per 100,000 population as against the all-India rate of 138 per 100,000 population. In the year 2019, there were 25,562 TB cases with 17,383 microbiologically confirmed and 8179 clinically confirmed cases. Also, there were 272 cases of MDR-TB in the state.[4]

Kerala is currently on track to eliminate tuberculosis by 2025.[5] However, in order to achieve its goal, there is an urgent need to supplement the existing TB prevention and control strategies that already in place.[6] Kerala health system came up with some unique TB patient support systems to facilitate the smooth transition of the TB patient through the treatment cascade without facing much delay.

Documentation of the TB patient support services will enable the replication of the services in similar settings and thereby facilitate patient centric care. The objectives of the current study were to qualitatively analyse the support systems provided for TB patients in Kerala and to assess the enablers and challenges faced during the provision of these services.

2. Methodology

The qualitative study using grounded theory approach was carried out after obtaining institutional ethical committee clearance. It was conducted at the town hall of Ernakulam district where the first meeting of the TB survivors of Kerala was held. It was attended by TB survivors, current TB patients and healthcare workers from all 14 districts of Kerala along with district health officials.

The study was conducted after briefing the purpose of the research to the participants. Informed consent and permissions for audio recording was obtained from the participants prior to the start of the study. A total of 14 in depth interviews were conducted among healthcare workers who are actively involved in the TB control activities from all the districts of Kerala. The healthcare workers included Treatment organizers, senior treatment supervisors, TB Health visitors, STEPS (System for TB Elimination in Private Sector) Coordinators & Senior TB Laboratory supervisors. Three focus group discussion (FGD) were conducted, out of which two were among TB survivors and another one among current TB patients. The interviews and FGDs lasted for 30–45 min. It was conducted using in-depth interview and FGD guides which were developed after extensive formative research. The data was collected till saturation was reached and till no new themes arose.

All the interviews and FGDs were conducted in the local language Malayalam and it was audio recorded. It was later transcribed verbatim and translated into English. The transcripts were then manually coded and emerging themes and sub themes were identified. Using data triangulation, conclusions were made.

3. Results

In order to get a holistic view of the TB Patient support systems in Kerala, we included the perspectives of both the healthcare providers as well as the patients. It was observed that all 14 districts of Kerala were actively involved in the fight against TB in order to eliminate it. In addition to the routine implementation of the National TB program (NTP), various patient support activities were being carried out through treatment support groups (TSG) established at the community level. These TSGs were found to provide ample support in various ways to the TB patient as he goes through the treatment cascade. The services provided by these TSGs were found to address not only the medical aspects but also the physical, mental, social and economic aspects as well. The main domains under which the themes identified were support services provided for getting diagnosis, after diagnosis of TB, prevention of TB and support provided by the private sector. The themes identified under each of these domains are as follows.

3.1. *Support services provided for getting diagnosis*

3.1.1. *Active case finding and vulnerability mapping*

Active case finding was found to be carried in all districts of Kerala. All of them stated that when a positive patient was identified, all his/her contacts were screened for TB every three months for two consecutive years. Also, in districts that completed vulnerability mapping, it was observed that regular screening of the vulnerable population was being carried out once in every three months. Those identified were

immediately were started on treatment and the others were continued to be screened once in every three months.

"We are going house to house using a checklist. If the score is above five or more we consider them as vulnerable are keep them under surveillance, with follow up checks every three months by accredited social health activist (ASHA) workers. Those showing symptoms would then be referred to the nearest centre for sputum testing…" — TB Health visitors.

It was observed that Idukki, Wayanad, Kollam, Kottayam, Pathanamthitta, Malappuram, Thrissur and Kannur districts had successfully completed the mapping of entire population and identified vulnerable individuals. Those individuals at higher risk of developing TB [Contacts, Individuals with diabetes, chronic smokers, chronic respiratory diseases etc.] were visited once in three weeks by ASHAs [community health volunteers] However districts like Kottayam, Pathanamthitta and Alleppey data was lost due to the floods and it has to be redone again.

3.1.2. *Sputum collection & transportation*

Sputum collection and transportation to nearest Microscopy centres or Universal Drug Susceptibility Testing (UDST) labs existed in all districts. The specimens were collected at Primary Health Centres and transported. It was interesting to note that, different districts utilized different mechanisms for sputum collection and transportation in order to reach the unreached. Specimen collection and transportation system minimises patient inconveniences, reduces out of pocket expenses and also prevent chance of airborne transmissions. It also ensures that testing happens among whom was identified as presumptive TB.

"In Wayanad, the ASHA's use a screening questionnaire and sputum is collected from those at risk and they transport it to the hospital. If the number of sputum samples is collected, JHIs cross check in the field by carrying out home visits." — TB Health visitor.

"The ambulance drivers and bus drivers support us in transporting the sputum samples to the district lab." — Treatment organizer from Idukki.

"A Whats App group has been formed and details of the place of sputum collection are posted in it. Based on these information, Kuddumbashree volunteers [women self-help group members] collect the sputum samples and drop them at the lab. Payment for them is paid from the revised national TB control programme (RNTCP) funds." — STEPS's coordinator from Thrissur.

While, in Kottayam district the bystanders of the patients brought the sputum sample for testing and the cost of transportation was reimbursed from RNTCP funds. In Ernakulam an integrated specimen collection transportation system exists in a hub and spoke model with two dedicated vehicles visiting institutions at fixed time to carry samples to district hubs. Indian Medical Association provided the necessary facilities for sputum collection & transportation from all private hospitals based on an NGO public -private partnership (PPP) scheme.

In short, districts have a locally customised plan for specimen collection and transportation.

3.1.3. *Access to Chest Xray*

Through a special order by state government all X rays for TB diagnosis are free at government hospitals. Also, an additional fund has been sanctioned by the state government for reimbursing x ray cost at Rs 200 per Xray for any patient taking Xray for TB diagnosis.

"Chest Xray is being outsourced to 8 private hospitals in Kollam city at a subsidized prize. Patients can take Xray from any of these hospitals with the referral slip, the program reimburses it." — TB Health visitor.

3.2. *Support services provided after diagnosis of TB*

3.2.1. *Creation of TSGs*

Few districts like Pathanamthitta, Kozhikode, Kannur, Kollam and Trissur have developed a system of TSGs for aiding a smooth transition through the treatment phase for the TB patients. TSGs are non-statutory body of socially responsible citizens and volunteers to provide social support to each needy TB patient safeguarding his dignity and confidentiality by ensuring access to information, free and quality services and social welfare programs, empowering the patient for making decision to complete the treatment successfully. The group is usually chaired by the president of Gram Panchayat (the lowest tier local self-government), its health standing committee chairperson or a local opinion leader. Members of the group are the Medical Officer [MO], multipurpose health worker (MPHW), community directly observed treatment (DOT) provider, experienced informal counsellors, community based or faith-based organization [FBO] members, Janamaithri police (citizen-friendly police), local philanthropists and other community volunteers. The needy patients are provided additional support by TSG, the need being assessed by the MO, MPHW or DOT provider. TSG links the patient to social welfare schemes, nutritional support project, Alcohol de-addiction or local benevolence. For example, a patient needs transportation support to go to DOT centre, a community volunteer or taxi driver may pick and drop him free of cost, or a local philanthropist may pay for the service. A patient tends to interrupt treatment would be counselled by the counsellor member. Emotional and spiritual support would be provided by the FBO member. This support on occasions has provided shelters to homeless TB patients, attendant service at hospital indoors and provision of resources to manage comorbidities such as diabetes and cardiovascular diseases.

Some districts like Kottayam, Palakkad, Idukki, Trivandrum did not have TSGs and they felt no need for it since the healthcare system was strong by itself.

3.2.2. *Transportation support*

Provision of transportation allowance was initiated for the first time in Pathanamthitta district, where TSG came forward with necessary fund for assisting people to come to the hospitals for treatment. In Palakkad and Ernakulam, the long-

distance patients are being endorsed with travel allowance. While in Wayanad districts, since a lot of tribal live in this area and the geographic terrain is quite difficult to reach hospitals, the TB patients are given additional Rs 500/per month as travel allowance for their twice monthly visits. This intervention was found to ensure treatment adherence.

"In Trivandrum, we have a system of strong Primary Health Centres with all necessary facilities nearby everywhere and there is no need for travel assistance." – TB health Visitor

3.2.3. Nutritional supplementation

The nutritional supplementation for TB patients varied across different districts. In some districts, the nutritional supplementation program was only for MDR TB patients and kits are provided to them during every month of treatment. In many districts nutritional kits consisting of mostly cereals & pulses along with oil are being provided from the supplyco [agency with government subsidy] either to the needy patient's home directly or to the TB centre from where patients pick up them up. These kits were provided either by the funding of the Panchayats [Local Self Government] or Philanthropists or NGOs. It was observed that some districts provided nutritional supplements only during special occasions such as Onam, Christmas, Ramzan, world TB day or during floods. Kits consisting of 5 kg rice, 5 kg pulses, oil, jaggery were given.

"In our district Ernakulam, we provide cooked meal in certain centres to TB patients coming for treatment and this was by contributions made by good citizens who are NRIs." – Ernakulam Treatment organizer.

"There are many tribal people on our district. They are unable to go to work due to TB and hence most of them starve. So, we utilize the tribal welfare funds and provide food kits through the Supply Co" – TB Health visitor of Wayanad.

It was observed that each district devised their own ways to provide nutritional support to TB patients. While, Calicut district got support from NGOs, the healthcare workers of Alleppey went out of their way and used their personal contacts to raise funds for providing food kits to TB patients. NGOs and rotary club also supported them in this venture. The system was not uniform access.

3.2.4. Support for tobacco & alcohol addictions

It was observed that in all districts, tobacco cessation clinics and counselling sessions were underway for patients who were started on Anti TB drugs. Prior to the start of the treatment they were counselled not to smoke or quit smoking if they were. This service was provided by medical officers, treatment organizers, STSs and STOs. However, some stated that this was done only for male patients who had a high probability of being smokers.

With regard to alcohol addictions, all patients are strictly warned against using alcohol while taking treatment. In districts like Calicut, Kasaragod, Ernakulam, Trivandrum, Idukki & Malappuram government de-addiction centres are present and severely addicted patients are send there. While, in the rest of the districts like Kottayam, Palakkad and others do not have de-addiction clinics and they are referred to private centres.

"One major problem that we face is that most patients refuse to admit that they are addicted to alcohol and we do not have government de-addiction centres in all districts …" – TB treatment organizer.

3.2.5. Pension schemes

TB patients with an income limit of less than Rs1Lakh were provided with Rs 1000/month till completion of treatment and an additional amount of Rs 500/month was given for nutritional supplementation as part of Nikshay Poshan Yojana. It was observed that these funds were reaching the patients directly through their bank accounts. However, certain delays in fund transfer have been observed. One of the concerns raised by some participants was that if a patient discontinued or delayed seeking treatment after diagnosis, they were missing out the pension for those months and if treatment was extended, some did not get pension for the extended months. However, this was not the case in all districts.

"Most of the tribal TB patients do not have an ID card or bank account. We then make arrangements to get them an ID card and open an account for them. Even though it's a lot of work, it's the only way and this way we also get their documentation done. Since it's a tribal district they get an additional Rs 500/- as travel support for visiting the doctor twice a month…. " – Treatment organizer from Wayanad district.

When asked whether direct transfer of funds or direct provision of nutrition kits was a better option, there was a mixed response regarding it.

"I don't approve of the direct fund transfer, the elderly don't know how to use their ATM cards… at the end the money ends up with their kids or grandchildren…." – Senior treatment supervisor.

"My family members used to feel happy when I used to bring food kits home. They usually used to give it during festival times … so it feels good that I am also bringing something home too…" – TB survivor.

Either way be it food or nutrition support patients were happy to receive both.

3.2.6. TB survivor program

A new initiative of utilizing TB survivors for creating awareness and providing support to TB patients have been set up at all districts. All participants stated that this program received good acceptance from all the districts.

"Most of us feel that this program will reduce the burden of the STS Officers. Even though it's not 100% effective, we believe that the TB survivors will have a greater acceptance from the patients rather by us. We believe it will definitely create a positive impact." – TB STS.

3.2.7. Fortnightly clinical review

Every TB patient is reviewed every fortnight by a medical officer in Primary Health Centre, at sub centre clinics or at houses. All visits are documented. This system has been established to identify and manage comorbidity as most of the TB patients have some co-morbidity including diabetes, hypertension etc. The system also proactively looks for adverse drug reactions by examining vision and offering free Liver function tests.

3.3. *Prevention of transmission of TB*

3.3.1. Implementation of cough corners, fast tracking

In order to prevent transmission of air borne diseases, patients suffering from TB and other pulmonary diseases are identified and fast tracked at the hospital registration desk itself. Special patient ID cards are given to such patients to decrease their waiting time for consultation, investigations and also at the pharmacy. Separate cough corners are implemented where the patient is provided with Airborne Infection Control (AIC) kits consisting of masks, disinfectants and information education and communication (IEC) materials. Patients requiring inpatient services are kept in isolation ward in order to prevent spread to others.

> *"yes…. we have provided all the education materials required to implement cough corner in private hospitals and I should say some of the private hospitals are functioning very well, much better than the government system" – Treatment organizer.*

> *"In our district, we have implemented cough corners in primary healthcare center (PHC) with the help of the ASHA's. They take turns each week to stay back at the out patient department (OPD) to run the cough corners. They give health education to the waiting patients, identity presumptive TB and send them directly for investigation. They also facilitate in fast tracking the suspected patients by making them jump the queue for doctor's consultation, pharmacy and labs. They will then continue to educate the people in the community" – Senior treatment supervisor.*

> *"We are made to feel like a VIP. Having TB is no longer a stigma at the health centres. We do not have to wait in queue to meet the doctor or for taking x ray…" – Current TB patient.*

> *"Implementing fast tracking in the private sector is a challenge…. we need the support of the administration. Moreover, during the fever season, fast tracking becomes nearly impossible because a lot of patients present with the same symptoms and giving preference to some would be difficult especially in the private sector." – STEPS Coordinator.*

The Government of Kerala has issued a notice directing all hospitals to follow air borne infection control practices. Participants stated that hospitals were all trying their best to implement the AIC however; they faced problems regarding the maintenance of appropriate ventilation practices due to infrastructure. Most hospitals were conducting training sessions for their staff and awareness sessions for their patients regarding AIC practices on a regular basis.

> *"maintaining appropriate ventilation practices in most hospitals is a challenge due to infrastructural changes that are required…. also the use of AC in this humid climate within in the OPDs …. .hence, most often AIC practices are limited to maintenance of cross ventilation in OPDs and supplying AIC kits to patients…" – STEPS Coordinator.*

3.3.1.1. 'Airborne Infection control Kits' and 'Handkerchief Revolution'. Airborne Infection control kits are being provided to all diagnosed TB patient. It consists of 5 washable reusable clothed mask, plastic spittoon for collecting sputum, disinfectant solution and education material on how to use it. This helps the TB patient to practise respiratory hygiene at home and prevent the disease to others.

Behaviour change communication for respiratory hygiene campaign titled 'handkerchief Revolution' happened in all districts by educating school children.

> *"I think the 'Thoovala Viplavam' or 'handkerchief revolution' campaign was carried out in all districts. The campaign was used to enlighten the general public on use of handkerchief as a hygiene and preventive measure for TB." – STEPS Coordinator.*

It was interesting to note that almost in every district it was linked with schools, highlighting the necessity of inculcating good habits since childhood. In some district's sponsorship from private firms and NGOs' had been observed. In Kottayam district, it was funded by a business tycoon and the program was conducted at a Mall which was a favourite spot for most people in the district.

3.3.2. Other initiatives

3.3.2.1. Stigma reduction & advocacy initiatives. TB Survivor's network came out as a stigma reduction initiative. Also maintaining confidentiality of TB patient is of prime concern to health care providers. Many TSGs provide service without knowing to whom the services are going to.

All districts were found to use creative measures to spread awareness and some of them were as follows:

> *"Since most people use autorickshaws as a medium of transport, posters containing health information regarding TB such as its signs, symptoms, diagnosis and treatment options of TB are displayed on them." – TB health visitor.*

Most participants stated that this method was found to be quite effective since, it provided a quick briefing regarding TB. However, its sustainability was quite unsure for most.

> *"We routinely give health education in schools, children are the best ambassadors. We, also train anganwadi so that they can create awareness in the community. In addition, we also train Kuddumbashree and mahatma gandhi employment guarantee act (MGNREGA) members" – Kannur Senior TB Laboratory supervisors.*

3.3.2.2. *Migrant support measures*. It was observed that some of the districts had their own innovative measures for supporting migrants.

> *"We have the 'Unite for Healthy Ernakulam' initiative where we use Kuddumbashree workers for community mobilization for TB control. Under this initiative, we regularly screen the migrants for TB under the 'Atithi Devo Bhava' campaign. We have also trained migrant link workers on TB and sensitised construction site owners to support anybody with TB" — Ernakulam senior treatment supervisor (STS).*

3.4. *Support services provided by the private sector*

3.4.1. *STEPS implementation*

STEPS evolved as a solution for ensuring Standards of TB Care in India (STCI) in a patient centric way for all patients reaching private sector. STEPS is envisioned as collective efforts by public and private sector for the benefit of society. STEPS Centre are a single window for notification, linkage for public health actions and treatment adherence support inside every private hospital. A central person (STEPS lead), nominated by the private hospital management and contact persons (STEPS link) in each in-house department work in a hub and spoke model. Functioning on STEPS centres are grounded on an 'after sales service model' based on self-initiated business promotion and customer loyalty, blended with the social responsibility of private sector. NTP extends customised support to each private hospital based on their demand. Specimen collection system, medicines for TB patients, AIC Kits are made available for free of cost at private hospitals.

> *"STEPS are being implemented in all districts. There are nearly 200 centres set up across different private hospitals, but if you asks about the effectiveness I must say, there is a variation from each hospital. But, it is effectively happening in all major hospitals." — Senior treatment supervisor.*

It was observed that STEPS was implemented in selected private hospitals across all districts which were having high TB patient load. Most of the participants stated that all the hospitals that they approached cooperated with them and were interested in being a part of the program. Staff nurse of private hospital follows up every TB patient diagnosed in their hospital every fortnight to ensure adherence, adverse drug reaction (ADR) and remind about next scheduled visit. If there is any interruption, local STS is informed. However, they felt that uniformity and program effectiveness varied widely between the hospitals.

3.4.2. *Linkages with the private sector*

One unique feature reported by all districts is the good linkages that have been implemented between the government and private sectors. This has enabled patients to avail free treatment from private sectors and notification of cases to the government sector. The private sector doctors are also being involved in the planning of the district activities.

> *"In Kasaragod district, the IMA was involved. IMA established a specimen collection system connecting all private hospital. Also IMA trained all doctors on STCI. STEPS ensured that there is a single window mechanism at all hospitals. Patient can go to any hospital of his/her choice. All services including our medicines are available in all hospitals." —Treatment organizer.*

4. Discussion

It was observed that under the national tuberculosis elimination program (NTEP) program, different TB support services were being provided across all the 14 districts of Kerala. Each of these initiatives were found to be unique in their own way for bridging the gaps in the in the continuum of care provided for TB patients. A wide range of support initiatives were found to facilitate early diagnosis, adherence to treatment, nutritional supplementation, transportation, social security measures, public private partnership initiatives, awareness and advocacy measures. However, these supportive measures were found not to be uniform throughout all districts. Some of these districts were found to have made up initiatives very innovatively based on their available resources. These supportive services were found to be in line with WHO ENGAGE TB programs for the integration of community-based TB activities into the work of NGOs and other Civil Society Organizations. Locally customised solutions for support by the districts are to be appreciated. Most of these initiatives were over and above the usual guidelines by the program. However the lack of standardized implementation of community-based TB activities, lack of appropriate indicators and difficulties in measuring the outcomes are all shortcomings of these support initiatives.[7]

Kerala shows that resources are available in the community in many forms. On the other side TB patients have many needs. And when the proactive health care providers decided to address the needs of the TB patients with the resources in the community, many patient support systems emerged. Most of the systems emerged as solutions from the grass root level and once found to be successful, got scaled up too many districts. It is observed that the health care providers and program managers went out of the way and outside the guidelines in search for support for TB patients.

Patient support is complex, more so in program settings. Kerala shows that it remains so only in the absence of high social commitment. Social support for TB care is no more a dream. It is a reality feasible under routine program conditions. Social inclusion is included in STCI. Its meaning is translated well by an empowered society.

The STEPS program was found to be implemented in selected hospitals of every district. This program was launched as part of Kerala Tuberculosis Elimination Mission. These STEPS centres are launched in association with JEET (Joint Effort for Elimination of TB) and NTEP. The aims of these centres are to extend the support systems to patients reaching the private sector also[8] This initiative was found to be

effective, however it has a long way to go for its complete implementation in the state.

In this study, we observed that implementation of AIC strategies in the hospitals were found to be difficult mostly due to infrastructural problems. Pre-existing infrastructure was also found to be an hindrance for making modifications suitable for appropriate AIC practices. Also it required a high commitment from the side of the hospital administrators. This finding was found to be similar to the situation in Karnataka where hospitals were found to have an unsatisfactory compliance to AIC guidelines. This was due to the lack of ownership and poor coordination between programme and hospital authorities.[9]

Nutritional supplementation was found to be crucial for the elimination of TB, however, ensuring sustainability of nutritional support was a major challenge faced by all districts. The guidance document by the central TB division regarding nutritional care and support for TB patients highlights the problem of under nutrition as a serious comorbidity of TB patients in India. It is stated to increase the risk of severe disease, relapse, mortality, drug toxicity and mal absorption.[10]

Under the NTEP, the health ministry has proposed direct benefit transfer to TB-affected families, to support them for provision of nutritious food.[11] These social protection schemes were found to be really good initiatives however fund shortages, lack of proper docu for starting bank accounts and lack of knowledge about e-commerce were all identified as major barriers.

The study observed that several agencies were actively involved in the delivery of these supportive measures such as Local Self Governments, ASHAs, Kudumbashree members, MGNREGA members, civil societies, Philanthropists, professional bodies, public and private agencies. This highlights the fact that these programs have a high community ownership even though it was not found to be uniform throughout the state. Moreover, studies in the past have also highlighted that women empowerment groups like Kudumbashree and MGNREGA have played a crucial role in increasing awareness among the general public as well.[12] The National Strategic plan for TB elimination in India 2017–2025 has identified community ownership to be the corner stone for TB elimination.[3] If first step in TB elimination is eliminating the burden due to TB for the patient, then Kerala shows that it could be achieved through community ownerships, proactive health system and high-level political commitments.

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Declaration of competing interest

The authors have none to declare.

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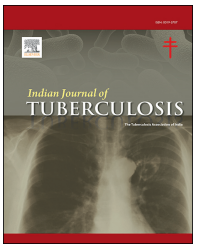

Original article

Transbronchial lung cryobiopsy by twin bronchoscopes (kissing technique)

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ABSTRACT

Objective: To introduce a new & novel method of obtaining big lung tissue samples by transbronchial lung cryobiopsy by twin bronchoscopes (kissing technique) in an advanced interventional pulmonology suite.

Methods: In patients of diffuse parenchymal lung diseases, transbronchial lung cryobiopsy were taken using this novel approach using simultaneously two bronchoscopes under C-arm guidance under conscious sedation. First, a standard fibreoptic bronchoscope was inserted intranasally and fixed just above the area to be biopsied, then fogarty's catheter was introduced through FOB's suction channel and protruded it at the biopsy site. Second, another video bronchoscope was introduced orally by the side of FOB and cryobiopsy were taken using cryobiopsy forceps. Immediately, Fogarty's catheter was inflated and sealed the opening from where biopsy was taken to stop the bleeding. Third Video bronchoscope was also used which went up to larynx to take photograph of two bronchoscopes kissing each other and entering the vocal cords only, after which it was withdrawn.

Results: Transbronchial lung cryobiopsy in patients of diffuse parenchymal lung diseases were taken using this novel approach. This new technique called twin bronchoscopy (Kissing technique) has been practiced for the first time, it's a technique about which we want the world to be known.

Conclusion: This new and novel two scope kissing bronchoscopy technique for TBLC under conscious sedation can be an alternative and fruitful method, especially the use of Fogarty's catheter to contain intra-bronchial bleeding. There is no deleterious effect on the patient and the patient can be discharged on the same day.

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1. Introduction

Transbronchial lung biopsy is common procedure performed in patients of Diffuse Pulmonary Lung Disease (DPLD). In patients of DPLD, a good and big tissue sample is always needed for definitive tissue diagnosis & treatment, and standard TBLB (Trans-bronchial Lung Biopsy) forceps yields much smaller samples.[1] Recently, the uses of cryoprobe is gaining acceptance where we are able to achieve adequate tissue to see the histo-pathological patterns.[2] The mean surface area of the biopsy sample is much bigger with cryoprobes as compared to standard TBLB.[3] Also, the cryoprobe biopsy samples are artifact-free & contain higher percentage of alveolated areas.[3,4] But, on the other hand, there is definite risk of bleeding and pneumothorax when we use transbronchial cryoprobes for biopsy.[5] To over-come these road-blocks, we have attempted a new & novel method of obtaining big lung tissue samples by transbronchial lung cryobiopsy by twin bronchoscopes (kissing technique) in an advanced interventional pulmonology suite where all the facil-ities are available to tackle any untoward incident.

2. Methodology

2.1. Equipments

The equipments used are:

- Cryo Machine - 1
- Cryoprobe 1–90 cm × 1.9 mm
- Normal FOB - 1 (PE-2 (Olympus) with outer diameter 4.2 mm & inner channel 2.2 mm
- Video bronchoscopes - 2
  - 1 video bronchoscope (T-150) with outer diameter 5.8 mm & inner channel 2.8 mm
  - Another similar video bronchoscope, only to take picture of two bronchoscopes kissing & entering through the vocal cords
- Fogarty's catheters - 2 (85 cm × 5 mm, to be filled with 1.5 ml of air)

2.2. Bronchoscopy suite

Our bronchoscopy suite is well equipped with all types of monitors, Boyle's apparatus, bag & mask ventilation, central O_2 & suction lines, ETT tubes and Rigid bronchoscope.

2.3. Procedure

The patient was given conscious sedation with midazolam & fentanyl. After taking all standard precautions, first, we inserted a standard FOB (Fibre-Optic Bronchoscope, outer diameter 4.2 mm, channel diameter 2.2 mm) intranasally & reached just above the area from where biopsy has to be taken; this site was determined pre-operatively by chest X-ray and CT scans. Then, we inserted a Fogarty's catheter through FOB's suction channel and protruded it at the biopsy site. The Fogarty's catheter was checked beforehand for any leaks. Now, we applied our novel approach and inserted another video-bronchoscope (VOB, outer diameter 5.8 mm, channel diameter 2.8 mm) by oral route through the bite-block and slipped it through the vocal cords by the side of the FOB (Fig. 1). Cryoprobe was inserted through the VOB channel, it was for-warded under the C-arm and when we were away from the pleura by 10–20 mm, we stopped and took the biopsy samples (Fig. 2), thus avoiding pneumothorax. The cryoprobe operates on Joule - Thompson effect where the compressed gas is released at high flow rate & upon expansion, it creates very low temperatures by latent heat of evaporation. The cooling agent used was N_2O (Nitrous Oxide) and the temperature rapidly dropped to −88 °C (Erbokryo CA; ERBE, Tubingero, Germany) as it is known that core tissue temperature must be rapidly reduced; and freezing of cells to −40 °C or below is associated with 90% cell death. The cryoprobe was cooled for 5 seconds & then both, cryoprobe and the VOB were withdrawn as a single unit. Immediately, we inflated the Fogarty's cath-eter (Fig. 3) and sealed the opening from where the biopsy was taken. After 3 minutes, we deflated the Fogarty's catheter & checked for the bleeding, if some bleeding was present, we instilled iced saline or Adrenaline with Xylocaine solution. After witnessing cessation of oozing, we repeated the pro-cedure in the same lobe but different segment and took a total of 3 specimens. The frozen biopsy tissue was thawed in saline (Fig. 4) & then transferred to formalin solution. Chest X-Ray was obtained 3 hours after the procedure. We did not observe any appreciable bleeding or pneumothorax.

We used third VOB and went up to larynx to take photo-graph of two bronchoscopes kissing each other and entering the vocal cords only, after which it was withdrawn.

Throughout the procedure, all the vital parameters were monitored and SpO_2 was not allowed to fall <94%, which was ensured by nasal cannula/face mask.

3. Discussion

There are no major limitations of this procedure using 2 bronchoscopes, one intra-nasally & one through the oral

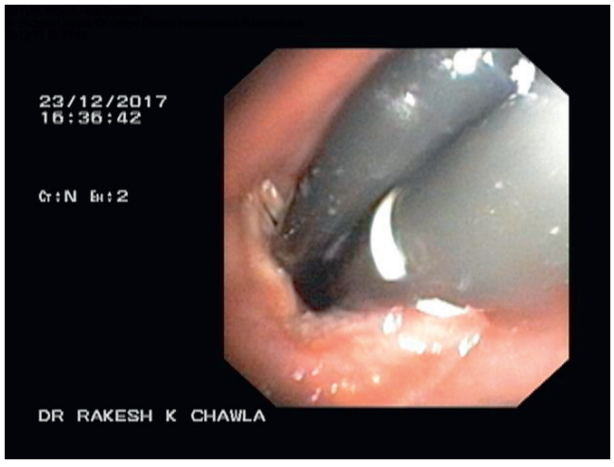

Fig. 1 – Both scopes kissing & entering through vocal cords.

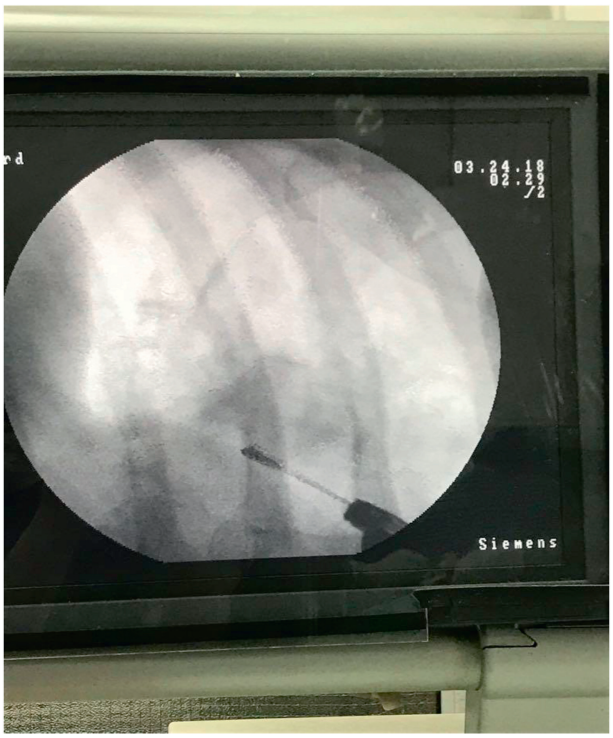

Fig. 2 – Cryobiopsy Forceps navigated with C-Arm.

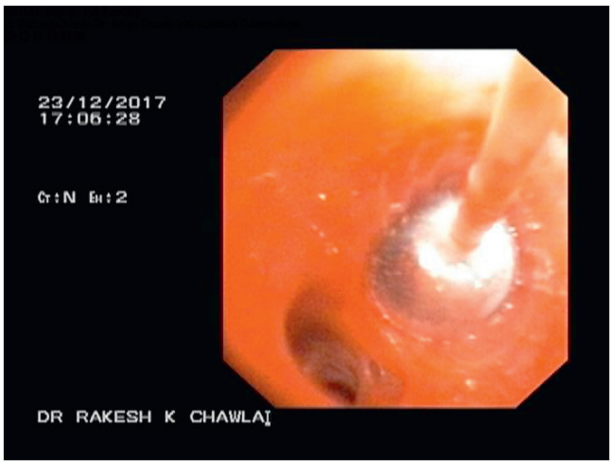

Fig. 3 – Inflated Fogarty's catheter.

cavity. We have utilized the intra-nasal FOB for inserting the Fogarty's Catheter and the oral video-bronchoscope for Cryoprobe biopsy. Theoretically, we can expect the patient to go into hypoxia, but as we experienced, there were no hypoxic events. As a precaution, the FIO_2 was kept higher and SpO_2 was maintained between 94 and 98%.

We did not experience any pneumothorax as the cryobiopsies were taken 10–20 mm away from the pleura, under the C-arm guidance, as has been tried before.[6]

There is high yield of diagnosis when cryoprobe biopsy samples are compared with standard TBLB. In a recent meta-analysis of seven studies, Johannson et al, 2016[7] have reported a diagnostic yield of 74% and 98%, with a pooled estimate of

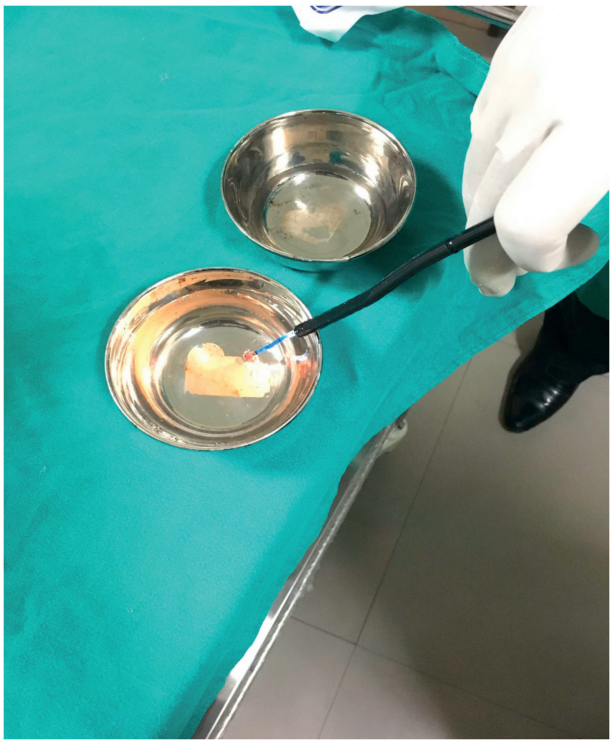

Fig. 4 – Extracted cryobiopsy specimen.

83% [95% CI, 73–94]. A definitive diagnosis was achieved in 85.1% of patients allocated to conventional TBLB compared with 95.0% who underwent cryobiopsy ($p < 0.001$).[8] Not only that, there were no differences in the incidence of significant bleeding.[8] It has been postulated that the freezing effect of the cryoprobe clots & coagulates the small vessels ruptured during the process of biopsy, thereby reducing the risk of significant bleeding.[3]

Pneumothorax is the most common complication of cryobiopsies, reported incidence rates vary from 0% to 30%.[7,9] However, there was no incidence of pneumothorax in our patient.

Intrabronchial bleeding is a relatively frequent side effect of TBLC but is usually kept under control when a Fogarty catheter is used.[7] We accomplished the same feat but with a different approach, we used the Fogarty catheter through intra-nasal FOB. Poletti et al, 2015[10] are also of the opinion that bleeding complications are significantly reduced when a Fogarty catheter is used.

However, we would like to point out that this modality must be attempted only in relatively stable patients and be performed by operators experienced in performing transbronchial lung cryobiopsies (TBLC). Also, the bronchoscopy suite should be equipped with all available facilities for handling the airway and to contain any contingency.

4. Conclusion

2-scope kissing bronchoscopy technique for TBLC under conscious sedation can be an alternative and fruitful method,

especially the use Fogarty's catheter to contain intra-bronchial bleeding. There is no deleterious effect on the patient and the patient can be discharged on the same day.

Conflicts of interest

The authors have none to declare.

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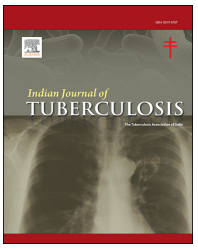

Original Article

Predictors of success and failure of non-invasive ventilation use in type-2 respiratory failure

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ABSTRACT

Background: Non-invasive ventilation is widely used now a days in patients with hypercapnic respiratory failure. Non-invasive ventilation can be used in Intensive Care Unit setting and wards provided trained staff is there to monitor.

Methods: This was a prospective observational study of 100 adult patients who were admitted with hypercapnic respiratory failure. Demographic information such as Age, Sex were recorded. Clinical parameters like Respiratory Rate, Heart Rate, Oxygen saturation and Arterial Blood Gas variables like pH, $PaCO_2$, HCO_3 were measured at the time of admission and at 1st hour, 4 hours and 24 hours after start of non-invasive ventilation. Outcome was recorded as success and failure with Non invasive ventilation.

Results: Out of 100 patients, 76 (76%) managed successfully with non-invasive ventilation and 24 patients (24%) needed intubation and invasive mechanical ventilation in this study. Majority of patients (76%) were with clinical diagnosis of Chronic Obstructive Pulmonary Disease. Respiratory Rate and Heart Rate were significantly lower and showed significant improvement at 1st hour, 4 hours and 24 hours in patients who successfully improved with Non invasive ventilation. Oxygen saturation was found to be significantly higher among patients successfully managed with Non invasive ventilation (84.35 ± 8.55 vs 76.87 ± 7.33) as compared to patients who required intubation. pH was found to be significantly higher (7.28 ± 0.06 vs 7.23 ± 0.05) in patients showing good response to Non invasive ventilation and improvement in pH at 1st hour, 4 hours and 24 hours was observed in patients successfully managed with Non invasive ventilation. $PaCO_2$ level was found to be significantly lower and significant improvement in $PaCO_2$ at 1st hour, 4 hours and 24 hours was seen in patients with Non invasive ventilation success.

Conclusion: Improvement in clinical parameters like respiratory rate, heart rate, Oxygen saturation and improvement in ABG variables like pH, PaCO2 after 1st and 4 hours of start of Non invasive ventilation and maintaining the improvement at 24 hours are predictors of success of non-invasive ventilation in hypercapnic patients.

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1. Introduction

Respiratory failure is a condition in which the respiratory system fails in one or both of its gas exchange functions, oxygenation of and/or elimination of carbon dioxide from mixed venous blood.[1] Hypercapnic or type −2 respiratory failure is defined as an arterial partial pressure of carbon dioxide ($PaCO_2$) greater than 45 mm Hg. Acute hypercapnic respiratory failure occurs due to inadequate alveolar ventilation, which is needed to maintain normal arterial oxygen and carbon di-oxide levels.[2]

Patients with hypercapnic respiratory failure, who fail to respond to conventional treatment like broncho-dilators, steroids, antibiotics and controlled oxygen, may be considered for Non Invasive Ventilation (NIV) or for endotracheal intubation and mechanical ventilation.[3]

Invasive mechanical ventilation is commonly employed in our intensive care units but NIPPV(Non Invasive Positive Pressure Ventilation) is used increasingly in patients with acute and chronic respiratory failure in recent years, due to its convenience, lower cost.[4]

Mechanical ventilators provide warmed and humidified gases to airways with specific volume pressure and time patterns. The ventilator serves as energy source for inspiration, replaces the muscles of chest wall and diaphragm.[5] Non-invasive ventilation is providing ventilatory support through upper airway of patient with some interface like face mask, nasal mask, nasal pillow by decreasing work of breathing and providing ventilation. Non-invasive ventilation increases alveolar ventilation without an artificial airway. Non-invasive ventilation can be used continuously as well as intermittently (see Tables 1–3).

Non-invasive ventilation in the management of acute type II respiratory failure patients represents one of the major technical advance in respiratory care over last decades.[6] Various studies have shown effectiveness of non-invasive ventilation in management of acute respiratory failure,[7–9] like in pneumonia, pulmonary edema and chronic[10–12] respiratory failure like neuromuscular disorder, abnormality of rib cage and chest wall, chronic obstruction of upper airway and central alveolar hypoventilation.

However now a days NIV is preferred over endotracheal intubation and invasive mechanical ventilation. Patient selection is important deciding factor in success of non-invasive ventilation. Various contraindications should be kept in mind while starting patient on NIV.

Patient should be monitored closely for signs of noninvasive ventilation failure like change in sensorium, increasing respiratory rate, not maintaining SpO_2(Oxygen Saturation), deterioration in parameters of ABG (Arterial Blood Gas) analysis and must be promptly intubated before a crisis develops. The application of NIV by trained intensive care unit team, with careful patient selection, should optimize patient outcomes.[13]

Table 2 – Results of multivariate logistic regression model of study variables (Clinical parameters and ABG variables).

Variables	Adjusted Odds ratio	95%CI		p-value
		Lower	Upper	
RR	0.86	0.78	0.96	0.008[a]
HR	0.90	0.83	0.97	0.005[a]
SpO_2	0.98	0.91	1.06	0.70
$PaCO_2$	0.96	0.90	1.02	0.22
PaO2	0.94	0.88	1.01	0.06
HCO_3	1.13	0.97	1.33	0.10

CI-Confidence interval
[a] Significant.

Table 1 – Clinical parameters and ABG variables associated with success and failure of NIV.

Variables		NIV Successmean ± SD/%	NIV failuremean ± SD/%	p- value
Age		64.99 ± 11.49	67.00 ± 9.78	0.44
RR	At Admission	30.83 ± 6.13	39.52 ± 4.14	0.0001*
	1 Hour	24.25 ± 3.30	36.10 ± 4.74	0.0001*
	4 Hours	21.28 ± 2.85	32.67 ± 4.61	0.0001*
	24 hours	19.29 ± 1.98	0.00 ± 0.00	
HR	At admission	114.43 ± 12.77	129.78 ± 7.79	0.0001*
	After 1 hour	97.60 ± 12.57	124.90 ± 7.96	0.0001*
	After 4 hours	88.34 ± 11.03	125.33 ± 4.61	0.0001*
	After 24 hours	83.26 ± 9.70	0.00 ± 0.00	–
SpO_2	At admission	84.35 ± 8.55	76.87 ± 7.33	0.0001*
	After 1 hour	91.03 ± 3.28	83.57 ± 2.89	0.0001*
	After 4 hours	93.36 ± 3.42	84.00 ± 7.21	0.0001*
	After 24 hours	94.41 ± 3.99	0.00 ± 0.00	–
pH	At admission	7.28 ± 0.06	7.23 ± 0.05	0.001*
	After 1 hour	7.35 ± 0.07	7.13 ± 0.10	0.0001*
	After 4 hours	7.37 ± 0.07	7.08 ± 0.05	0.0001*
	After 24 hours	7.39 ± 0.05	0.00 ± 0.00	–
$PaCO_2$	At admission	72.01 ± 13.41	75.39 ± 15.87	0.03*
	After 1 hour	65.12 ± 12.78	80.33 ± 16.80	0.0001*
	After 4 hours	61.45 ± 14.27	97.50 ± 20.35	0.0001*
	After 24 hours	56.84 ± 13.73	0.00 ± 0.00	–

Table 3 – Distribution of patients with different underlying diseases enrolled in the study.

Sr No.	Diagnosis	No. of patients
1	COPD with acute exacerbation	77
2	Bronchial Asthma with acute exacerbation	8
3	Obstructive Sleep Apnoea	6
4	Interstitial Lung Disease with acute exacerbation	3
5	Viral Pneumonia	3
6	Bronchiectasis	3

Determination of predictors of success and failure of non-invasive ventilation is important in choosing patients to be managed with NIV.

Patients who respond well to non-invasive ventilation are managed with non-invasive ventilation and discharged after improvement. Bi-PAP(Bilevel Positive Airway Pressure) device is advised at home if needed. Rest of the patients who deteriorate with non-invasive ventilation can be intubated and put on invasive ventilator support early. This decreases the mortality and morbidity associated with delay in putting the patients on invasive mechanical ventilation.

2. Material and methods

A prospective, observational study conducted from January 2017 to November 2018. We enrolled 100 patients fulfilling inclusion-exclusion criteria.

2.1. *Selection criteria-*

2.1.1. *Inclusion criteria*

- ➢ Patients with age over 18 years.
- ➢ Patients able to breathe spontaneously.
- ➢ Patients with respiration rate >24 or tachypnea with signs of increased work of breathing (using accessory muscles or paradoxical breathing).
- ➢ Patients with PaCO2>45 on ABG
- ➢ Patients with pH < 7.35 on ABG

2.1.2. *Exclusion criteria*

- ➢ Patients who are not willing to participate in the study
- ➢ Patients having symptoms suggestive of unstable angina, congestive heart failure, shock, arrhythmias, severe hypoxia and hemodynamically unstable patients.
- ➢ Patients having uncontrolled vomiting.
- ➢ Patients with copious upper Gastrointestinal bleed.
- ➢Patients having total upper airway obstruction.
- ➢ Patients with pH < 7.14 on arterial blood gas analysis
- ➢ Uncooperative, unconcious patients and patients who needed intubation on admission to protect airways.
- ➢ Patients with facial trauma or surgery or anatomical abnormality

2.2. *Data collection techniques and tools*

Among patients admitted in ICUs(Intensive Care Unit) and HDU(High Dependency Unit) of the hospital (where study was conducted), patients who presented with hypercapnic (type-2) respiratory failure, eligible patients fulfilling the inclusion-exclusion criteria were enrolled after consent.

History was recorded on predesigned and pretested proforma. Descriptive data including name, age, sex, height, weight, personal history, past history etc. were recorded. Body mass index (BMI) was calculated according to Quetlet's formula and patients were categorized accordingly. A thorough clinical examination was carried out. Patient's Respiratory Rate, Blood Pressure, Oxygen Saturation were taken at the time of admission. ABG analysis was done at the time of admission before starting of NIV support. Routine investigations were done at the time of admission including chest x-ray. In all patients, NIV was initiated in intensive care units and high dependency unit of hospital with an IPAP of 12cm of H_2O and EPAP of 6cm of H_2O which was gradually adjusted according to patient comfort and ABG analysis.

Patient's respiratory rate, blood pressure, oxygen saturation and ECG were continuously monitored. ABG was repeated after 1 hour, 4 hour and 24 hours of start of NIV. The discontinuation of NIV was based upon clinical judgment and arterial blood gas analysis.

If satisfactory degree of patient comfort, ventilation and oxygenation was not achieved, ABG was repeated in between. Patient was taken for mechanical ventilation, when there was any deterioration.

In this study, we have taken **outcomes** as:

- ➢ NIV success/Not intubated- Treatment with NIV was considered successful if there was decrease in RR (Respiratory rate) to < 24/minute, improvement in tachycardia i.e. HR (Heart Rate) improved to <100/minute, pH became > 7.35 with fall in PaCO2, thereby avoiding endotracheal intubation and mechanical ventilation.
- ➢ NIV failure/Intubated – NIV **failure** was defined as endotracheal intubation and invasive mechanical ventilation after start of NIV or death.

Predictors observed in our study: Age, Gender, Body Mass Index, History of fever, History of previous ICU admission, Comorbidity, Respiration rate, Heart rate, Oxygen saturation, pH, $PaCO_2$, PaO_2, Random Blood Sugar, Serum albumin, Consolidation on chest x-ray.

2.3. *Statistical methods*

Continuous variables are presented as mean ± SD. Categorical variables are expressed as frequencies and percentages. The results are presented in frequencies, percentages and mean ± SD. The Chi-square test was used to compare categorical/dichotomous variables. The Unpaired t-test was used to compare continuous variables. The p-value <0.05 was considered significant. All the analysis was carried out on SPSS 16.0 version (Chicago Inc., USA).

3. Results

Out of 100 patients, 76 (76%) managed successfully with non-invasive ventilation and 24 patients (24%) needed intubation and invasive mechanical ventilation in this study. Majority of patients (76%) were with clinical diagnosis of COPD(Chronic Obstructive Pulmonary Disease) with acute exacerbation with hypercapnic respiratory failure. Mean age was 64.99 years in cases with success of non-invasive ventilation and 67 in cases with failure of non-invasive ventilation.

History of fever at the time of admission was found to be significantly (p value: 0.001) associated with failure of NIV. Success of NIV among patients with history of fever was significantly less (41.7%) compared to patients without history of fever (95.3%).Patients with history of previous ICU admission were found to have more failure (69.2%) compared to without history of previous ICU admission (8.1%) in this study. Patients with associated co-morbidities were found to have less success with NIV (37.1%) compared to patients without co-morbidities (96.9%) in this study. In the study, success of NIV use was 90.5% among normoglycemic patients and 45% among hyperglycemic patients. NIV was successful in 88% patients with normal serum albumin whereas 40% among patients with low serum albumin. Consolidation in chest X-ray was associated with failure of non-invasive ventilation in this study. Success of NIV among patients with consolidation in chest x-ray was 12.5% whereas 88.1% in patients without consolidation. As shown in table- 1, in our study, we found that respiratory rate was significantly (p value:0.0001) lower among patients who were successfully managed with NIV at the time of admission (30.83 ± 6.13) as compared to patients who needed intubation (39.52 ± 4.14) and also after 1 hour, after 4 hours and after 24 hours. In our study, heart rate was found to be significantly lower (114.43 ± 12.77) among the patients of successful non-invasive ventilation use than failure (129.78 ± 7.79) at the time of admission. Also improvement in HR was seen in NIV patients after 1hour (97.60 ± 12.57), 4 hours (88.34 ± 11.03) and 24hours (83.26 ± 9.70) of start of non-invasive ventilatory support. In this study, SpO_2 was found to be significantly ($p = 0.001$) higher among patients successfully managed with NIV (84.35 ± 8.55 vs 76.87 ± 7.33) as compared to patients who required intubation. In our study, we observed that the pH was found to be significantly ($p < 0.01$) higher among the patients of successful non-invasive ventilation use (7.28 ± 0.06 vs 7.23 ± 0.05) than failure and we observed improvement in pH with time in patients with successful NIV. In our study, we observed that $PaCO_2$ was found to be significantly lower among the patients of successful non-invasive ventilation use (72.01 ± 13.41 vs 75.39 ± 15.87) than failure at admission and we observed improvement in $PaCO_2$ with time in patients who were managed successfully with NIV. We found that mean PaCO2 after 1hour (65.12 ± 12.78) and after 24 hours (56.84 ± 13.73) in patients successfully managed with non-invasive ventilation. Table- 2 shows the results of multivariate logistic regression model. The multivariate logistic regression analysis revealed that RR ($p = 0.008$) and HR ($p = 0.005$) were significantly associated with success of non-invasive ventilation use.

The results are presented in frequencies, percentages and mean ± SD. The Chi-square test was used to compare categorical/dichotomous variables. The Unpaired t-test was used to compare continuous variables. The multivariate logistic regression analysis was carried out to find the strength of association. The odds ratio (OR) with its 95% confidence interval (CI) was calculated. The p-value <0.05 was considered significant. All the analysis was carried out on SPSS 16.0 version (Chicago Inc., USA).

4. Discussion

Non – invasive ventilation is ventilation strategy between invasive mechanical ventilation and no ventilator support at all. It is more commonly used in management of Type-2 or hypercapnic Respiratory failure as compared to hypoxemic respiratory failure. Non-invasive ventilation should be considered in patients with acute exacerbation of COPD with respiratory acidosis (pH < 7.35) persisting despite of all possible medical treatment and controlled oxygen inhalation therapy. Patient should be selected appropriately keeping in mind various factors related to success and failure. The selection process involves a number of factors, including the patient's clinical characteristics and risk of failure on NIPPV and finally it becomes a clinical judgement depending largely on physician experience. Predictors of success of NIPPV[14] include a better neurological status, ability to protect the airway, and no more than moderate acid–base or gas exchange derangement. Several studies have also found that improvements in pH, arterial PCO2, and level of consciousness within the first hour or two of NIPPV initiation as strong predictors of success.[14] In our study, maximum patients were of COPD with acute exacerbation with hypercapnic respiratory failure, other underlying diseases seen in our study were Bronchial Asthma with acute exacerbation, Obstructive Sleep Apnoea, Interstitial Lung Disease with acute exacerbation, Viral Pneumonia, Bronchiectasis.

In our study, we found that non-invasive ventilation was successful in 76 cases out of 100 cases (76%) whereas 24 cases out of 100 (24%) were intubated and taken on invasive mechanical ventilation due to derangement in ABG parameters, persistent tachypnea. A similar study conducted by Battacharyyaet al[15] in 2011 to determine early predictors of success of non-invasive positive pressure ventilation in hypercapnic respiratory failure showed that 76% cases had improvement in clinical and ABG parameters with non-invasive positive pressure ventilation even after 24 hours and 24% cases failed to respond to NIPPV. A study by Ashok kumar et al[16] in 2015 showed that in 77.4% cases Non-invasive positive pressure ventilation was successful where as 22.6% cases needed intubation and invasive mechanical ventilation. In a recently published retrospective study on 119 consecutive patients presenting with acute hypercapnic respiratory failure and meeting criteria for NIV use, Salahuddin et al[17] observed that overall survival rate was 76.5%, and intubation rate was 12.6%. Statistically significant improvements were observed in the pH and PCO2 at 24 hours and 48 hours compared to

baseline (7.28 vs 7.37, P < 0.001; 74.2 vs 65, P < 0.001). A serum HCO_3> 35 mEq/L (adjusted odds ratio 0.9; 95% CI 0.83, 0.98,P < 0.015) was found to have identified those patients who were less at risk for intubation. On multivariate regression analysis, sepsis at admission was found to have increased mortality (adjusted odds ratio 26.4; 95% CI 2.3, 304, P < 0.009).

In current study, non-invasive ventilation was successful in 76% patients whereas 24% patients were intubated and taken on invasive mechanical ventilation due to derangement in ABG parameters, persistent tachypnea, tachycardia. The usefulness of the present study lies in management of patient with hypercapnic respiratory failure and it showed that improvement of HR, RR, pH, and PCO_2 at first hour in patients who were put on NIPPV is very likely to be maintained at four and 24 hours. Hence these patients improved over a period of few days and were discharged from the hospital, being put on appropriate medical treatment. On the contrary, patients showing deterioration in HR, RR, pH, and PCO_2 after one and four hours required to be kept under very close observation. They are very likely to require intubation in case of any further deterioration.

It is evident from the current study as well as previous studies discussed that timely initiation on non-invasive ventilation in hypercapnic respiratory failure except contraindicated can prevent endotracheal intubation and mechanical ventilation and hence associated complications.

5. Conclusion

- Out of 100 patients, 76 (76%) managed successfully with non-invasive ventilation and 24 patients (24%) needed intubation and invasive mechanical ventilation in this study.
- Improvement in clinical parameters like respiratory rate, heart rate, SpO2 and improvement in ABG variables like pH, PaCO2 after 1st and 4 hours of start of NIV and maintaining the improvement at 24 hours proved to be predictors of success of non-invasive ventilation in hypercapnic patients in this study.
- In this study, absence of comorbidity, normal BMI and overweight patients, normal RBS, absence of consolidation on chest x-ray showed to be predictors of success of non-invasive ventilation in hypercapnic patients although not statistically significant.
- In this study, history of fever, history of previous ICU admission, presence of comorbidity, low BMI (underweight patients), high respiratory rate (tachypnea), tachycardia, low SPO_2, low pH, high $PaCO_2$, low HCO3 on ABG, low and high RBS, low serum albumin (under nutrition) and consolidation on chest x-ray showed to be predictors for failure of non-invasive ventilation in hypercapnic patients. So, these factors should be kept in mind while deciding ventilator support in such patients.

Conflicts of interest

The authors have none to declare.

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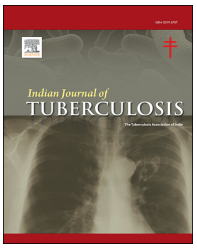

Original Article

A study of multidrug resistant tuberculosis among symptomatic household contacts of MDR-TB patients

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ABSTRACT

Background: Diagnosis and management of multidrug-resistant tuberculosis (MDR-TB) remains a global challenge and is associated with high morbidity and mortality. Burden of TB among symptomatic household contacts of MDR-TB is not extensively studied and screening of symptomatic contacts may provide a better opportunity for optimum management and effective TB control.

Methods: This prospective observational study was conducted in the department of Tuberculosis & Chest diseases, S.N. Medical College, Agra from February 2016 to January 2018. The study recruited 271 symptomatic household contacts of 87 index MDR-TB cases. Symptomatic contacts were screened for active disease and latent TB infection. Risk factors for the spread of disease were also looked for.

Results: Out of 271 symptomatic household contacts, 97 (35.79%) had active TB. Among 97 diseased, 62 (22.87%) had MDR-TB and 35 (12.91%) had drug-susceptible TB. 124 contacts (45%) had latent TB infection. Risk factors associated with occurrence of TB included age less than 18 years (OR = 7160, p = 0.1908, RR = 0.8082, p = 0.1887), male sex (OR = 2.3108, p = 0.0021, RR = 1.7444, p = 0.0034), Sibling as index case (OR = 0.6404, p = 0.0804, RR = 0.7520, p = 0.0806), lack of BCG vaccination (OR = 1.7763, p = 0.0271, RR = 1.4338, p = 0.0247) malnutrition (OR = 1.8980, p = 0.0138, RR = 1.5166, p = 0.0159) and lower socioeconomic status (OR = 3.2399, p < 0.0001, RR = 2.1524, p < 0.0001).

Conclusion: The high case detection rate by screening symptomatic household contacts shows MDR-TB is highly transmissible and household contacts are at a higher risk of developing active disease. It provides an opportunity for early diagnosis, adequate treatment, and interrupt the chain of transmission. Identifying risk factors help prevent the progression of latent TB infection to active disease.

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1. Introduction

Tuberculosis (TB) is the 10th leading cause of death worldwide, and over the last decade, it has been the leading infectious cause of death.[1] Several efforts are being taken to curb TB, but drug resistance especially multidrug-resistant tuberculosis (MDR-TB) poses a significant threat to public health and obstacle in effective TB control worldwide.[2] Globally in 2018, an estimated 3.4% of new cases and 18% of previously treated cases had MDR-TB.[1] India is one among the 30-high burden MDR-TB countries with an estimated 1,35,000 cases detected annually. Early diagnosis and definitive treatment and follow up are crucial in achieving the vision of the World health organization (WHO) of "A world free of TB". As close contacts of MDR-TB patients are expected to be at a higher risk of contracting infection and disease, contact screening is highly recommended especially in high burden countries.[3] Close contact is defined as living in the same household with the index MDR-TB case or spending many hours a day together in the same indoor space.[4] Factors determining the risk of contact developing TB depend on the infectiousness of the index TB case, duration, and proximity of the contact, and host immunity.[5–8] Disease onset may vary occurring from a few weeks to years with 90% developing the disease within 2 years and nearly all within 3 years.[9,10]

Contact screening is an active case-finding strategy to increase the detection of cases.[11] Early case detection and appropriate treatment are considered pillars of any national TB program and this will go on a long way in decreasing morbidity, mortality due to the disease, and ultimately TB elimination. Though TB among household contacts has been described extensively in the literature, there is limited Indian data regarding MDR-TB among household contacts and have not been extensively studied to date. Few studies have also shown MDR strains are less transmissible than drug-susceptible TB.[12,13] Our study was undertaken to estimate the prevalence of MDR-TB among household contacts of MDR-TB cases and gain insight into the plausible factors responsible for the spread of the disease.

2. Materials and methods

2.1. *Study design and setting*

This was a prospective observational study conducted in the Department of Tuberculosis and Chest diseases, Sarojini Naidu Medical College, Agra. The study enrolled patients over 24 months from February 2016 to January 2018. All diagnosed cases of MDR-TB in the study period were enquired about their household contacts and their contact numbers obtained. Telephone calls and home visits were made to these contacts and counselled to getting screened for pulmonary TB. All household contacts who were willing to participate in the study were asked to give written consent. A total of 271 patients were enrolled in our study.

2.2. *Inclusion criteria*

Household contacts of laboratory-confirmed MDR-TB index cases with symptoms including fever, cough, hemoptysis, night sweats, anorexia, and weight loss.

2.3. *Exclusion criteria*

Not giving informed consent.

3. Data collection

A Questionnaire was used for screening the household contacts to collect.

- Demographic data (age, sex, relation and contact duration with index case)
- BCG vaccination
- Nutrition
- Socioeconomic status
- History of TB, Any other TB cases in the family apart from index case (Secondary case)
- Comorbid medical conditions.

4. Definitions

Index Case: First Individual in the house to be diagnosed as MDR-TB after January 2016.

Secondary Case: Any household member developing TB after an index case.

Household contacts: Household contacts were defined as individuals who shared the same kitchen and sleeping area as the index case for at least 3 months before the diagnosis of the index case.

Symptomatic household contacts: household contacts of MDR-TB cases who were symptoms of TB such as cough with or without expectoration for more than 2 weeks, low-grade fever, loss of appetite, significant weight loss, and hemoptysis. Symptomatic contacts were screened for latent infection and active disease.

5. Screening investigations

1. Microbiology:
   a) Sputum for Acid-fast bacilli (AFB) by Ziehl Neelsen (ZN) method (one morning sample and one spot sample).
   b) Sputum for CBNAAT/Gene Xpert for determination of Rifampicin resistance (MDR-TB)
   c) Sputum for Line probe assay (LPA) For detecting Isoniazid (INH) resistance
   d) Sputum for *Mycobacterium tuberculosis* (M. TB) Liquid culture and sensitivity (c/s) (MGIT) for species identification and drug susceptibility testing (DST).

Sputum for AFB and CBNAAT were done in all symptomatic household contacts. LPA and M. TB C/S were done as and when needed. Those who were not able to expectorate, induced sputum using 3% saline was obtained. If sputum could not be obtained even after induction, a clinicoradiological diagnosis of TB was made.

2. Radiology: Chest X-Ray (CXR) PA view was done for all. CXR lateral views and CT thorax as needed.
3. Tuberculin sensitivity test (TST): After ruling out active disease, to look for latent infection.
4. HIV testing: After getting informed consent.

Those with extrapulmonary signs and symptoms were investigated for extrapulmonary TB.

6. Data analysis

Data were collected as per the protocol. Various statistical methods were applied as per requirement. Continuous variables were described as Mean ± SD and categorical variables were described in %. Prevalence of Latent TB and TB disease (drug-susceptible and drug-resistant) was calculated in the household contacts. Chi-square test was used to compare the prevalence rate of drug-susceptible and drug-resistant groups. Relative risk and odds ratio were used to find risk factors for the occurrence of tuberculosis. P-value <0.05 was considered significant. Z score or standard deviation (S.D) was calculated using anthropometric data of the study participants. −2S.D−−3S.D was labelled undernourished and less than −3 S.D as severe undernourishment.

7. Observation and results

A total of 285 symptomatic household contacts of 87 index MDR-TB cases were enrolled in the study after fulfilling the inclusion criteria. However, 9 participants withdrew consent, 4 contacts had shifted out and 1 death (myocardial infarction). So, a final of 271 cases were enrolled. Among 271, 97 of these contacts had active TB (62 MDR-TB and 35 drug-susceptible TB). Further 124 contacts had latent TB showing positive tuberculin sensitivity test (TST) > 10mm. 50 symptomatic contacts were free of infection and disease, with their symptoms due to other respiratory diseases (Fig. 1 and Fig. 2).

Demographic data including age, sex, relationship with index cases, and socioeconomic status of all household contacts were collected (Table 1). The symptomatic contacts were divided into 2 age groups (less than 18 years and 18 years and above.) For socioeconomic status, modified Kuppuswamy classification was used. As good nutrition is associated with increased immunity to acute and chronic respiratory infections including TB, nutritional status was assessed among the study participants. It was found that nearly 50% were undernourished and only 3% were severely malnourished (Table 2 and Fig. 3).

36 participants (13.29%) had co-morbid illnesses. The most frequent co-morbid illness was Diabetes Mellitus (23 contacts). Other comorbidities included chronic kidney disease, chronic liver disease, Rheumatoid arthritis and 2 contacts from a single household tested positive for HIV infection.

Among the diseased contacts, around 90% had pulmonary TB. Bacillus Calmette-Guerin (BCG) vaccination status was evaluated among the study participants. Nearly 40% of the contacts were not immunized (Table 3). Table 3 showing characteristics of household contacts who were screened for TB infection and disease (see Table 4).

Risk factors for the occurrence of TB in the study population included age less than 18 years (OR = 0.7160, RR = 0.8082) ($p > 0.5$), male sex (OR = 2.3108, RR = 1.7444) ($p < 0.5$), sibling as index MDR-TB case (OR = 0.6404, RR = 0.7520) ($p > 0.5$), lower socioeconomic status (OR = 3.2399, RR = 2.1524) ($p < 0.5$), lack of BCG immunization (OR = 1.7763, RR = 1.4338) ($p < 0.5$) and undernutrition (OR = 1.8980, RR = 1.5166) ($p < 0.5$) (Table 4).

8. Discussion

Screening of household contacts yielded a high case detection rate with 97 (35.79%) symptomatic contacts developing the disease. This is a very high yield compared to a similar study in Lima, Peru by Grandjean et al[12] showing a yield of 5%. Similar studies done in Tanzania[14] and Uganda[15] showed a yield of 6.4% and 3.5% respectively. However, in both the studies, all contacts irrespective of the symptoms were screened. The high yield in our study could be attributed to the enrolment of only symptomatic household contacts. In our study,12.9% had drug-susceptible TB, 45% had latent TB, and nearly 18% of symptomatic contacts had an unrelated upper respiratory tract infection. As TB contacts are considered a high-risk population for active disease, the latent TB patients were initiated on daily Isoniazid monotherapy for 6 months in accordance with WHO updated and consolidated guidelines for programmatic management of latent tuberculosis infection.[16]

Among the diseased contacts, 62 (22.87%) had MDR-TB. These results are consistent with other similar studies by Becerra et al[17] which showed 40% of contacts developed MDR-TB and Ejaz Qadeera et al[18] in which 54 (31.3%) symptomatic contacts developed MDR- TB. However, in a similar study done in Ethiopia,[19] 10% of symptomatic contacts developed MDR-TB. MDR-TB is readily transmissible[20] and household contacts of MDR-TB cases are at a higher risk of getting infection and disease than drug-susceptible TB.[4,17] This may be due to the fact, contacts of MDR-TB patients are exposed for a longer duration due to delay in the diagnosis, appropriate treatment and follow up.[4,21] This highlights the importance of contact investigation for early detection and treatment to reduce MDR-TB transmission.[3,17]

Demographic data and risk factors for the occurrence of TB among study participants were evaluated. Our study revealed the majority of study participants 56.83% were less than 18 years of age. The mean age was 16.5 years. Most of the study participants were males 59.78% in our study with a male: female ratio of 1.5:1. This might be because of the fact in rural areas with low socioeconomic status females are given less health care than males. In our study, siblings as index cases

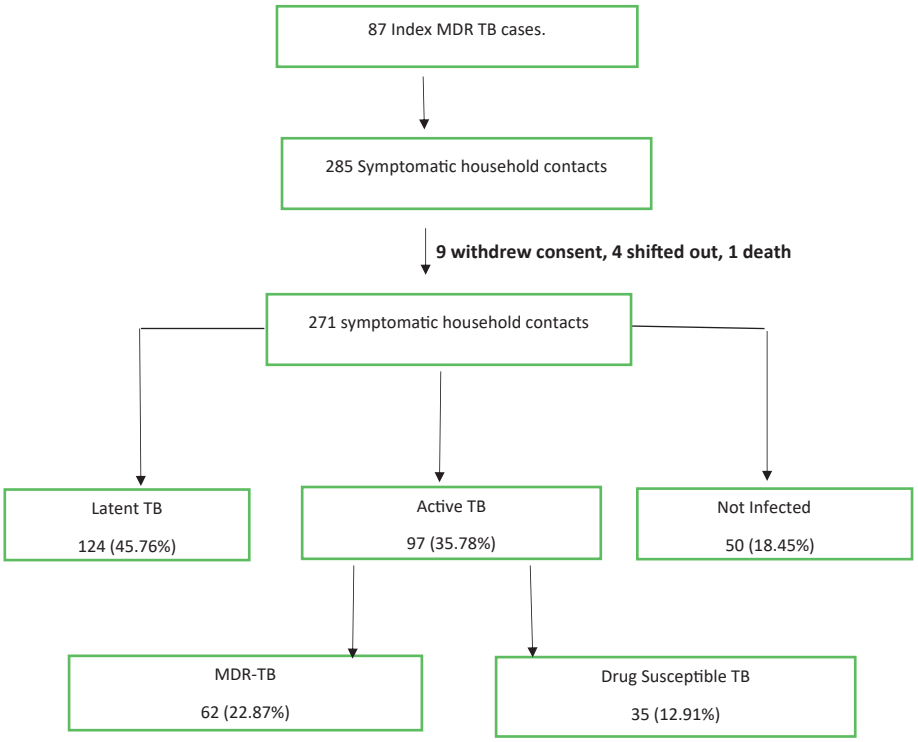

Fig. 1 – Flow diagram showing recruitment for the study and outcome of symptomatic household contacts.

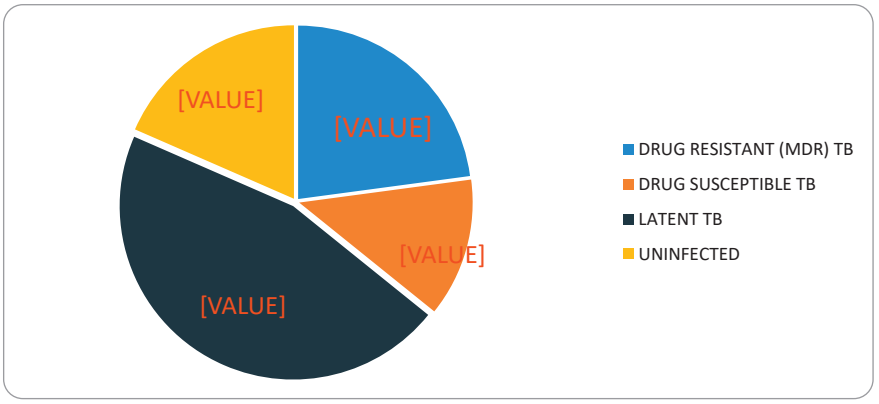

Fig. 2 – Showing distribution of study participants according to disease.

Table 1 – Demographic data of study participants.

Parameters	Variables	No. of contacts	Percentage
Age	<18 years	154	56.83
	>18 years	117	43.17
Sex	Male	162	59.78
	Female	109	40.22
Index case	Sibling	145	53.51
	Parents	70	25.83
	Others	56	20.66
Socioeconomic status	Upper	4	1.48
	Upper middle	9	3.32
	Lower middle	120	44.28
	Upper Lower	113	43.17
	Lower lower	25	9.22

Table 2 – Distribution of study participants according to nutritional status.

Malnutrition status	Number	%
No under nutrition(<2SD)	125	46.13
Under nutrition (−2SD–3SD)	136	50.18
Severe undernutrition(<−3SD)	10	3.69
Total	271	100

posed a slightly increased risk for the spread of TB, though statistically not significant. This could be attributed to the fact that siblings spend most of the time together. In a study to find out the various risk factors for the occurrence of TB, Seddon et al did not find any association between the relationship

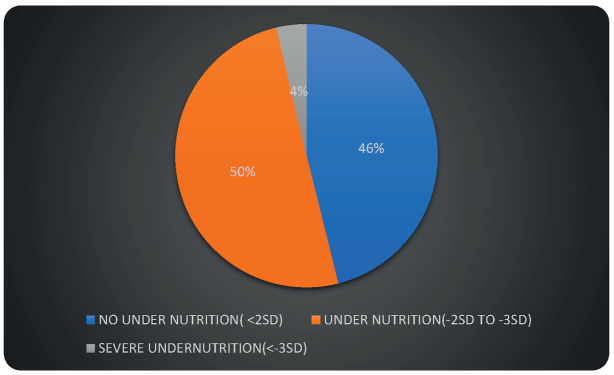

Fig. 3 – Distribution of study participants according to nutritional status.

Our study also showed the majority of diseased (57%) belonged to the lower socioeconomic class and had an increased risk of TB. A study by Lisa et al,[25] found an association between lower socioeconomic class and higher TB prevalence. This can be explained by the fact that due to poverty, there may be overcrowding and lack of adequate ventilation in their houses. Also, respiratory etiquettes and safe cough hygiene practices may not be practiced due to a lack of education. Our study showed BCG vaccination was protective and unvaccinated households had an increased risk of TB (RR = 1.4338; p = 0.0247) (OR = 1.7763; p = 0.0271). Similar observations were made by Lisa et al (25). BCG vaccination is significant especially in young household contacts as it confers

Table 3 – Screening Parameters of Household contacts.

Parameters	Variables	No. of contacts	Percentage
Sputum	Positive	82	30.26
	Negative	157	57.93
	Not able to produce sputum	32	11.81
CXR	Abnormal	109	40.22
	Normal	162	59.78
TST	Positive	172	63.47
	Negative	99	36.53
Co morbid illness	Present	36	13.29
	Absent	235	86.71
Site of TB	Pulmonary	88	90.72
	Extrapulmonary	09	9.28
BCG vaccination	Immunized	169	63.57
	Not immunized	102	36.43

Table 4 – Risk factors for the occurrence of tuberculosis in the study population.

Variables	Parameters	OR/RR	95%CL	P value
Age	<18 years	OR = 0.7160	0.4341–1.810	0.1908
		RR = 0.8082	0.5884–1.1102	0.1887
Sex	Male	OR = 2.3108	1.3539–3.9439	0.0021
		RR = 1.7444	1.2028–2.5299	0.0034
BCG Status	Unimmunized	OR = 1.7763	1.0673–2.9563	0.0271
		RR = 1.4338	1.0470–1.9635	0.0247
Index case	Sibling	OR = 0.6404	0.3886–1.0554	0.0804
		RR = 0.7520	0.5462–1.0354	0.0.806
Nutrition status	Under nutrition	OR = 1.8980	1.1397–3.1608	0.0138
		RR = 1.5166	1.0810–2.1279	0.0159
Socioeconomic status	Lower	OR = 3.2399	1.9145–5.4830	<0.0001
		RR = 2.1524	1.5036–3.0811	<0.0001

with the index case and the occurrence of TB.[22] We found a statistically significant association between undernourished contacts and TB disease. Nutrition plays an important role in boosting the host's immune response against infection including TB.[23] In our study, contacts who were well-nourished did not have TB. Further, malnutrition increases the risk of progression of infection to disease[23] and malnourished individuals are prone to develop disseminated disease.[24]

protection against TB complications and disseminated disease.[26]

9. Strengths and limitations of the study

This study had several strengths. First, the study was conducted in a large PMDT site (Agra) which has a heterogenous population hence they ought to be considered

generalizable to similar urban and rural settings in the rapidly changing settlement classifications within India and similar South Asian countries. Second, the data collection was robust and meticulous. The study has a few limitations. First, the study had a small sample size due to the inability to trace all index patients and their contacts. Second, some presumptive TB cases refused to be tested for TB. This may have led to a significant underestimation of the actual burden of TB and MDR-TB. Third, no data was collected from those who did not give consent. These participants were likely different from the consenting ones and reasons for not consenting should be collected if other such studies are conducted in the future.

10. Conclusion

Our study showed a high burden of TB (more than 1/3rd) among symptomatic household contacts of index cases of MDR-TB. Further, nearly 2 out of every 10 symptomatic contacts screened, had MDR-TB. It highlights the importance of screening symptomatic household contacts which will help in early diagnosis, definitive treatment, and possible cure. It will also reduce the transmission of MDR- TB in the community, decrease morbidity, mortality, and help to achieve the dream of global TB eradication. Tracing symptomatic contacts could be a high yielding strategy and should be considered especially in high burden TB countries. The study also sheds light on the risk factors associated with TB transmission. Steps have to be taken to ensure universal BCG vaccination, adequate nutrition, raise awareness of TB spread, and safe cough hygiene practices.

Presentation at a meeting

None.

Authors contribution

Benhur Joel Shadrach, Concepts, Design, Definition of intellectual content, Literature search, Data acquisition, Data Formal analysis, Statistical Formal analysis, Manuscript preparation, Manuscript editing, Manuscript review, Guarantor. Santosh Kumar, Concepts, Design, Definition of intellectual content, Literature search, Data acquisition, Data Formal analysis, Statistical Formal analysis, Manuscript preparation, Manuscript editing, Manuscript review. Kunal Deokar, Concepts, Design, Definition of intellectual content, Literature search, Data acquisition, Data Formal analysis, Statistical Formal analysis, Manuscript preparation, Manuscript editing, Manuscript review. Gajendra Vikram Singh, Concepts, Design, Definition of intellectual content, Literature search, Data Formal analysis, Manuscript review. Hariharan, Concepts, Design, Definition of intellectual content, Literature search, Data Formal analysis, Manuscript review. Rishabh Goel, Concepts, Design, Definition of intellectual content, Data Formal analysis, Manuscript review.

Informed consent

Informed written consent was obtained from the patient to publish his clinical details and investigations. The patient understands that his name and initials will not be published but anonymity cannot be guaranteed.

Conflicts of interest

All authors have none to declare.

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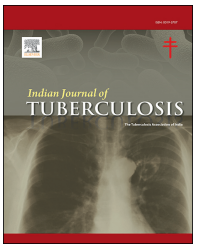

Original Article

Risk factors for death during treatment in pulmonary tuberculosis patients in South India: A cohort study

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ABSTRACT

Objective: Identifying the risk factors for deaths during tuberculosis (TB) treatment is important for achieving the vision of India's National Strategic Plan of 'Zero Deaths' by 2025. We aimed to determine the proportion of deaths during TB treatment and its risk factors among smear positive pulmonary TB patients aged more than 15 years.
Study design: We performed a cohort study using data collected for RePORT India Consortium (Regional Prospective Observational Research in Tuberculosis).
Setting: Revised TB Control Program (RNTCP) in three districts of South India.
Participants: The cohort consisted of newly diagnosed drug sensitive patients enrolled under the Revised National TB Control Program during 2014–2018 in three districts of southern India. Information on death was collected at homes by trained project staff.
Primary outcome measures: We calculated 'all-cause mortality' during TB treatment and expressed this as a proportion with 95% confidence interval (CI). Risk factors for death were assessed by calculating unadjusted and adjusted relative risks with 95% CI.
Results: The mean (SD) age was of the 1167 participants was 45 (14.5) years and 79% of them were males. Five participants (0.4%) were HIV infected. Among the males, 560 (61%) were

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tobacco users and 688 (75%) reported consuming alcohol. There were 47 deaths (4%; 95% CI 3.0–5.3) of which 28 deaths (60%) occurred during first two months of treatment. In a bivariable analysis, age of more than 60 years (RR 2.27; 95%CI: 1.24–4.15), male gender (RR 3.98; 95% CI: 1.25–12.70), alcohol use in last 12 months (RR 2.03; 95%CI: 1.07–3.87), tobacco use (RR 1.87; 95%CI: 1.05–3.36) and severe anaemia (RR 3.53: 95%CI: 1.34–9.30) were associated with a higher risk of death. In adjusted analysis, participants with severe anaemia (<7gm/dl) had 2.4 times higher risk of death compared to their counterparts.

Conclusion: Though deaths during TB treatment was not very high, early recognition of risk groups and targeted interventions are required to achieve zero TB deaths.

1. Introduction

Tuberculosis (TB) is a major public health problem globally. It is the leading cause of death from a single infectious agent and is the ninth leading cause of death worldwide. In 2017, there were an estimated 10 million people with TB, among whom 0.3 million died with concurrent HIV infection and 1.3 million died without HIV infection.[1] India accounts for 27% of the overall global TB mortality and 32% of the TB deaths among HIV uninfected TB patients.[1] India aims to eliminate TB by 2025, a half decade before the Sustainable Development Goals (SDGs) developed by the United Nations. Compared to a 3% per year fall in global rate, in India despite various efforts the fall in TB mortality rate is only 1.7% and TB deaths have dropped from 423,000 in 2016 to 410,000 in 2017, which is inadequate to achieve the ambitious target.[2] India's National Strategic Plan (NSP) 2017–2025 aims to achieve a 90% reduction in the estimated mortality due to TB (from 32 per 100,000 population to 3 per 100,000 populations) by 2025.[3] Though interventions like HIV testing, screening for diabetes and drug resistance have improved the TB treatment outcomes and death during treatment remains a challenge.

Case-fatality rates among adults during TB treatment were ranged from 1.8% to 33.3% in India.[4] The risk factors for all-cause mortality during TB treatment varied based on the extent of TB incidence and HIV prevalence. In general, male gender, higher age group, low body mass index (BMI) < 18.5 kg/m^2, tobacco and alcohol use, delay in treatment initiation, poor treatment adherence, co-existence of diabetes or other co-morbidities, anaemia, drug resistant state, severity of TB, presence of cavity in chest x-ray and HIV-positive status were associated with a higher TB mortality.[5–13] A large number of studies from India reported risk factors for death using routinely collected data in the program which had information on a limited number of variables.[4] The role of anaemia, functional impairment at the time of diagnosis (performance status), duration of illness before treatment and diabetes in relation to deaths have not been explored in detail in the Indian setting. Also over the years, several interventions under the National Tuberculosis Program (NTP) could have altered the risk profile for death among TB patients. In this context, knowledge on characteristics of patients who die during the course of treatment could help identify vulnerable groups and help the NTP to plan targeted interventions.

During 2014–2018, the RePORT India Consortium (Regional Prospective Observational Research in Tuberculosis) established a cohort of pulmonary TB patients in three districts of southern India to study biomarkers for risk of treatment failure. Patients in this cohort were enrolled from the NTP and information on several possible risk factors for death was collected as part of the study. This provided an opportunity to explore the characteristics of patients who died during TB treatment.

Specific objectives of the present study, using the data from RePORT India cohort, was to describe:

a) the number and proportion of deaths during TB treatment
b) timing of deaths from initiation of TB treatment and
c) risk factors for deaths.

2. Methods

2.1. Study design

This is a retrospective analysis of the data collected from the cohort established by the RePORT India Consortium as described below.

2.2. RePORT International

The Regional Prospective Observational Research in Tuberculosis (RePORT) International is a consortium of regional cohorts (RePORT India, RePORT Brazil, RePORT South Africa, RePORT China, RePORT Philippines and RePORT Indonesia) that implemented a common protocol for data and specimen collection. Objectives and composition of RePORT International are described elsewhere.[14,15]

One of the five teams under RePORT India, i.e. Jawaharlal Institute of Postgraduate Medical Education & Research (JIPMER), Puducherry and the Boston Medical Centre, New Jersey have established a pulmonary TB case cohort of adults and children $\geq$ 6 years to identify biomarkers for risk of TB treatment failure and risk of development of TB in household contacts. TB cases diagnosed under NTP in the three districts (Puducherry, Cuddalore and Villupuram) were included in the cohort since 2014. The eligibility criteria for inclusion into the RePORT India cohort were all newly diagnosed smear positive

(at least 1+ acid fast bacilli) and culture confirmed pulmonary TB, who should not have taken more than three doses of anti-TB medications, were more than five years of age, were willing to get tested for HIV, were not diagnosed with drug resistant-TB (MDR-TB/XDR-TB) or had contact with a known MDR-TB/XDR-TB patients, were not too sick to be enrolled (Karnofsky score >50) and willing to stay in the study area.

Details on tobacco use, alcohol use, household food security, severity of TB (Karnofsky scores), diabetes status and HIV status were collected within seven days of TB diagnosis. Field teams visited the TB patients at baseline enrolment and two and six months after enrolment (or at the end of treatment). Treatment outcomes including deaths were verified during visits to the patient home at the end of treatment. All the information obtained above was recorded in project-specific case report forms (CRF) and these were scanned and transferred to data coordinating centre at Boston Medical Center with Verity TeleForm Information Capture System software V10.8 (Sunnyvale, CA, USA), read and uploaded into a Microsoft Access (Seattle, WA, USA) database.

2.3. *Study setting*

The Union territory of Puducherry is the erstwhile French colony in the southern region of India, It comprises of four enclaves namely viz: Pondicherry, Mahe, Yanam and Karaikal. This study covers Pondicerry enclave of the Union Territory of Puducherry (population ~ 1.3 million) and two adjoining

Table 1 – Association of socio-demographic characteristics with mortality during tuberculosis treatment in three districts of South India, 2014–2018 (N = 1167).

Characteristics	Total	Deaths	Unadjusted RR (95% CI)	p value
	N (%)[a]	n (%)[b]		
Total	**1167**	**47 (4.0)**	–	–
Age (in years)				
Less than 60	983 (84.2)	33 (3.4)	1	
60 and above	184 (15.8)	14 (7.6)	2.27 (1.24–4.15)	0.008
Gender				
Male	918 (78.7)	44 (4.8)	3.98 (1.25–12.70)	0.02
Female	249 (21.3)	3 (1.2)	1	
Marital status				
Never Married	207 (17.7)	4 (1.9)	1	
Married/Living together	836 (71.6)	34 (4.1)	2.10 (0.76–5.86)	0.16
Separated/divorced/widowed	124 (10.7)	9 (7.3)	3.78 (1.18–11.94)	0.03
Education (years of schooling)				
No formal Education	189 (16.2)	5 (2.7)	1	
1–5	263 (22.5)	13 (4.9)	1.87 (0.68–5.15)	0.23
6–10	489 (41.9)	21 (4.3)	1.62 (0.62–4.24)	0.32
>10	226 (19.4)	8 (3.5)	1.34 (0.45–4.02)	0.6
Employment				
Employed	914 (78.3)	38 (4.2)	1	
Unemployed	181 (15.5)	9 (5.0)	1.19 (0.59–2.42)	0.62
Student	72 (6.2)	0	–	
Monthly household income in INR[c]				
<3000 (42.3 US$)	135 (11.8)	10 (7.4)	2.07 (1.05–4.07)	0.03
≥3000 (42.3 US$)	1006 (88.2)	36 (3.6)	1	
Residence[d]				
Urban	563 (49.0)	22 (3.9)	1	
Rural	585 (51.0)	25 (4.3)	1.09 (0.62–1.92)	0.76
Religion				
Hindu	1034 (88.6)	45 (4.4)	2.89 (0.71–11.79)	0.14
Others	133 (11.4)	2 (1.5)	1	
Caste[e]				
Scheduled caste[f]	312 (27.1)	8 (2.5)	0.57 (0.27–1.2)	0.14
Other Castes	838 (72.9)	38 (4.5)	1	
Year of enrolment				
2014	159 (13.6)	6 (3.8)	1	
2015	218 (18.7)	8 (3.7)	0.97 (0.34–2.74)	0.96
2016	219 (18.8)	9 (4.1)	1.09 (0.39–2.99)	0.87
2017	363 (31.1)	20 (5.5)	1.46 (0.59–3.56)	0.41
2018	208 (17.8)	4 (1.9)	0.51 (0.15–1.78)	0.29

[a] Column percentage
[b] Row percentage, RR- Relative risk, CI-Confidence interval
[c] Data missing for 26 participants
[d] Data missing for 19 participants
[e] Data missing for 17 participants
[f] Socially disadvantaged as per Constitution of India.

districts of the state of Tamil Nadu i.e., Villupuram (population ~ 3.5 million) and Cuddalore (population ~ 2.6 million). At the sub-district level, Tuberculosis Units covering a population of 0.25 million which act as nodal points for TB control activities. Under NTP, sputum microscopy (two sputum samples) remain the mainstay of diagnosis; since November 2017, upfront chest x-ray and universal drug susceptibility testing for all diagnosed TB cases was also implemented. Upon diagnosis of TB, patients are initiated on TB treatment at nearest peripheral health institutions. Newly diagnosed TB patients receive thrice weekly doses of anti-tuberculosis drugs for six months under direct observation followed by two months of intensive phase (2HRZE: H=Isoniazid, R = Rifampicin, P=Pyrazinamide, E = Ethambutol) and four months of continuation phase (4HRE). Since November 2017, daily regimen was introduced and fixed dose combination (FDC) drugs of 4HRZE (FDC) and 3HRE (FDC) are provided.

Demographic and disease related information, co-morbidity status (HIV, diabetes), drug adherence and programmatic treatment outcomes were recorded in a Patient Card and Tuberculosis Treatment Register. Death due to any cause during TB treatment was recorded in the above records

Table 2 – Association of clinical and behavioural characteristics with mortality during tuberculosis treatment in three districts of South India, 2014–2018(N = 1167).

Characteristic	Total	Deaths	Unadjusted	p value
	N (%)[a]	n (%)[b]	RR (95% CI)	
Total	**1167**	**47 (4.0)**	–	–
Sputum smear grading at diagnosis				
1+	405 (34.7)	18 (4.4)	1.15 (0.59–2.24)	0.69
2+	375 (32.1)	14 (3.7)	0.96 (0.47–1.97)	0.92
3+	387 (33.2)	15 (3.9)	1	–
Karnofsky score at diagnosis				
50–60	237 (20.3)	15 (6.3)	1.83 (1.01–3.34)	0.05
>60	930 (79.7)	32 (3.4)	1	
Random blood sugar				
<200mg/dl	826 (70.5)	39 (4.7)	2.04 (0.96–4.31)	0.05
≥200mg/dl	345 (29.5)	8 (2.3)	1	
Body mass index[c](kg/m2)				
<18.5	712 (61.0)	32 (5.3)	2.03 (0.99–4.15)	0.06
18.5–22.9	342 (29.3)	9 (2.6)	1	
≥23.0	113 (9.7)	0	–	–
Alcohol use in past 12 months				
Yes	688 (58.9)	35 (5.1)	2.03 (1.07–3.87)	0.03
No	479 (41.1)	12 (2.6)	1	
Tobacco use[d]				
Yes	566 (48.5)	30 (5.3)	1.87 (1.05–3.36)	0.04
No	601 (51.5)	17 (2.8)	1	
Co-morbidity[e]				
Present	168 (14.4)	38 (3.8)	1	
Absent	999 (85.6)	9 (5.4)	1.41 (0.69–2.86)	0.34
Duration of symptoms				
> one month	221 (18.9)	11 (5.0)	1.31 (0.68–2.53)	0.43
≤one month	946 (81.1)	36 (3.8)	1	
HIV status				
Sero-positive	5 (0.4)	0 (0.0)	–	–
Sero-negative	1162 (99.6)	47 (4.1)	–	–
Sputum smear status at two months				
Positive	173 (14.8)	6 (3.5)	0.84 (0.36–1.9)	0.69
Negative/No sputum	994 (85.2)	4 (4.1)	1	
Severe anaemia (<7gm/dl)[f]				
Yes	32 (2.9)	4 (12.5)	3.53 (1.34–9.30)	0.011
No	1073 (97.1)	38 (3.5)	1	
Household food insecurity[g]				
Yes	245 (33.7)	14 (5.7)	1.62 (0.81–3.23)	0.17
No	482 (66.3)	17 (3.5)	1	

[a] Column percentage
[b] Row percentage, RR- Relative risk, CI-Confidence interval
[c] BMI measured at baseline
[d] Tobacco use-current use of both smoke and smokeless form of tobacco in last one month
[e] Co-morbidities such as asthma, hepatitis, renal disease, cancer and breathing difficulty as reported by the participants
[f] Data missing for 62 participants
[g] Level of Food insecurity was assessed using the Household Food Insecurity Assessment Scale (HFIAS) for Measurement of Food Access-FANTAIII and Data missing for 440.

by a Senior Treatment Supervisor after verification with the TB treatment provider or family members.

2.4. Study population

For the present study, patients aged 15 years and above enrolled in RePORT India cohort between May 2014 and October 2018 were included.

2.5. Data extraction, analysis, and statistics

Data were extracted from the RePORT India project database in a de-identified manner and analysed using STATA 12 software (StataCorp LP, College Station, Texas). Deaths due to any cause (all-cause mortality) during TB treatment were summarized as proportions with 95% CI. Association of socio-demographic, clinical and behavioural characteristics with death during TB treatment was assessed using chi square test and unadjusted relative risks with 95% CI were calculated. A p value of less than 0.05 was considered to be statistically significant. Multivariable analysis using log binomial model was done to calculate adjusted Relative Risks (aRR) with 95% CI. The risk estimation in the present study was analysed for all participants, including those lost to follow-up. However, risk estimations excluding those lost to follow-up were not very different. The results of analysis excluding those lost to follow-up are also provided in supplementary tables.

3. Results

A total of 1167 pulmonary TB patients were included. The mean (SD) age was 45 (14.5) years and 79% of the patients were males. Socio-demographic characteristics of the cohort are shown in Table 1. Of the total, 16% (n = 184) were older adults (aged 60 years or more), and 12% (n = 135) had a monthly family income less than 3000 INR (~42 US$). Half of the patients were residing in rural areas.

Clinical and behavioural characteristics are described in Table 2. Regarding the functional impairment at the time of diagnosis, 237 patients (20%) had Karnofsky scores between 50 and 60. In total, 712 patients (61%) were underweight (body mass index less than 18.5 kg/m^2) and duration between the onset of TB symptoms and treatment initiation was more than one month in 19% of patients. Among males, 61% were either current or past tobacco users and 75% reported consuming alcohol in past 12 months. Severe anaemia (haemoglobin <7gm/dl) was present in 3% of patients.

There were 47 deaths (4.0%; 95% CI 3.0–5.3) during TB treatment (Table 3); 6.6% (n = 77) were lost to follow-up and 87% (n = 1012) had successfully completed treatment (cured or treatment completed). Of 47 deaths, 28 (60%) occurred during the first two months (intensive phase) of treatment and 15% deaths (n = 7) during third month (Table 4).

In unadjusted analysis (Tables 1 and 2), age 60 years or more (RR-2.27; 95%CI: 1.24–4.15), males (RR-3.98; 95% CI: 1.25–12.70), marital status as separated/divorced/widowed (RR-3.78; 95%CI: 1.18–11.94), a household income less than INR 3000 (~42US$) (RR-2.07; 95%CI: 1.05–4.07), alcohol use in last 12 months (RR-2.03; 95%CI: 1.07–3.87), tobacco use (RR-1.87; 95%CI: 1.05–3.36) and severe anaemia (RR-3.53: 95%CI: 1.34–9.30) were associated with higher risk of death. In adjusted analysis (Table 5), patients with severe anaemia (<7gm/dl) had a 2.4 times higher risk of death compared to those who had a haemoglobin levels 7gm/dl or more at the time of diagnosis (aRR - 2.44; 95% CI: 1.04–5.74).

4. Discussion

In this cohort of newly diagnosed pulmonary TB patients from southern India, the mortality rate during treatment was less than 5% and more than half of the deaths occurred in first two months. We identified a few sub-groups with higher risk for death such as elderly (60 years or more), male, patients with low monthly income, severe anaemic and those with a history of substance abuse (tobacco or alcohol).

Our study has following strengths. First, the data were part of the RePORT India prospective cohort and the data were collected by trained field teams at the homes of the patients. Standard operating procedures were followed for anthropometry measurements and blood sample collection for haemoglobin estimation. Completion of data forms was checked by a data manager ensuring quality of the data. Second, treatment outcomes were confirmed by house visits. This averted the possibility of unreported deaths in patients who were lost to follow up. Third, the cohort study had detailed information on risk factors for death (severity of TB, haemoglobin level, alcohol and tobacco use, food security) which are not routinely collected under NTP.

The following are the limitations of the present study. First, the cohort had strict inclusion criteria which could have introduced a selection bias resulting in a low risk cohort for mortality (e.g., exclusion of individuals with a low Karnofsky score at baseline). Second, we assessed 'all-cause mortality', whereas all deaths may not be attributable to TB. However, since deaths during first two months of initiation of treatment were high, these deaths may be related to TB as borne out by

Table 3 – Treatment outcome of the new smear positive pulmonary tuberculosis patients in three districts of South India, 2014–2018 (N = 1167).

End of TB treatment outcomes	N (%)
Cured[a]	881 (75.5)
Treatment completed[b]	131 (11.2)
Lost to follow-up[c]	77 (6.6)
Treatment failed[d]	31 (2.7)
Died	47 (4.0)

[a] Cured - microbiologically confirmed TB patients at the beginning of treatment who was smear or culture negative at the end of the complete treatment.
[b] Treatment completed - TB patient who completed treatment without evidence of failure or clinical deterioration, but with no record to show that the smear or culture results of biological specimen in the last month of treatment was negative.
[c] Lost to follow-up - TB patient for whom treatment was interrupted for one consecutive month or more.
[d] Treatment failed - TB patient whose biological specimen is positive by smear or culture at end of treatment.

Table 4 – Distribution of deaths during tuberculosis treatment in three districts of South India, 2014–2018(N = 47).

Months after initiation of treatment	n (%)
One	14 (29.8)
Two	14 (29.8)
Three	7 (14.9)
Four	3 (6.4)
Five	3 (6.4)
Six months or more	6 (12.8)

other studies.[16–18] Ascertaining cause of death by verbal autopsy would have added value to the study. Third, the cohort under study does not include patients who were obtaining treatment from the private sector. The characteristics of such patients could be different and death rates can vary in this group. Fourth, since number of deaths was low, our study was under-powered to assess some of the risk factors. The results based on the univariate analysis are discussed below.

Under NTP among the cohort of newly diagnosed pulmonary patients in 2016, death rates were ~4% for the states of Tamil Nadu and Puducherry which is similar to our study.[19] Studies from southern part of India (2005–2009) and Central India (2004–2009) involving patients from public sector reported death rates of 6% and 5% respectively which included smear negative, extra pulmonary and previously treated categories of patients.[11,20] However, these studies could have underestimated the deaths as a significant proportion of deaths could have gone unreported among the lost to follow up patients. In our study about three fifths of deaths occurred during first two months; other studies from India and outside have reported higher occurrence of deaths during this period.[11,21,22] Early recognition of risk groups at diagnosis and targeted care in the form of hospitalization or close monitoring in the community may be tried.

Despite being a cohort at low risk of death (drug sensitive, newly diagnosed smear positive pulmonary TB patients, low HIV prevalence of 0.4%, not severely ill) the death rate was high in the cohort studied. The risks were highest among males and those with severe anaemia. Higher risk among males can be attributed to very high levels of tobacco (61%) and alcohol use (75%). One of the study areas (Puducherry) ranks high in alcohol use in the country as taxes are lower in this district compared to other districts.[23] Though India's NTP recommends screening for substance abuse (tobacco or alcohol) at the time of TB diagnosis and linking to de-addiction services, the implementation is sub-optimal.[24] Addressing tobacco and alcohol use may help reduce mortality and help improve other poor treatment outcomes (lost to follow up,

Table 5 – Multivariable analysis showing association of socio-demographic, clinical and behavioural characteristics with mortality during tuberculosis treatment in three districts of South India, 2014–2018(N = 1167).

Characteristic	Total	Deaths	aRR (95% CI)	p value
	N (%)[a]	n (%)[b]		
Total	**1167**	**47 (4.03)**	–	–
Age (in years)				
Less than 60	983 (84.2)	33 (3.7)	1	
60 and above	184 (15.8)	14 (7.6)	1.75 (0.87–3.53)	0.12
Gender				
Male	918 (78.7)	44 (4.8)	3.79 (0.94–15.23)	0.06
Female	249 (21.3)	3 (1.2)	1	
Marital status				
Never Married	207 (17.7)	4 (1.9)	1	
Married/Living together	836 (71.6)	34 (4.1)	1.48 (0.52–4.21)	0.46
Separated/divorced/widowed	124 (10.7)	9 (7.3)	3.17 (0.94–10.70)	0.06
Monthly household income in INR [c]				
<3000 (42.3 US$)	135 (11.8)	10 (7.4)	1.81 (0.87–3.74)	0.11
≥3000 (42.3 US$)	1006 (88.2)	36 (3.6)	1	
Alcohol use in past 12 months				
Yes	688 (58.9)	35 (5.1)	1.78 (0.52–2.16)	0.69
No	479 (41.1)	12 (2.6)	1	
Tobacco use[d]				
Yes	566 (48.5)	30 (5.3)	1.05 (0.51–2.16)	0.89
No	601 (51.5)	17 (2.8)	1	
Severe anaemia(<7gm/dl)[e]				
Yes	32 (2.9)	4 (12.5)	2.44 (1.04–5.74)	0.04
No	1073 (97.1)	38 (3.5)	1	

aRR-adjusted relative risk CI-Confidence interval risk based on log binomial model, included variables age, gender, marital status, monthly household income, alcohol use in past 12 months, tobacco use, and severe anemia which were significant at p value < 0.05 in univariate analysis.

[a] Column percentage

[b] Row percentage

[c] Data missing for 26 participants

[d] Tobacco use-current use of both smoke and smokeless form of tobacco in last one month

[e] Data missing for 62 participants.

treatment failure and relapse). Only three percent of the cohort had severe anaemia but risks for deaths were about three-fold higher. The underlying reasons for anaemia among TB patients need to be evaluated to understand the cause for high mortality in this group. Diagnosing severe anaemia at peripheral health institutions using point of care tests can be used to initiate timely referral for evaluation, which is not currently part of TB care under NTP. Elderly (aged 60 years or above) constituted 16% of our cohort and was another high-risk group for deaths. Delays in accessing care, financial dependence, co-morbidities, poor TB treatment adherence, staying alone and decreasing immunity may possibly contribute to higher mortality. National programs should link the elderly patients to the existing social security schemes and may consider increase in the number of house visits by community TB workers. Undernutrition can be cause and effect of TB. Three-fifths of our TB patients were underweight and studies have shown it as an important risk factor for death. Nutritional assessment and counselling and linkage to direct benefit schemes (Nikshay Poshan Yojana), where monthly financial assistance towards nutritional need for all TB patients was implemented since 2018 and it is a welcome step.

To conclude, a significant proportion of newly diagnosed pulmonary TB patients died during the course of treatment. Since, more than half of deaths occur early during treatment, thorough evaluation of risk factors for death at the time of diagnosis needs to be emphasized. Older adults (more than 60 years), male gender, and alcohol user needs vigilant care.

Author contributions

Substantial contributions in the conception and design were done by JR, PC, SS, PT, NH, JE, PS and MD. JR and PC worked along with JE, NH, SS, SL, GR, SKS, SK, R and VM involved in training and monitoring of the project staffs, quality checking of data collection process, and facilitated the data acquisition. Analysis, interpretation of data and drafting of the manuscript was done by JR, PC, SS, PT, MD, SL, and VM. All authors were involved in revising the manuscript critically for important intellectual content.

Ethics and consent

RePORT India study protocol was reviewed and approved by Institute Ethics Committee of JIPMER (JIP/IEC/2013/4/194) and Institute Review Board of Boston Medical Centre (H-32657/07-05-2017). Approval for secondary data analysis for this study was obtained from Ethics Advisory Group of the International Union against Tuberculosis and Lung Disease, Paris, France (EAG/122/18).

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Paper context

National strategic plan 2017–2025 aims to achieve 90% in TB mortality India by 2025. More than half of the TB deaths do occur in the first two months of TB treatment. Though deaths related TB could have happened before diagnosis, between diagnosis and treatment initiation, and after treatment, allowing a patient to die while they are under the program monitoring is unacceptable (missed opportunity). Identifying the at-risk group for deaths would enable program manager to strengthen specific intervention to reduce mortality significantly.

Conflicts of interest

The authors have none to declare.

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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.2020.09.022.

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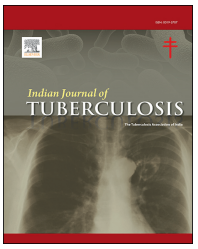

Original Article

Bronchial artery embolization: A gratifying life-saving procedure

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ABSTRACT

Background: Bronchial artery embolization (BAE) is an urgent life-saving procedure in patients with massive hemoptysis.

Material and methods: This was a single center observational study wherein patients presenting with hemoptysis were evaluated and underwent BAE. Initially, a descending thoracic aortogram was performed to identify culprit vessels followed by selective catheterization of the involved vessels. Abnormal bronchial artery morphology included hypertrophied and tortuous bronchial artery (BA), focal hyperemia and hypervascularity, shunting into pulmonary artery or vein, extravasation of contrast into the lung parenchyma/cavity and BA aneurysms. Selective embolization was done using either gelfoam or polyvinyl alcohol particles. Post-procedure, follow-up was done at one month and six months with outcomes defined in terms of recurrence of hemoptysis.

Results: A total of 187 patients underwent BAE with post-tubercular sequalae being the most common diagnosis in 157 (84%) followed by idiopathic bronchiectasis in 19 (10.2%) and aspergilloma in 7 (3.7%). A total of 246 vessels were embolized with right sided BA being more commonly involved as compared to left [143 (76.5%) vs. 35 (18.7%); $P < 0.0001$]. Complete resolution was observed in 183 (97.8%) 24 hours post procedure. Recurrence was reported in 34 (18.2%) patients with higher frequency in diabetics, patients with active tuberculosis and presence of aspergillomas. Multi-variate logistic regression analysis showed that diabetes, presence of an aspergilloma and feeding vessels from internal mammary artery were independent predictors of recurrent hemoptysis. Most of the complications were minor except paraparesis observed in two patients.

Conclusion: BAE is a safe and effective procedure for the treatment of hemoptysis of different etiologies.

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1. Introduction

Hemoptysis is a common cardinal symptom among patients with chronic lung disorders and can often lead to life-threatening respiratory emergencies.[1] In countries such as India with a huge burden of tuberculosis, clinicians frequently come across patients with massive hemoptysis in the emergency department.[2] Mortality in these patients can be as high as 50% with most of the deaths occurring due to asphyxiation of blood rather than exsanguination mandating a prompt therapy.[3] Traditionally, surgery was considered as the definitive cure for hemoptysis however, elective surgical intervention has a mortality rate of around 18% which increases to 40% when performed on an emergent basis.[4] In addition, a majority of these patients are poor surgical candidates due to the underlying chronic lung condition thus, precluding surgery even in some of the life-threatening cases.

Bronchial artery embolization (BAE), a technique first described by Remy et al[5] in 1973, has been considered as the most effective minimally invasive strategy for the control of life-threatening hemoptysis. It not only serves as the first line therapy in these patients but also acts as a bridge while providing a more definitive medical/surgical intervention. The rationale for use of BAE in hemoptysis stems from the fact that in nearly 90% of cases, the source is a bronchial artery while in the remaining patients its either pulmonary artery or non-bronchial systemic arteries.[6] This technique involves bronchial angiography and selective catheterization of the affected arteries followed by injection of the appropriate embolic material.

BAE has a good initial treatment success rate however, in a significant proportion of cases, recurrences are known to occur requiring repeat embolization or surgery.[2] Complications of BAE are few and often self-limiting however, neurological complications such as paraparesis can be quite devastating. Technological advancements in the form of availability of better hardware, use of micro-catheters for super-selective embolization and newer embolizing material have lowered the complication rates in patients undergoing BAE.[2,6] This study endeavors to determine the clinical characteristics, etiology, safety and efficacy of BAE as well as predictors of recurrence in patients presenting with hemoptysis and undergoing BAE.

2. Materials and methods

This was a single center observational study carried out in the department of cardiology in close liaison with the department of pulmonary medicine over a period of 18 months in a tertiary care medical center. Patients presenting with hemoptysis were initially evaluated in the department of pulmonary medicine which included a detailed history taking, clinical examination, routine investigations including coagulation profile, chest radiograph and computed tomography (CT) of the chest (wherever feasible). Subsequently, they were referred to us for BAE following the initial medical therapy.

2.1. *Embolization procedure details*

Following a written informed consent, the patients were immediately shifted to the catheterization laboratory for performance of BAE under local anesthesia. The use of conscious sedation was avoided fearing the risk of respiratory depression and subsequent consequences in these patients. All the procedures were performed using the common femoral arterial approach using the 6 French (F) vascular sheath. A descending thoracic aortogram using a 5F pigtail catheter using non-ionic contrast medium was performed prior to BAE in order to identify the number and location of the bronchial arteries. This was followed by selective catheterization of the involved vessels using the reverse curve or Judkin's right (JR-4) diagnostic catheter (depending on the availability). Pre-procedure chest radiography or CT scan helped us to identify the primary area of interest which was then confirmed based on findings on selective angiography of the involved bronchial artery. The bronchial arteriogram morphologies included (a) hypertrophied and tortuous bronchial arteries including the cork screw appearance (Fig. 1A); (b) focal hyperemia and hypervascularity (Fig. 1B and C); (c) extravasation of contrast into the lung parenchyma/cavity (Fig. 1D) (d) shunting into pulmonary artery or vein (Fig. 2A); (e) bronchial artery aneurysms (Fig. 2B). All abnormal vessels were embolized in the area of interest in the same sitting depending on the technical feasibility. In all patients where an artery of Adamkiewicz was identified on aortogram, the procedure was immediately abandoned. In addition, non-bronchial systemic arterial collaterals from the left and right internal mammary (Fig. 3A and B), subclavian and intercostal arteries (Fig. 3C) were also looked for. The primary embolic material used was either Spongostan standard gelfoam particle (1 × 1 × 1 mm) (Johnson & Johnson medical limited, Skipton, UK) or Contour Emboli polyvinyl alcohol [PVA] particles (355–500 μm) (Boston Scientific, Natick, MA). The embolic material was injected slowly and repeat angiograms were performed intermittently as spinal and other collateral vessels may open up as distal vessel gets occluded (Fig. 4A and B). The end point for the embolization was loss of hypervascularity in the feeding vessel and presence of vascular stasis in the involved vessel.[2,6] Post embolization, bronchial arteriograms were performed confirming success of the procedure (Fig. 5A and B). All these patients were then observed in the cardiac intensive care unit for a period of 24 hours post procedure which also included neurological evaluation. Subsequently, they were followed up after one month and six months. Outcomes post BAE were defined in terms of recurrence of hemoptysis with immediate clinical success being described as complete cessation or significant decrease in hemoptysis post 24 hours following BAE. Recurrences were defined as significant hemoptysis occurring post discharge requiring urgent medical attention in form of hospitalization, bronchoscopy, repeat BAE or surgery.[2]

2.2. *Statistical analysis*

Descriptive statistics was obtained for all the study subjects with continuous data being expressed as mean ± SD while categorical data as number or proportions. Comparison of the

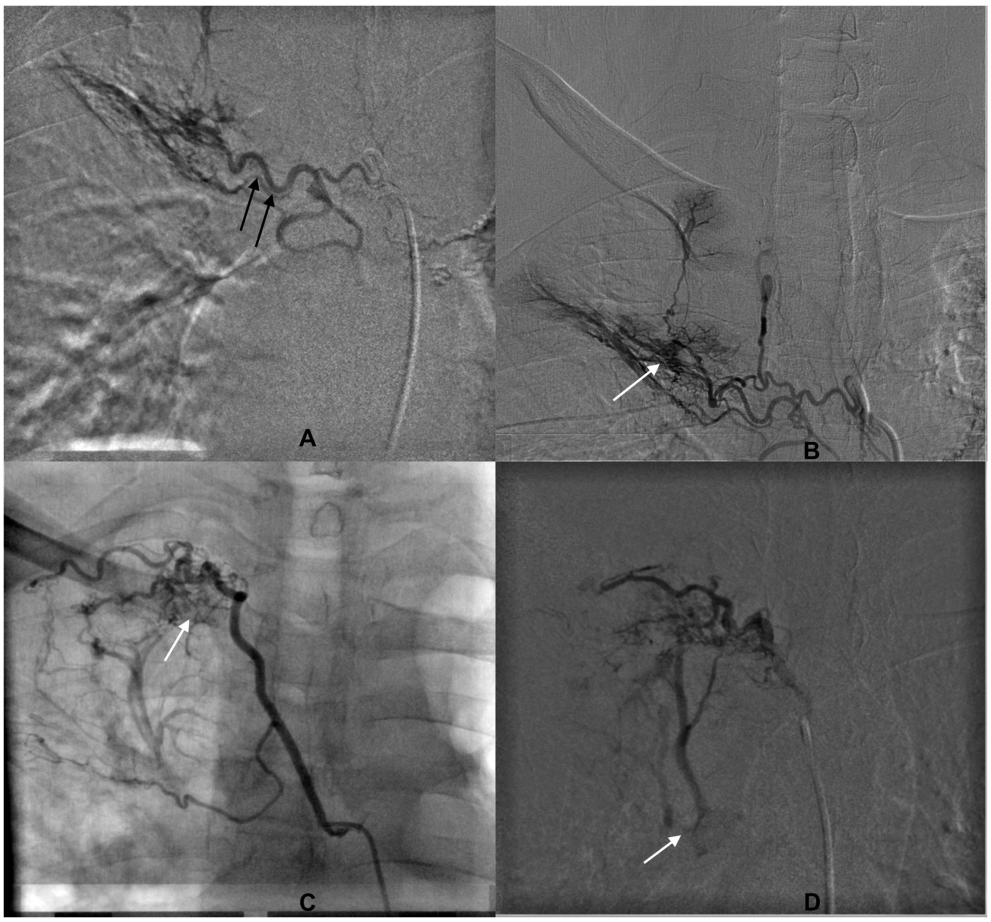

Fig. 1 – A: Right bronchial angiogram (digital subtraction angiographic image) showing hypertrophied and tortuous right bronchial artery giving a corkscrew appearance (black arrows). B: Right bronchial angiogram (digital subtraction angiographic image) showing focal hyperemia (white arrow) in right bronchial artery in a 45-year-old male with massive hemoptysis. C: Right bronchial angiogram showing hypervascularity (white arrow) in right bronchial artery in a young male presenting with hemoptysis. D: Right bronchial angiogram (digital subtraction angiographic image) showing free spillage of the contrast material from the right bronchial artery (white arrow) suggestive of broncho-pulmonary shunting.

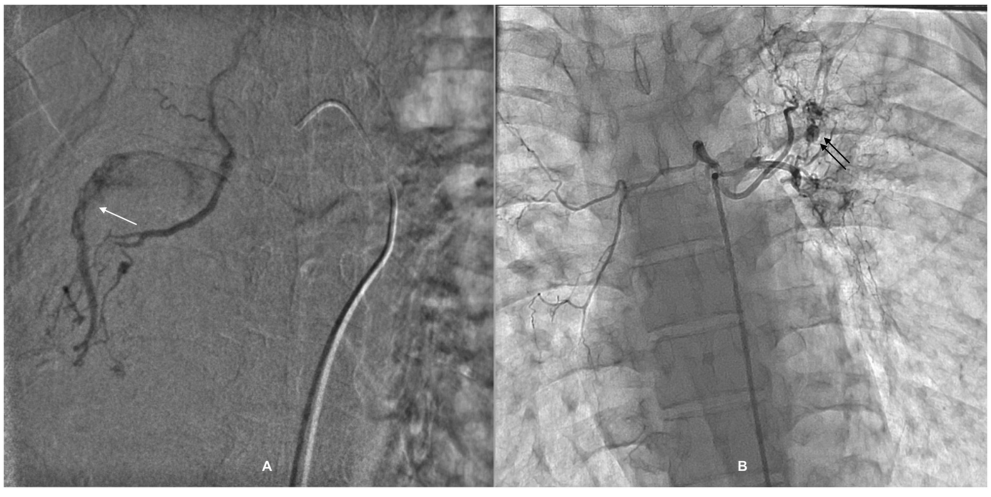

Fig. 2 – A: Right bronchial angiogram (digital subtraction angiographic image) showing spillage of the contrast material from the right bronchial artery (white arrow) into the pulmonary vein. B: Left bronchial angiogram showing the presence of a bronchial artery aneurysm along with tortuous and hypervascular bronchial artery (black arrows).

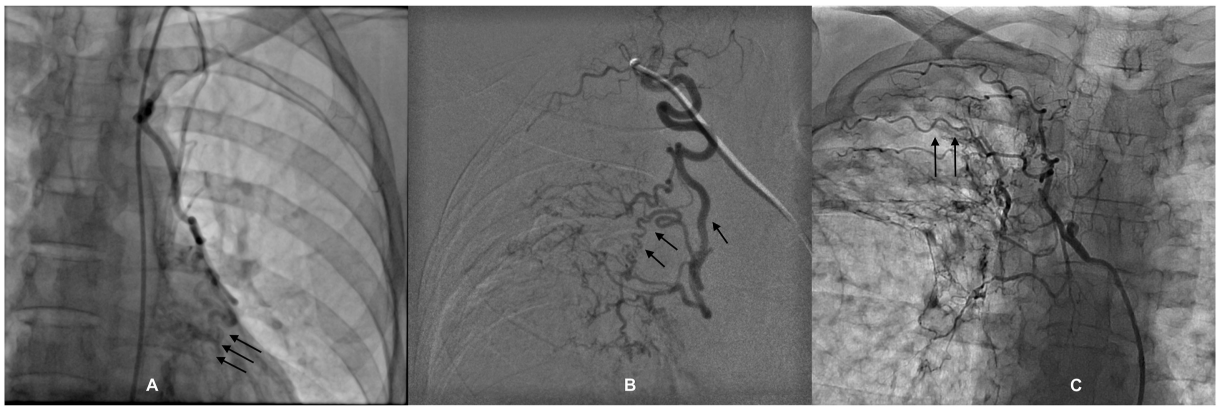

Fig. 3 – A: Selective left internal mammary angiogram showing multiple tortuous hypervascular branches supplying a lesion in the left lower zone (black arrows). B: Selective right internal mammary angiogram (digital subtraction angiographic image) showing multiple small tortuous branches supplying a hypervascular lesion in the right upper lobe (black arrows). C: Selective intercoastal angiogram on the right side showing multiple tortuous and hypervascular intercoastal arteries (black arrows) in the right upper zone fibrotic lesion.

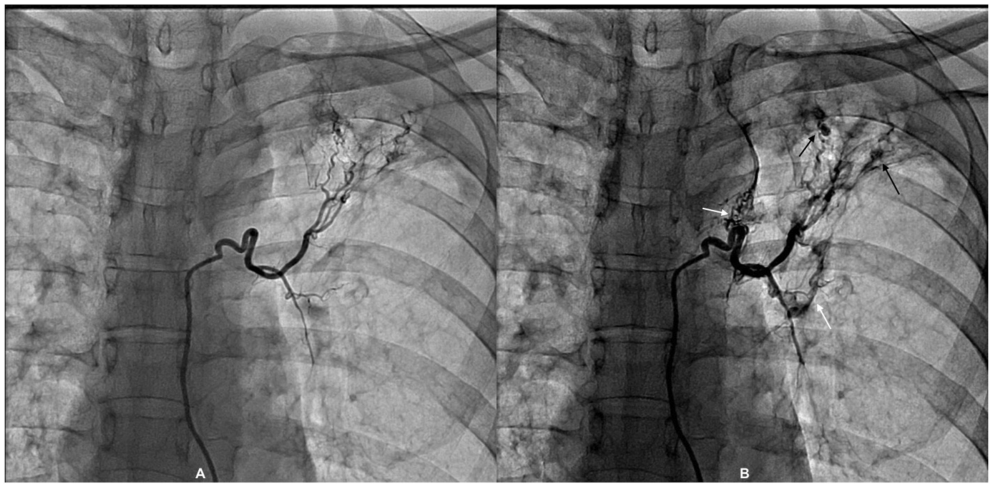

Fig. 4 – A: Left bronchial angiogram prior to embolization showing the presence of a multiple tortuous vessels in the left upper zone fibrotic lesion. B: Left bronchial angiogram repeated midway during the embolisation procedure showing vascular stasis in the distal vasculature with appearance of multiple bronchial artery aneurysms (black arrows) and new feeder vessels from proximal vessels (white arrows). These bronchial artery aneurysms (black arrows) were only visualized when there was a stasis in the distal vasculature and redirection of flow of contrast in proximal vasculature.

means of the continuous data was done using the Student's t-test. Similarly, the categorical variables were compared using the χ^2 test. Multi-variate logistic regression analysis was done to determine the independent predictors for recurrence following BAE. Analysis was performed using statistical package for the social sciences version 24.0 (IBM Corporation, Armonk, NY, USA). A P-value of <0.05 was considered statistically significant. A written informed consent was obtained from all patients prior to the performance of BAE. The study was approved by the institutional human ethics committee.

3. Results

A total of 187 patients underwent BAE over a period of 18 months from January 2018 till June 2019. The mean age of the patients was 42.2 ± 12.4 years with a majority of them being males (94.1%). Cough and hemoptysis were the major symptoms seen in all patients followed by dyspnoea in 148 (79.1%), wheezing in 56 (29.9%) and fever in 7 (3.7%) patients. Massive or life-threatening hemoptysis [defined as hemoptysis >300 mL/day or associated with hemodynamic compromise][2] was documented in 16 (8.5%) patients. A significant proportion of the enrolled subjects (159 [85%]) reported prior history of anti-tuberculous therapy while active tuberculosis was seen in 2 (1.1%) patients. A history of smoking (beedi/cigarette/hookah) was reported in 128 (68.4%) patients (Table 1). Post-tubercular sequalae was the most common presenting diagnosis (157 [84%] patients) followed by idiopathic bronchiectasis (19 [10.2%]), aspergilloma (7 [3.7%]), lung malignancy and active pulmonary tuberculosis in two patients (1.1%) each. All the patients with an aspergilloma were a

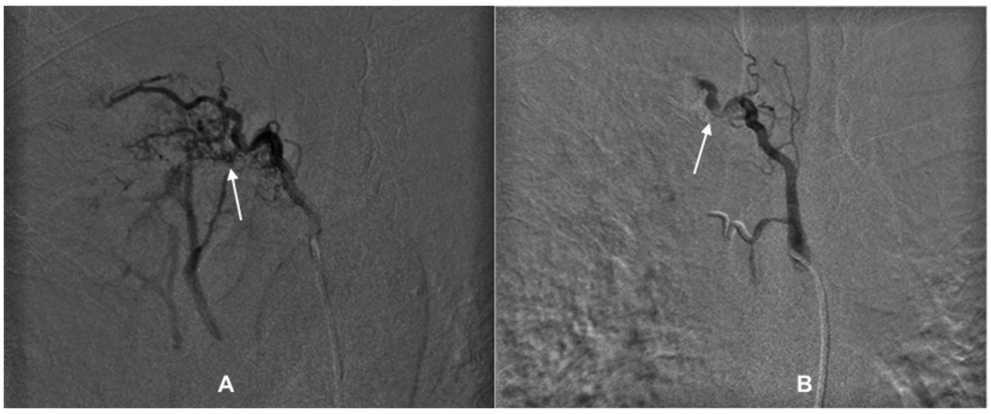

Fig. 5 – A: Right bronchial angiogram (digital subtraction angiographic image) prior to embolization showing the presence of a multiple tortuous vessels supplying a hypervascular staining lesion (white arrow) in the right upper zone. B: Right bronchial angiogram (digital subtraction angiographic image) done post embolization showing vascular stasis along with disappearance of the hypervascular lesion (white arrow) in the right upper zone.

Table 1 – Demographic profile of patients who underwent bronchial artery embolization.

Number (n)	187
Sex (Male/Female)	176/11
Mean age	42.17 ± 12.42 years
Duration of symptoms	8.1 ± 4.2 days
Clinical symptoms	
Cough	187 (100%)
Hemoptysis	187 (100%)
Dyspnea	148 (79.1%)
Wheezing	56 (29.9%)
Fever	7 (3.7%)
Massive hemoptysis	16 (8.5%)
Smoking	128 (68.4%)
Prior anti-tubercular therapy	159 (85%)

part of the post-tubercular sequalae. None of the patients had a history of bleeding diathesis and PT-INR levels were normal in all of them.

A total of 246 vessels were embolized in 187 patients including both bronchial as well as non-bronchial systemic arteries. Gelfoam was used for embolization in 175 (93.5%) patients while the remaining patients underwent BAE using PVA particles. Right sided bronchial arteries were more commonly involved as compared to the left sided bronchial arteries [(143 (76.5%) vs. 35 (18.7%)); $P < 0.0001$]. Right intercostobronchial trunk (Fig. 6) were embolized in 59 (38.1%) patients. Non-bronchial systemic arteries too were embolized with intercostals in 29 (15.5%), internal mammary artery in 14 (7.5%) and subclavian artery in 4 (2.1%) patients. Complete resolution of hemoptysis was observed in 183 (97.8%) in the first 24 hours post procedure while recurrence was seen in 34 (18.2%) patients over a period of six months of follow-up of whom 28 (82.4%) underwent a repeat embolization. Patients with recurrence (n = 34) had significantly higher number of diabetics, greater sputum and cartridge based nucleic acid amplification test positivity, higher frequency of aspergillomas, active pulmonary tuberculosis and internal mammary artery involvement. There was no significant difference in terms of age, sex distribution, smoking status and target

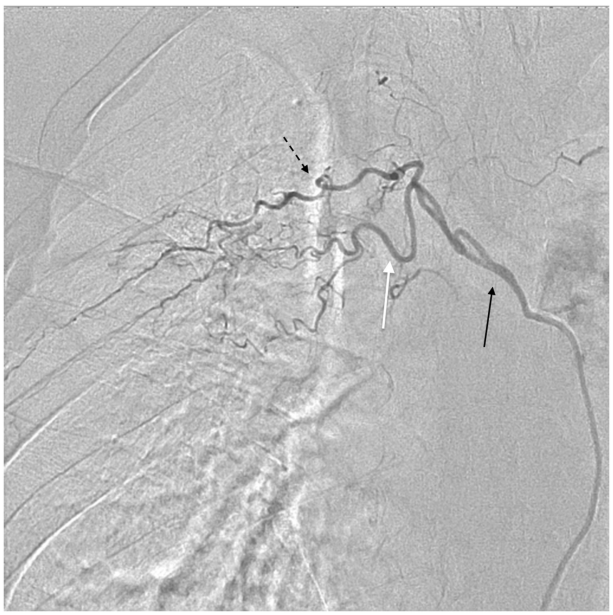

Fig. 6 – Right bronchial angiogram (digital subtraction angiographic image) showing the presence of a right intercostobronchial trunk (black arrow) from which arises an intercostal artery (black dashed arrow) and a bronchial artery (white arrow).

bronchial arteries in patients with recurrence as compared to those without (Table 2). Multi-variate logistic regression analysis showed that diabetes, presence of an aspergilloma and feeding vessels from internal mammary artery were the independent predictors of recurrent hemoptysis (Table 3).

Pleuritic chest pain was the most common complication observed in 47 (25.1%) patients which was mostly transient and resolved spontaneously or with mild analgesics. Dysphagia was seen in 25 (13.4%) patients and was mostly mild and resolved spontaneously. Neurological complications in the form of paraparesis was observed in 2 (1.07%) patients. There was a remarkable recovery seen in one patient within 48 hours while the other one had persistent neurological

Table 2 – Comparison between patients with and without recurrence of hemoptysis post bronchial artery embolization.

	Patients with recurrence (n = 34)	Patients without recurrence (n = 153)	P-value
Age	42.56 ± 15.14	42.08 ± 11.78	0.84
Sex (M/F)	31/3	145/8	0.65
Diabetes Mellitus	10 (29.4%)	11 (7.2%)	**<0.0001**
Sputum AFB positivity	2 (5.9%)	0 (0%)	**0.003**
CBNAAT positivity	3 (8.8%)	1 (0.6%)	**0.003**
Diagnosis			
Post-tubercular sequalae	22 (64.7%)	135 (88.2%)	**0.001**
Idiopathic bronchiectasis	4 (11.7%)	15 (9.8%)	0.732
Aspergilloma	5 (14.7%)	2 (1.3%)	**<0.0001**
Malignancy	1 (2.9%)	1 (0.6%)	0.24
History of anti-tubercular therapy	29 (85.3%)	130 (84.9%)	0.91
Smoking status	23 (67.6%)	105 (68.6%)	0.91
Target vessels			
Right bronchial artery	24 (70.6%)	119 (77.8%)	0.37
ICBT	4 (11.8%)	17 (11.1%)	0.91
Left Bronchial artery	7 (20.6%)	28 (18.3%)	0.75
IMA	6 (17.6%)	8 (5.2%)	**0.01**
Sub-clavian artery	1 (2.9%)	3 (1.9%)	0.72
Intercoastal artery	7 (20.6%)	22 (14.4%)	0.36

Abbreviation - AFB: acid fast bacilli; CBNAAT: cartridge based nucleic acid amplification test; F: female; ICBT: intercostobronchial trunk; IMA: internal mammary artery; M: male. A P value of <0.05 was considered as significant.

Table 3 – Independent predictors of recurrence of hemoptysis post bronchial artery embolization.

	Odds Ratio (OR)	95% CI	P-value
Age	1.01	0.97–1.06	0.39
Diabetes Mellitus	6.09	1.98–18.76	**0.002**
Smoking	0.65	0.24–1.79	0.41
Aspergilloma	25.30	4.10–155.91	**<0.0001**
Sputum AFB positivity	1.0	0.97–1.04	0.66
CBNAAT positivity	1.99	0.02–18.02	0.76
IMA involvement	6.89	1.81–26.11	**0.005**

A P value of <0.05 was considered as significant.

deficit six months post procedure. Access site complications were seen in 6 (3.2%) patients in the form of hematoma formation in four and pseudoaneurysm formation in two patients. Post manual compression, both these pseudoaneurysm had resolved. There were no deaths during or post BAE within the six months of follow-up period.

4. Discussion

Our study showed that BAE is a safe and effective procedure for the control of hemoptysis. Most of the patients in our series were males with a mean age of 42.1 years. A review of the literature on BAE from India (Table 4) too reported similar findings with majority of patients being in the age group of 40–50 years.[7–24] In our series, post-tubercular sequelae (Fig. 5A) was the most common diagnosis in patients with hemoptysis. This goes to show that tuberculosis is still quite rampant and hemoptysis is frequent among patients with sequalae of pulmonary tuberculosis. In one of the largest series by Bhalla and colleagues,[15] post-tubercular sequalae too was the foremost cause of hemoptysis (74%) in patients undergoing BAE. Similarly, in the study by Khoja,[10] post-tubercular fibrocavitary lesion (50.4%) were most commonly associated with hemoptysis. In one of the recent series from India, Mishra et al,[24] too had reported post-tubercular bronchiectasis to be the most common reason of hemoptysis in patients undergoing BAE. Idiopathic bronchiectasis (Fig. 5B) and aspergillomas (Fig. 5C) were the other causes of hemoptysis documented in our series. Hemoptysis in patients with aspergillomas usually occurs due to mechanical irritation by the fungal ball and release of proteolytic enzymes such as hemolytic endotoxins and trypsin. These episodes of hemoptysis are often long standing and recurrent despite multiple BAE attempts.[25]

Data regarding the etiology of hemoptysis varies with post-tubercular sequelae being the primary etiology in series published from Asia while the western data reported more of bronchiectasis, malignancy and lung abscess.[2] In the series of 69 patients published from United States, Tom et al[26] reported that sarcoidosis and cystic fibrosis were two most common indications (36%) for performance of BAE while tuberculosis/post-tubercular sequalae comprised only 8% of cases. Though patients with active tuberculosis may present with hemoptysis, its response to anti-tuberculous therapy is remarkable. In our series, hemoptysis in patients with active tuberculosis was uncommon being reported in only 2 patients, a finding consistent with other large series on BAE from the Indian sub-continent.[2,7,15,24]

The main source of bleeding in our series were the bronchial arteries with right sided involvement being significantly higher than left. This was followed by involvement of non-bronchial systemic arteries such as IMA, subclavian and intercoastal arteries. Similar findings were reported in the study by Lee et al[27] and Chan et al.[28] A search for non-bronchial systemic arteries as feeder vessels should always

Table 4 – Review of the studies on bronchial artery embolization published from India.

S no.	Author/Year (Study design)	No. of pts/Age	Diagnosis	Embolizing material	Follow-up period	Initial clinical success	Recurrence	Mortality	Complications
1	Ramakantan R et al,[7] 1996 (Prospective)	140/31.5 years	Tuberculosis (active/re-activation): 123 (88%) Aspergilloma: 17 (12%)	Gel foam*: all patients	180 days	102/140 (73%)	38/140 (27.1%)	3/140 (2.14%)	Chest pain: 33/140 (23.5%) Pain in left side of orbit/ forehead: 9/140 (6.4%) Paraparesis: 2/140 (1.4%) (transient) Dysphagia: 1/140 (0.7%)
2	Mani S et al,[8] 1997 (Prospective)	37/41.5 years	NA	Gelfoam*	180 days	33/37 (89%)	4/37 (10.8%)	1/37 (2.7%)	Fever: 3/37 (8.1%) Dysphagia: 1/37 (2.7%) Neurological complications: Nil
3	Dwivedi MK et al,[9] 1999 (Prospective)	50/40.5 years Three patients did not undergo embolisation	Post-tubercular sequalae: 50 (100%)	Gelfoam*	180 days	45/47 (95.7%)	2/47 (4.3%)	NA	Transient chest pain: 18/47 (38.3%) Dysphagia: 2/47 (4.3%) Neurological complications: Nil
4	Khoja AM,[10] 2003 (NA)	280/NA	Post-tubercular fibrocavitary lesion: 141/280 (50.4%) Post-tubercular bronchiectasis: 27/280 (9.6%) Active tuberculosis (sputum AFB+): 102/280 (36.4%) Active tuberculosis (sputum AFB-): 6/280 (2.1%) Aspergilloma: 4/280 (1.4%)	PVA, gelfoam*, coils	180 days	255/280 (91%)	28/280 (10%)	1/280 (0.4%): unrelated to the procedure	Fever: 265/280 (94.6%) Chest pain: 97/280 (34.6%) Dysphagia: 13/280 (4.64%) Paraparesis: 2/280 (0.7%)
5	Singhal S & Banode P,[11] 2011 (Prospective)	11/40 years	Active tuberculosis: 6 (55%) Bronchiectasis: 5 (45%)	PVA, Gelfoam	365 days	NA	1/11 (9.1%)	NA	NA
6	Whig J et al,[12] 2011 (Abstract) (Retrospective)	110/46 years	Post tubercular bronchiectasis: 53 (48%) Active pulmonary tuberculosis: 40 (36%) Mycetoma: 11 (10%) Pneumonia: 4 (6%) Pulmonary embolism: 1 (0.9%) Unknown: 1 (0.9%)	PVA*, coils, Gelfoam	NA	102/110 (92.7%)	10/110 (9.1%)	1/110 (0.9%)	Perforation of bronchial artery: 2/110 (1.8%) Transient chest pain: 10/110 (9.1%) Secondary infection: 1/110 (0.9%)

7	Anuradha C et al,[13] 2012 (Prospective)	58/43 years	Post tuberculosis sequelae: 44/58 (76%) Active tuberculosis: 14/58 (24%)	PVA	432 days	54/58 (93.1%)	27/58 (46.5%)	7/58 (12.1%)	Chest pain: 20/58 (34.5%) Dysphagia: 3/58 (5.1%) Dissection: 2/58 (3.4%) Fever: 1/58 (1.7%) Contrast reaction: 1/58 (1.7%) TIA: 1 (1.7%)
8	Bhargava J et al,[14] 2014 (Retrospective)	40/NA	Fibro-cavitary disease: 18 Bronchiectasis: 12 Malignancy: 1 Tuberculosis infection/infiltration: 7 Aspergilloma: 2	Gelfoam*	180 days	NA	3/40 (7.5%)	0	Fever: 4/40 (10%) Neurological complications: Nil
9	Bhalla AS et al,[15] 2015 (Retrospective)	334/41 years	Post-tubercular sequalae: 248/334 (74.2%) Bronchiectasis: 34/334 (10.2%) Tumours: 2/334 (0.6%) Acute infections: 13/334 (3.9%)	PVA*, gelfoam, NBCA	NA	312/334 (93.5%)	42/334 (12.6%)	1/334 (0.3%)	Dissection and rupture: 9/334 (2.3%)
10	Narasimhalu N et al,[16] 2015 (Prospective)	30/47.8 years	Post-tubercular sequalae: 19/30 (63.3%) Active tuberculosis: 7/30 (23.3%) Aspergilloma: 2/30 (6.6%) Bronchogenic carcinoma: 2/30 (6.6%)	PVA*, gelfoam, coils	90 days	30/30 (100%)	8/30 (26.7%)	NA	27/30 (90%): minor complications
11	Rajani M et al,[17] 2015 (Prospective)	25/NA	Bronchiectasis: 25 (100%)	PVA*, coils, Gelfoam	3 years	NA	NA	3/25 (12%)	NA
12	Gupta A et al,[18] 2015 (Only Abstract)	43/49.5 years	Tuberculosis/post-tubercular sequalae: 100%	PVA*	180 days	43/43 (100%)	20/30 (66.6%)	NA	NA
13	Bhardwaj R et al,[19] 2016 (Prospective)	74/46.7 ± 14.6 years	Tuberculosis: 64/74 (Active: 7; Treated: 57) Bronchiectasis: 2/74 Aspergilloma: 2/74 Unknown cause: 6/74	PVA*	365 days	74/74 (100%)	13/74 (17.5%)	3/74 (4.1%)	Nil
14	Gupta S et al,[20] 2017 (Only Abstract) (Prospective)	29/NA	Tuberculosis: 65% Bronchiectasis: 13.7% Aspergilloma: 13.7%	PVA, microcoils	180 ± 150 days	NA	1/29 (3.4%)	NA	Nil

(*continued on next page*)

Table 4 – (*continued*)

S no.	Author/Year (Study design)	No. of pts/Age	Diagnosis	Embolizing material	Follow-up period	Initial clinical success	Recurrence	Mortality	Complications
15	Bhattacharya D et al,[21] 2017 (Only Abstract) (Retrospective)	107/36.4 years	Bronchiectasis: 47 (43.9%) Tuberculosis: 36 (33.7%) Malignancy: 13 (12.1%) Mycetoma: 7 (6.5%) Necrotizing pneumonia: 2 (1.9%) Unknown: 2 (1.9%)	PVA	180 days	98/107 (91.5%)	9/107 (8.4%)	NA	Local hematoma: 3/107 (2.8%)
16	Ingole S et al,[22] 2017 (Prospective)	40/NA	Pulmonary tuberculosis: 40 (100%)	NA	180 days	NA	4/40 (10%)	NA	Chest pain: 10/40 (25%) Paraparesis: 1/40 (2.5%)
17	Prakash S et al,[23] 2017 (Prospective)	35/48.3 years	Acute infective pathology: 12/35 (34.2%) Active tuberculosis: 11/35 (31.4%) Post tubercular sequalae: 10/35 (28.5%) Pulmonary Aspergilloma: 2/35 (5.7%)	PVA*, coils, Gelfoam	90 days	32/35 (91.4%)	6/35 (17.1%)	2/35 (5.7%) Cardiac arrest: 1 Massive bleed: 1	Chest pain: 7/35 (20%) Transient dissection: 1/35 (2.8%) Monoparesis: 1/35 (2.8%)
18	Mishra A et al,[24] 2018 (prospective)	52/48 ± 18 years	Post-tubercular bronchiectasis: 23/52 (44%) Chronic pulmonary tuberculosis changes: 11/52 (21%) Aspergilloma: 7/52 (13%) Non-tubercular bronchiectasis: 3/52 (6%) Malignancy: 1/52 (1.9%)	PVA, gelfoam	35 days	48/52 (92%)	2/52 (3.8%)	2/52 (3.8%)	Chest pain: 5/52 (9.6%) Puncture site re-bleed: 1/52 (1.9%) right lower extremity monoparesis: 1/52 (1.9%)

Abbreviations: AFB: acid fast bacillus; NA: not available; PVA: Poly-vinyl alcohol; TIA: transient ischemic attack.

be made as it has been shown that embolization of these vessels leads to better control of hemoptysis with far lower recurrence rates. A multitude of embolic agents such as gelfoam, PVA particles, coils and glue have been used for BAE with varying results. Gelfoam forms a cost-effective treatment option however, recurrences are known to occur as it gets reabsorbed over a period of time. In a study by Hahn et al[29] comparing gelfoam with PVA found that there was no significant difference between these two agents immediately post procedure and after one month. However, PVA had better mid-term results at 12 months with fewer recurrences. Data on the other embolic agents are often limited and conflicting.[2]

Various studies have documented the immediate clinical success rates ranging from 70 to 99%.[2,7–24] In the series by Bhalla et al,[15] immediate clinical success was reported as 93.5% while in our study, it was 97.8%. Multiple studies have shown that recurrence rates vary from 9.8% to as high as 57.5%.[2,7–24] In our study too, the recurrence rate was reported in 18.2% over a period of six months of follow-up. Despite the use of newer embolizing materials and availability of better hardware in the catheterization laboratory, the recurrence rates have not gone down. In the systematic review by Bhalla et al[2] recurrence rates in series published prior to 2010 was 15.5–47% while post 2010 it was 9.8–57.5%. Previous studies have shown that diabetes mellitus, presence of an aspergilloma and a shunt lesion were associated with increased recurrences.[18,30] Our study too showed that diabetes, aspergilloma and IMA as target vessel are independent risk factors associated with recurrence.

BAE is usually a safe procedure with major complications being far and few. In our series, the most common complication was chest pain which was transient and self-limiting. Most of the studies on BAE have reported chest pain, dysphagia and post-embolization syndrome (fever, leukocytosis and pain) to be the most common complications following the procedure. Neurological complications such as transient or permanent paraparesis/paraplegia have been reported to occur in 0.6–4.4% of patients undergoing BAE.[2] This is due to ischemia of the spinal cord as a result of inadvertent embolization of spinal arteries arising from the bronchial arteries. Two schools of thought exist regarding performance of BAE in patients with visible anterior spinal arteries on the bronchograms. While one group of authors[31,32] consider visibility of anterior spinal arteries as an absolute contraindication for BAE, the other group favors use of microcatheters for super selective angioembolization in such cases.[2] However, presence of the artery of Adamkewich is an absolute contraindication for BAE. In our series, two patients developed paraparesis with complete recovery in one of them. In the largest retrospective study from India,[15] neurological complications were documented in 2.3% of patients while a recent study reported it in 1.9%.[24] Other less common neurological complications include transient ischemic attack or stroke and cortical blindness mostly due to embolizing material crossing bronchopulmonary anastomoses.[2] Local site complications such as femoral puncture site hematomas and pseudoaneurysm as well as contrast medium hypersensitivity are known to occur albeit rare. In our study, hematoma and femoral artery pseudoaneurysm was reported in six and two patients respectively.

To the best of our knowledge, ours is one of the largest prospective study on BAE from India with the literature review showing that most of the previous studies on this topic have been retrospective in nature. In addition, we tried to evaluate the factors that are responsible for recurrence of hemoptysis in these patients. The limitations of our study were that it was a single center study with a limited duration of follow up for 6 months post procedure. Secondly, gelfoam was used as an embolizing material in a majority of patients. This was due to the fact that most of these patients had financial liabilities and could not afford the costlier PVA particles hence, necessitating the use of gelfoam. Despite the use of gelfoam, we achieved a modest success rate at six months of follow-up with fewer complication rates.

5. Conclusion

BAE is a safe and effective life-saving procedure for the immediate control of hemoptysis. In developing countries such as India with a significant burden of tuberculosis and its sequalae, there is an ever-increasing population of patients presenting to the emergency department with hemoptysis. BAE has revolutionized the management of these patients for whom surgery was often the only resort. However, it should be kept in mind that BAE is not the sole panacea in all patients with hemoptysis and often serves as a bridge therapy until definitive treatment options are formulated.

Conflicts of interest

The authors have none to declare.

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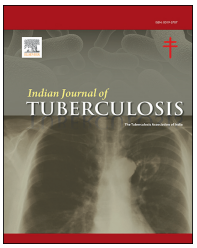

Original Article

Pharmacy based surveillance for identifying missing tuberculosis cases: A mixed methods study from South India

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ABSTRACT

Background: No Indian studies have assessed the implementation of recent policy on pharmacy based surveillance and its contribution in TB notification. So, this study was conducted with objectives to describe: a) pharmacy based TB surveillance and TB notification, and b) experiences of pharmacy based surveillance implementation from the programme managers and pharmacists perspective.

Methods: A mixed methods study—quantitative (cross-sectional) and qualitative (in-depth interviews) in two selected districts Dharmapuri and Salem districts of Tamil Nadu State, India.

Results: In 2018, 45 (11%) of 397 pharmacies in Dharmapuri and 90 (6%) of 1457 pharmacies in Salem districts reported sale of anti-TB drugs to 1307 and 1673 persons respectively. Upon validation through direct patient contact 942 (72%) persons in Dharmapuri and 863 (52%) persons were identified as previously 'un-notified' TB patients. These patients constituted 20% and 29% of the total TB cases notified in Dharmapuri and Salem respectively. The enablers for implementing this activity were: understanding the importance of notification, availability of resources (manpower, computers) to record, report and validate the patient data, repeated trainings and partnerships. The barriers were: patients' hesitancy to share their details to pharmacists (confidentiality), cumbersome recording and reporting process, difficulties in recording patient details during high workload busy business hours.

Conclusion: This process contributed about one-fourth of the TB patients notified in these districts. Its implementation needs to be strengthened and should be scaled up in other parts of the country.

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1. Introduction

India contributes a quarter of global tuberculosis (TB) burden with an estimated annual incidence of 2.8 million patients. However, in 2017, only 1.9 million patients were notified—about0.9 million were'missing',[1] the missing TB cases are presumed to be either undiagnosed or diagnosed and treated in the vast private sector but not notified to the public health authorities. Detection, notification and providing quality assured TB services to the missing TB patients is an essential step to End TB by 2025 in the country.[2,3] Hence several efforts are being made to engage the vast private health sector in the country and get the information on TB patients diagnosed and treated by them.[4]

Private pharmacies play an important role in providing TB treatment in India as it is the point of anti-TB drug sale for TB patients diagnosed and treated in the private sector.[5,6] An analysis of the sale of anti-TB drugs in the country indicated that the quantum of anti-TB drugs sold is huge and could possibly be used to treat 65–117% of new incident TB cases.[7] Therefore, it was strongly felt that engaging pharmacies could help in obtaining information on the TB patients diagnosed and treated in the private sector. To this effect the Government of India released a Gazette Order on March 16, 2018 making notification of TB patients by private practitioners, laboratories and pharmacies mandatory.[8] Accordingly to the Gazette Order, all pharmacies are expected to share the details of patients and their providers for whom they have sold the anti-TB drugs in a structured format on a monthly basis. Thereafter, these patients are contacted and verified by public health authorities or their authorized representatives. This process is called as "Pharmacy based surveillance". This will help public health authorities to deliver quality assured anti-TB services as well as get a relatively more accurate measure of the disease burden in the country.[9]

This pharmacy based surveillance is similar to the inventory or record linkage studies reported from other countries.[10–12] Previous studies in India have assessed ways to engage the pharmacies in TB control activities,[5,13–15] however none of the studies have assessed the pharmacy based surveillance implementation in national TB programme and its contribution in TB notification. In this study, conducted in two districts of the South Indian State of Tamil Nadu, we describe: a) pharmacy based TB surveillance and TB notification, and b) experiences of pharmacy based surveillance implementation from the perspectives of programme managers and pharmacists.

2. Methods

2.1. Study design

This was a mixed methods study with quantitative (cross-sectional study) and qualitative component (in-depth interviews with pharmacists and TB programme managers) in a concurrent design.[16]

2.2. Setting

2.2.1. General

Tamil Nadu is a southern state in India implementing the Government of India's National Tuberculosis Elimination Programme (earlier named Revised National TB Control Programme, RNTCP- during the study implementation period) for the last 20 years. The two districts where the study was conducted were: a) Dharmapuri—a district located in North western part of State with 1.6 Million population and b)Salem—a relatively larger district situated south of Dharmapuri with 3 million population.

2.2.2. Specific setting

All Pharmacy or anti TB Drug sale points in the state have been mapped by the staff of the RNTCP by assigning a unique Identification number (HFID-Health facility identification number) to them. Information about the movement of anti-TB drugs from the major druggists to the individual sale points (private pharmacies) in the districts were shared by the drug controller officials to the RNTCP. In each district all pharmacies maintain a register called "schedule H1 register" to document patient and provider information if they have sold any of the drugs listed in the schedule H1 of the Drugs and Cosmetics (Fourth Amendment) Rules, 2013.[17,18] Anti-TB drugs are listed in the schedule H1 and therefore all persons to whom they have sold anti-TB drugs at listed in this register. Thereafter, on a monthly basis they have to submit the information on the persons to whom they have sold anti-TB drugs on a structured format [Annexure III of the Gazette Order[8]] to the public health authorities. Apart from this, District Drug Controller Officials (Drug Inspectors) collect sales data of anti-TB drugs as per the inventory records from all the pharmacies and this information is also shared to the RNTCP programme managers.

The information thus obtained is validated by RNTCP staff [public-private mix (PPM) coordinator and/or Senior treatment supervisor (STS)]. Patients are first contacted telephonically to verify the information shared by the drug inspectors. After verification, more information about TB treatment (type of TB, category of Anti-Tb drugs prescribed, treatment outcome) for each patient is obtained by visiting the patient. Patients thus verified are notified to the RNTCP through Nikshay[19](an integrated web based TB notification platform developed by RNTCP). Thereafter, patients are followed up by the RNTCP health workers as per the programme guidelines. The roles of pharmacists, District PPM Coordinators, STS and other non-Government organisations (NGOs) are givenin Table 1.

In Dharmapuri, a total of 337 Pharmacies andhave been mapped of which 45 pharmacies stock anti-TB drugs and in Salem 1457 pharmacies have been mapped of which 90 pharmacies stock anti-TB drugs.

2.3. Study population

2.3.1. Quantitative

The study population included all the patients who purchased anti-TB drugs from pharmacies and were recorded in Schedule H1 register in pharmacies and shared with RNTCP

Table 1 – Designated roles of personnel involved in TB Notification under the Revised national TB Control program in two study districts in Tamil Nadu, India, 2018.

1	Pharmacy/Druggist/Chemist/Retailer	Record and report the sale detail in the prescribed formats namely - Schedule H1 drug register[17] - Annexure III of Gazette Notification register[8] - Report the Sales detail to the Office of the Drug controller
2	District Private Partnership Mix Coordinator (DPPMC)	Collection and collation of the above reports from Retailers. Validation of the individual patient details thus collected; Sharing Patients list with the STS for field verification and validation Notifying in Nikshay[19] after validation
3	Senior Treatment Supervisor (STS)	Validation of the individual patient details by field verification and with their own TB register
4	JEET Coordinator (Joint effort for Elimination of TB)-NGO Partner	Collaborating with Private Practitioners and Pharmacies and RNTCP In Improving Private TB notification as the main focus

between 01st January and 31st December 2018 across two districts- Dharmapuri and Salem in Tamil Nadu State.

2.3.2. *Qualitative*

For the Qualitative part, Pharmacists, RNTCP staff (PPM coordinator, STS)of the 2 districts involved in validation and notification of TB cases from pharmacies were selected by purposive sampling technique to ensure maximum variation.

For pharmacies, we selected a mix of small and large pharmacies; stand-alone pharmacy and those attached with hospitals. For interviews with RNTCP staff, PPM coordinators and STS who were involved in validation and TB notification were selected. The RNTCP staffs from Dharmapuri district were from same office as that of the principal investigator (AF), however, they were informed about the objective of the qualitative interviews and it was clearly mentioned to them that it would not hamper the routine work relationship. For all other participants, they did not know the interviewer and met the interviewer face-to-face at the time of interview.

2.4. *Data variables, sources and data collection*

For the quantitative component, data were sourced from the routine pharmacy validation notification database (based on Schedule H1 register reports from each pharmacy, Annexure III and Anti-TB Drug Sales report from Whole sale Dealers). Data variables included total pills sold, number of prescriptions, number of patients purchased TB pills, number of patients with multiple entries in Schedule H1 register, patients with invalid address/phone numbers, patients validated by STS, patients reported to Nikshay.[19] The data was extracted pertaining to the period 01 January to 31 December 2018 by principal investigator (PI) in February2019.

For the qualitative component, in-depth interviews were held with six pharmacists and four RNTCP staffs (PPM coordinator, STS) about their experiences related to implementing pharmacy-based surveillance. The median experience of the selected pharmacists in dispensing TB drugs was 6 years and 4 were pharmacists attached to hospital. The mean duration of work experience of the RNTCP staffs were 5 years. Prior to the interview, the participants were explained on the study purpose and informed consent was obtained for the interview and for audio-recording. The interviews were conducted in conference halls of District TB Centre—Dharmapuri and Salem—where privacy was ensured. The participants were reimbursed for transportation and provided lunch for the day of the interview. No cash incentives were given to the pharmacists for participation.

Separate interview guides were used for pharmacists and RNTCP staff. No repeat interviews were conducted. Interviews with pharmacists were continued until saturation was achieved. The interview session with each participant lasted between thirty to forty minutes. All interviews were conducted by the principal investigator [female, with Bachelor of Medicine and Bachelor of Surgery (MBBS) degree, Masters in Public Health (MPH) with experience in qualitative research methods; working at Dharmapuri district-RNTCP, Tamil Nadu, India] and in local language (Tamil in which the principal investigator was fluent). The questions were presented in everyday language. Field notes were taken during the interview. The interviews were audio-recorded and transcribed in Tamil by a trained translator. The transcripts in Tamil were translated in English by the principal investigator and information was corroborated with the field notes.

2.5. *Data analysis and statistics*

2.5.1. *Quantitative*

The data were extracted from Pharmacies validation-notification electronic database (Microsoft Excel 2010) from January–December 2018 for two districts. This data was analysed separately for Dharmapuri and Salem districts and summarize during numbers and proportions. Key analytic output was to assess the actual number of persons who purchased anti-TB drugs (as reported in Schedule H1 register of all pharmacies in both districts), of those who purchased, the number (and proportion) validated and notified in Nikshay.

2.5.2. *Qualitative*

Manual content analysis was carried out and themes and subthemes related to experiences related to pharmacy surveillance and TB notification were developed by two independent researchers (AF and MD). No pre-defined themes were used. Transcripts and themes were reviewed by a third person (KM) to reduce subjective bias and enhance interpretive credibility. Disagreements in the content analyses were resolved through discussion. To anonymise the quotations that were used to illustrate the themes, pharmacists were identified as 'P' and programme managers as 'PM'.

2.6. Ethics

Ethics approval was obtained from the Institutional ethics committee of the Government Dharmapuri Medical College, Dharmapuri, Tamil Nadu, India, and the Ethics Advisory Group of the International Union Against Tuberculosis and Lung Disease, Paris, France. For the quantitative component, aggregate data is presented in the paper. For the quantitative component of the study, written informed consent was taken from the study participants as per the consent process submitted to the ethics committees.

3. Results

3.1. Pharmacy based TB surveillance and TB notification

A total of 45 (11%) of 397 existing pharmacies in Dharmapuri and 90 (6%) of 1457 pharmacies in Salem submitted their Schedule H1/Annexure III reports during January to December 2018. According to information obtained from Sales report and Wholesale distributors, 140,731 and 94,605 anti-TB (ATT) tablets were sold in Dharmapuri and Salem respectively (Fig. 1).

In Dhamapuri district, as per these reports, a total of 1307 patients had purchased ATT in Dharmapuri district. On validation by RNTCP staff, 163 were multiple entries of same patients; 168 were patients with invalid addresses, phone numbers and 34 received ATT for non-TB diseases. As a result, of the 1307, 942 (72%) patients were validated as TB patients and notified in Nikshay. In Salem district, 1673 patients had purchased ATT drugs, of whom863 (52%)patients were validated as TB cases and notified to Nikshay. These validated and notified TB cases constituted 20% and 29% of the total TB cases notified during 2018 in Dharmapuri and Salem respectively (Table 2). As a proportion of private sector notifications in 2018, the 942 cases and 863 cases accounted for 64% in Dharmapuri and 97% in Salem districts respectively.

3.2. Pharmacy based surveillance implementation experiences

In-depth interviews were conducted with six pharmacists and four RNTCP staff to explore the enablers and barriers for pharmacy based surveillance and TB notification. The themes pertaining to enablers and barriers overlapped for pharmacists and programme managers and therefore they are described together (Fig. 2).

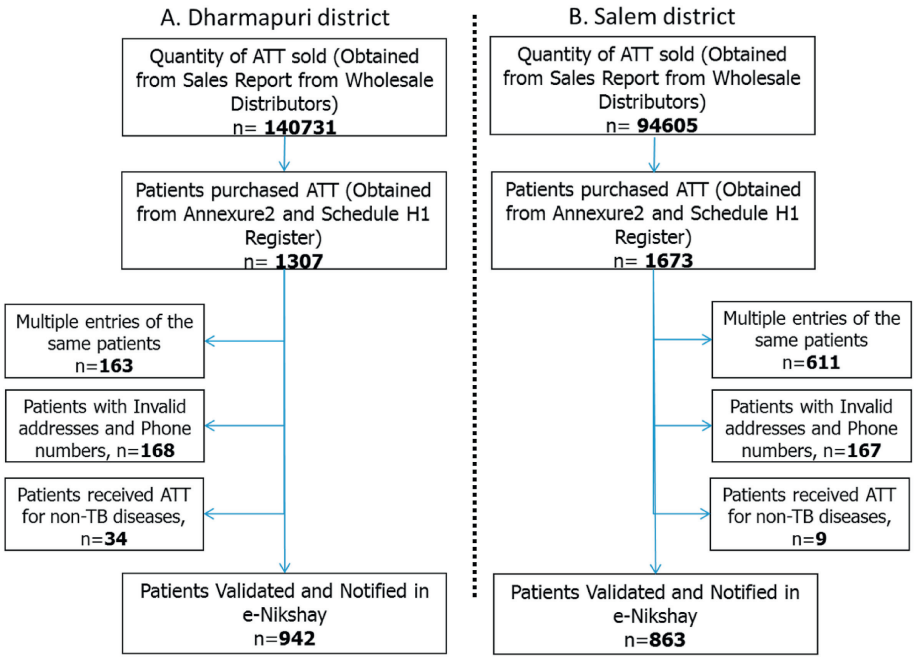

Fig. 1 – Pharmacy surveillance and TB notification cascade in a) Dharmapuri and b) Salem district, Tamil Nadu, January–December 2018.

Table 2 – Contribution of Pharmacy based surveillance report to the annual TB Notification in Dharmapuri and Salem districts of Tamil Nadu, India, 2018.

Notification	Dharmapuri	Salem
Total TB patientsnotified	1577	3033
Total TB patients notified from the Private sector	331	1396
Patients notified as a result of Pharmacy surveillance	942 *[20% of total TB patients notified; 97% of private sector TB patients notified]*	863 *[29% of total TB patients notified; 62% of private sector TB patients notified]*

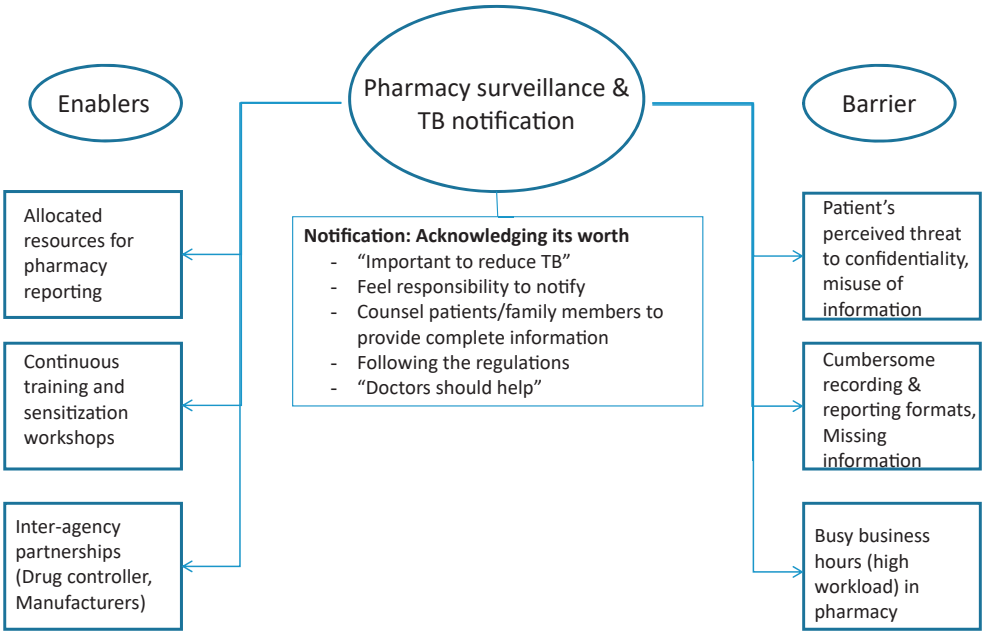

Fig. 2 – Enablers and barriers for pharmacy-based surveillance and TB notification in Dharmapuri and Salem district, Tamil Nadu, India, January–December 2018.

A good understanding of the importance of notification, availability of resources (manpower, computers), repeated trainings/workshops and inter-agency partnerships were identified as enablers while patient's perceived threat to confidentiality, cumbersome recording and reporting process, busy business hours (high workload) were identified as barriers.

3.2.1. *Notification: acknowledging its importance*

The pharmacists and programme managers recognized the importance of TB notification in reducing TB burden. They mentioned that pharmacies played a role in TB notification and it was their responsibility to complete the required information in reporting formats (Schedule H1 register and Annexure III) as per the regulations.

"I feel it is important to notify TB to Government for the future of TB patients' welfare." (P-1)

The participants identified that the awareness about TB notification was still low in patients, thus they had to provide repeated counselling to patients and family members for providing personal details (address, phone numbers, bank accounts) in Schedule H1 register.

"I counsel them and tell them about the disease and treatment aspects."(P-3)

However, the participants felt that private practitioners could support the TB notification process by either notifying themselves or advising the patients to provide details while purchasing the drugs (being an essential requirement for notification process).

I request the treating physicians should counsel their patients in this regard (about TB notification). (P-2)

3.2.2. *Enablers and barriers for pharmacy surveillance and TB notification*

The pharmacists and programme managers mentioned several enablers and barriers that can be summarized under three themes.

3.2.2.1. *Enablers for pharmacy surveillance:*

i. Allocation of adequate resources

The pharmacists and programme managers believed availability of computers; dedicated staff [PPM co-ordinator] and being attached to hospitals contributed in completion of information and helped in TB notification.

"Easy to capture notification because of man power and well-equipped structure" (PM-1)

"Since all information in Schedule H1 register is entered in our computer system, it is easy to give the report in Annex III." (P-6)

ii. Continuous training and sensitization workshops

Multiple trainings and sensitization workshops organized by District TB Officers at regular intervals for pharmacies helped the pharmacists to orient towards the reporting formats (Schedule H1 register and Annexure III). These sessions also helped programme managers in understanding and addressing the challenges faced by pharmacists during the preparation of reports.

"Now after repeated training and sensitization to hospital and pharmacy by DTO, now made easier and effective" (PM-3)·

iii. Inter-agency partnerships

The participants mentioned that engaging Drug Inspectors and Drug-control officers helped in in validation of Schedule H1 registers and TB notification. Few individual pharmacists had stopped stockingATT drugs and were willing to stock government anti-TB drugs (fixed dose combinations)to support the TB programme.

"The help of drug inspectors in ensuring complete and quality report (Inter – agency Co-operation) is sought by us" (PM-3).

3.2.2.2. Barriers of Pharmacy surveillance

i. Patient's perceived threat to confidentiality

The participants mentioned that the patients had fear of being singled out because of TB and would start a verbal dual because of the stigma attached to tuberculosis. Some patients felt shameful to be labelled as a TB patient. They feared that the personal details would be misused and would provide fake phone numbers. The patients did not allow programme managers to visit their homes.

"Patients are very apprehensive in sharing their address and phone numbers. They give wrong phone numbers and addresses."(P-1).

"Patients do not want us to come home- stigma/confidentiality." (PM-2).

ii. Cumbersome recording and reporting process; missing information

The reporting formats (Schedule H1 register and Annexure III) required complete information about patient's name, phone number, address and doctor's prescription, which was often difficult to obtain from patients. Doctor's prescriptions were also incomplete with missing information on date of diagnosis or date of starting treatment. The pharmacists felt the information was being duplicated in these two formats, and simpler format may ease the process.

"When I ask for annexure III supplied from the RNTCP,pharmacist insist that I take the same format given to drug inspectors."(PM-3).

The participants mentioned that the patients did not have money for complete course of treatment leading to multiple purchases in a single month, which led to multiple entries of same patient in reports. There were instances when doctors directly purchased ATT drugs from wholesalers, which were not captured in pharmacy surveillance.

"Patients are not buying the tablets required for entire course of treatment as they do not have money."(P-5)

"Pharmacies supplying ATT only to doctors at discount – not captured even by Drug Inspectors".(PM-4).

iii. Busy business hours (High workload) in pharmacy

Overwhelming business hours hamper getting information from patients whensaleswere prioritized. In addition, crowded Pharmacies acted as disablers in obtaining patient information.

"When the pharmaceutical shop is crowded and when we ask for phone numbers the patients are apprehensive to say it loud and write it in a piece of paper" (P-3)

4. Discussion

This is the first study describing the implementation of pharmacy based surveillance system in the country and the number of TB notifications resulting from itunder routine programmatic conditions. Previous study had highlighted the high volume of anti-TB drug sales and an indirect estimate of the patients receiving treatment in private sector,[7] and this study describes the process of surveillance-validation-notification of pharmacy data under RNTCP.

The major strength of the study was that it describes routine programme process and data. Therefore, the data presented in this manuscript reflects ground level reality. In addition, the study also had a qualitative component which has given further insights into the enablers and barriers for implementing this activity at the field level.

The major limitations of this study were: a)the study was carried out in two districts of Tamil Nadu that was selected based on convenience. Therefore, it may not represent the implementation of pharmacy surveillance in Tamil Nadu or India. b) As this study was done under routine programmatic conditions, the qualitative interviews were conducted by the principal investigator who was the programme manager of one of the district. It is likely that the pharmacies and RNTCP programme staff may not have given information on all the enablers and barriers in an objective manner. We tried to minimizethis by explaining to the interviewees the objective of the study beforehand and by giving them assurance that the information shared will be kept confidential and it willnot affect the future work relationship. However we do admit that this is inadequate and there could be social desirability bias in their responses. Therefore the list of enablers and barriers that we have described in our study may not be comprehensive.

Despite these two major limitations, the study findings highlight several important issues that are of public health relevance.

First, only 11% and 6% of the pharmacies in the districts had submitted the data on anti-TB drug salesduring January to December 2018. The actual number of pharmacies that sold anti-TB drugs, but had not reported about this sale during the year is unknown. Therefore there could be an underestimate in the proportion of the pharmacies that sold the anti-TB drugs to TB patients. Efforts must be made to bridge this gap

in recording and reporting anti-TB drug sales through supportive supervision and monitoring.

Second, we found difficulty in interpreting the aggregate data on the number of anti-TB drugs sold (that was reported by the Wholesalers and pharmacies to the drug controllers' office) and extrapolating it to the possible number of individual-patients to whom these drugs were sold. The aggregate data indicated the number of pills/tablets sold and not the nature of anti-TB drugs sold. For instance if there wasa sale of one tablet/pill each of Isoniazid, Rifampicin, ethambutol and pyrazinamide as individual drugs then it was counted as 'four' drugs/pills and one tablet of the same drugs sold as fixed dose combination was counted and reported as sale of 'one' drug/pill. Given this scenario, we advise programme managers to be cautious in interpreting the data on the aggregate number of anti-TB drugs sold in the market especially when extrapolating it to the number of patients. We did not explore solutions to this problem in our study and therefore we are unable to make recommendations for addressing this issue.

Third, of the patients recorded and reported (in Schedule H1 register& Annexure III), about 70% patients in Dharmapuri and 52% in Salem were validated and notified as TB cases in Nikshay. The remaining were either multiple entries of same patient, or patients who were receiving anti-TB drugs for non-TB diseases or patients who could not be validated due to incomplete addresses and phone numbers. However, in both the districts the number and proportion of TB patients notified as TB cases in Nikshay as a result of pharmacy based surveillance was huge. The country has been identifying ways to increase engagement of private sectors in TB notification, as part of National Strategic Plan 2017-25[3], and implementation of pharmacy surveillance appears to be a huge step in the right direction towards capturing information on all TB patients treated in the country especially in the private sector.

Fourth, the study identified three key enablers that aided in the implementation of pharmacy based surveillance in these districts. First, pharmacies and the local RNTCP programme staff were convinced about the importance of notifying TB cases to the public health authorities and were equipped with additional resources (dedicated staff, computers, space) for recording, reporting and validation of the patient data. Second, periodic trainings, workshops, review meetings that were held by the district TB officers helped all stakeholders to assign and maintain top priority to this activity. Third, the study found that the pharmacy surveillance process involved interactions between multiple agencies (wholesalers, pharmacists, drug-controller office, National TB programme officials) and cross-validations of data between agencies. Thus, establishing and maintaining a harmonious working relationship between the staff of these involved agencies helped in successful implementation of this programme in these areas.

Lastly, one of the major barriers reported by the pharmacists in documenting the patient details on the Schedule H1 register was in convincing patients to give their personal information. The pharmacists reported that patients perceived fear, shame and threat to confidentiality in giving their personal information. TB control programmes must devise ways to empower/educate pharmacists to address these genuine patient concerns pertaining to maintain confidentiality of data andalso fulfil the public health responsibility of notifying such cases to the RNTCP. The other major barriers related to the cumbersome recording and reporting formats, difficulties in filling patient details during busy business hours can be addressed by simplifying the recording and reporting formats. Identifying optimal solutions for addressing these barriers is a subject matter for future research studies.

5. Conclusion

This study on pharmacy surveillance gave important insights about the status of implementation, the contribution of this surveillance system to the overall TB notification numbers, enablers and barriers for implementing this activity at the field level. We recommend that the implementation of this surveillance system must be further strengthened. This will help in eliminating TB in India by providing information on the magnitude of TB cases diagnosed and treated in the private sector and linking patients to quality assured anti-TB services.

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Conflicts of interest

The authors have none to declare.

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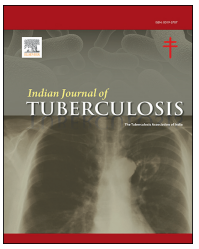

Original Article

Delay in diagnosis of tuberculosis and related factors from a district in Kerala, India

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ABSTRACT

Background: Early diagnosis and treatment of tuberculosis is of vital importance both to cure patients and to reduce transmission for effective control of tuberculosis, It is important to know whether tuberculosis is diagnosed in time and also what causes delay if any.
Objectives: The study was conducted with the objective of knowing the time taken to diagnose tuberculosis from the onset of symptoms and to identify the causes for delay if any.
Methods: A study was conducted in the District of Malapppuram Kerala, South India among newly diagnosed smear positive tuberculosis patients. 489 patients were interviewed soon after diagnosis and their socio-demographic characteristics and details from onset of symptoms to diagnosis were collected using a structured format.
Results: The mean time taken by the patient for consultation after onset was 36 days and the mean time for diagnosis was 42 days and total time until diagnosis was 78 days. 72.8% patients consult within 6 weeks of onset and 74.7% are diagnosed within 6 weeks of consultation. The delay for diagnosis was more with private institutions. Diagnosis took less time when government facilities are consulted and when cough was a prominent symptom. Socio demographic factors are seen not affecting the time.
Conclusions: There is delay in diagnosing tuberculosis especially with private health providers and more efforts are required to reduce the same.

1. Introduction

Tuberculosis is a major Public Health Problem in India which accounts for one fifth of the global burden and is highest burden among all countries.[1] Avoiding delay in diagnosing tuberculosis is important both to provide better prognosis to the patient and to interrupt transmission of the disease in the community.[2,3] Most transmissions are likely to occur during the period between onset of symptoms and initiation of treatment. It is also observed by Madebo et al that the bacillary number on the smear increases as the disease progresses; and patients become more infectious resulting in increased chances for transmission.[4] Therefore in an effective TB control program, early diagnosis and initiation of treatment is vital. The goal of Revised National Tuberculosis Control Program (RNTCP) is to reduce the

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transmission of Tuberculosis in the community while decreasing morbidity and mortality.[1]

Identifying the factors related to delay in diagnosing is crucial in preventing spread of tuberculosis. It is observed by researchers in different parts of the world that factors associated with delay in diagnosis differ according to geographic regions and among ethnic groups.[5] Different studies show that the mean delay for the patient to consult a Health facility after the onset of symptoms (patient delay) varies. Similarly the delay in the system to arrive at a diagnosis (health system delay) also varies. In some studies the patient delay was more where as in others the systems delay.[5]

The District of Malappuram has the largest population among all the districts in Kerala. It differs from other districts socio-demographically and culturally. Till recently it was considered to be a socially and educationally backward district. The district is behind other districts in achieving other health program goals like immunization coverage and also TB detection rates.

TB case detection still remains far below the target in Malappuram District. The data available with the TB Centre as quarterly reports shows that the TB detection rate was 46% and the highest detection rate achieved in any quarter was 52% only.[6] There are various reasons for the same. Around 70% of diagnostic and curative services for all diseases are being catered by private hospitals and practitioners.[7] At present data is not available on the interval between onset of symptoms and diagnosis of Tuberculosis with the District TB Centre. It is also not clear whether delay occurs from the part of the patient to report or because of the delay in the system in arriving at early diagnosis once they report. Nor are the factors associated with such delay if any available. There are only very few studies available from India on this topic when the 20% of the global Burden of tuberculosis is in India. The present study is an attempt to detect the delay if any, in diagnosis of TB in the District and the factors associated with it. Such data can be useful in future for implementing appropriate strategies to bring down the delay. Better case detection can lead to acceleration in the reduction in transmission of tuberculosis. Early diagnosis followed by prompt treatment is envisaged under Revised National Tuberculosis Control Program (RNTCP).

Analysis of the factors leading to delay is crucial in combating the transmission. Institute of General Practice and Community Medicine, University of Oslo, conducted a review of 58 studies and showed that the total diagnostic delay ranges from 60 to 90 days with a mean of 72 days and a standard deviation of 28 days.[5] The longest total delay in diagnosis of >120 days were reported from high endemic countries. In some studies the main part of the delay was resulting from the patient not reporting to the health facility in due time, where as in some other studies the main part of the delay was shown to be from the health care system.[5] Different studies have found out socio economic, socio demographic and other clinical conditions as risk factors for the delay.

1.1. *Objectives*

a. To find out the duration between onset of symptoms and the diagnosis of Tuberculosis in New sputum positive cases in Malappuram District.
b. To find out the factors related to delay in diagnosis in the above cases.

2. Methods

The present study was conducted among the newly diagnosed sputum positive cases in the District of Malappuram, Kerala India. A structured format was developed and pilot tested for collection of data which included patient's socio-demographic characteristics, history of symptoms, history of visits to health facilities and the time taken for diagnosis. Addresses of new cases were obtained from all the designated microscopic centers as and when sputum positivity was detected. All new smear positive cases were visited soon after sputum positivity was diagnosed and data was collected from 489 such diagnosed cases over a period of 6 months (2 quarters) from June through December 2016. The data was collected from the patients by paramedical persons and interns who were trained to do the work. The interview was completed within few days of diagnosing them, either at the treatment centers or at their residence. The data was entered in computer program Microsoft excel; new variables created by transforming the data and analyzed using SPSS.

2.1. *Working definitions*

Patient delay was calculated as duration in days from the onset of symptoms to the first visit to a health provider for these symptoms. If the patient has consulted a health facility by two weeks of onset it was treated as no delay.

System delay was calculated as the duration in days from the 1st visit of the patient to a health provider to the date when sputum result was made available. If the sputum test result was made available within one week it was treated as no delay for the purpose of this study.

The study was financed by RNTCP operational Research funds. There is no conflict of interest involved and a statement to this effect is attached.

3. Results

Data was obtained by interviewing 489 newly diagnosed cases of sputum positive tuberculosis over 6 months using a structured format. Additional qualitative variables were computed after entering the data in excel format, like socio economic status, whether delay was present or not, whether cost

Table 1 – Socio-demographic characteristics of the patients studied (n = 489).

Age group		Number	Percentage
	20 and below	33	6.7
	21–40	122	24.9
	41–60	217	44.4
	61–80	110	22.5
	above 80	7	1.4
Gender			
	Female	150	30.7
	Male	339	69.3
Socio economic Status[a]			
	Upper Class	3	0.6
	Upper Middle	24	4.9
	Lower middle	37	7.6
	Upper Lower	336	68.7
	Lower class	89	18.2

[a] Kuppusamy's Classification of socio-economic status.

involved is high or not etc. Patients interviewed included 150 women (30.7%) and 339 men (69.3%), the age ranging between 12 and 85 with a mean of 48.16 years, belonging to socio economic classes as shown in Table 1.

The median time taken for consultation from the onset of symptoms was 20 days where as the median time for diagnosis from the first consultation was 25 days (The mean was 36.3 days and 41.9 days due to extreme values with few patients). The total time taken from onset of symptoms till diagnosis was median 51 days and mean 78.3 days as in Table 2. This means that half of the patients had the first consultation with in 3 weeks of onset of symptoms while for half of the patients it took more than 25 days for diagnosis after first consultation. Correlation between the patient delay and diagnostic delay was analyzed using Pearson's correlation which showed a weak correlation only with a correlation coefficient of 0.497 ($p = 0.01$). It is observed that 72.8% cases consulted within 6 weeks of onset and 11.9% of cases are diagnosed within a week, 40.3% within 3 weeks and 74.7% within 6weeks once they consult (Table 3).

Bivariate analysis showed that factors like age, gender, education income or socio economic status had no significant relation with delay in diagnosis either from patient side or from the health system. If cough was presented as the prominent symptom the diagnosis the likelihood of diagnosing within one week was better as shown by fisher's exact test (p value 0.028) when compared those presented with other symptoms. Presence of co-morbidities is not affecting the time taken. Other symptoms like fever weight loss tiredness when presented without cough was associated with significantly more delay in diagnosis compared to those presenting with cough (p value 0.02)

Table 2 – Median and Mean time taken for consultation, diagnosis and total time for both.

	Median delay in days	Inter quartile range[a] in days	Mean	Std. deviation
Time taken for consultation	20.	10–35	36.2	68.5
Time taken for diagnosis after 1st consultation	25	14–48	41.8	55.7
Total delay for both	51.	31–82	78.3	104.0

[a] Range of values between 25th percentile and 75th percentile.

Table 3 – Showing delay for consultation (patient delay) and delay for diagnosis in days (n = 489).

Delay	Number	Percentage	Cumulative Percentage
Patient delay			
2 weeks or less (no delay)	171	35.0	35.0
2–6 weeks	185	37.8	72.8
more than 6 weeks	133	27.2	100.0
Diagnostic delay			
<1 week **(no delay)**	58	11.9	11.9
1–3 weeks	139	28.4	40.3
3–6 weeks	168	34.4	74.7
6 weeks to 3 months	80	16.4	91.0
>3 months	44	9.0	100.0

Of the 489 patients, 211 (43%) consulted a government facility from the beginning and remaining 278 consulted a private facility. If the patient consulted a government institution initially, the delay in diagnosis was significantly lower as shown in Fig. 1. (t test. $P = 0.004$). Also the number of visits to the diagnostic facility was lesser and the total cost till diagnosis was less with government facilities (Fig. 2.). Other diagnostic tests like x-rays, CT scans and blood tests were carried out more if the patient consulted private hospitals or practitioners.

When enquired about the reason for delay in consultation, many patients could not give a valid reason for the delay. Among the reasons given by them were self -treatment for cough, mild and vague symptoms which were neglected, presence of other diseases like diabetes, and personal and family problems.

Diagnostic delay in private hospitals was associated with the initiation of other laboratory tests first, like blood tests x-rays and CT scans before sputum examination was done and hence leading to delay. Even though 57% of patients had their first consultation with private or other system consultants, only 31% of these facilities were having a designated microscopy centre attached to their institutions. In the case of government doctors or centres, all had access to a designated microscopy centre. The diagnostic delay was significantly more in case of private doctors and institutions without a DMC (mean 50 days) when compared to those attached to a designated microscopy centre (mean 39 days) as the completion of sputum examination took less time ($p = 0.015$).

Patients reported high expenses incurred until diagnosis the cost being significantly higher in Private Institutions but government institutions also had considerable expenses. The

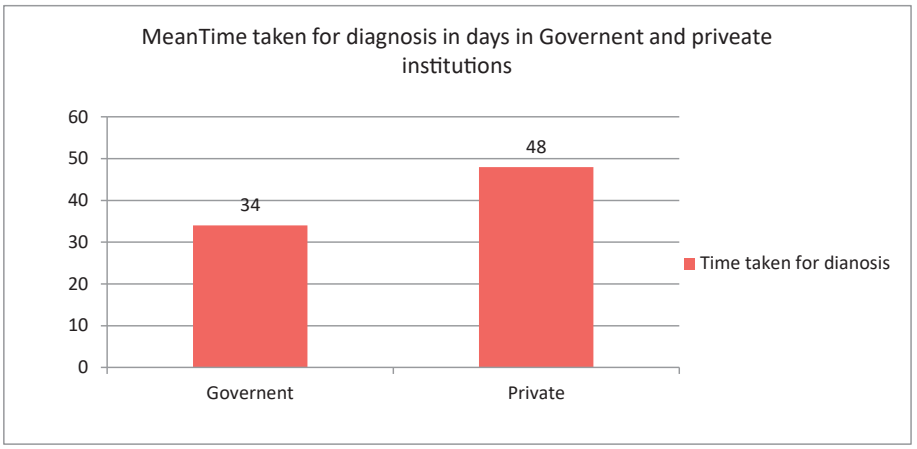

Fig. 1 – Comparison of diagnostic delay in government and Private Facilities.

reported cost included personal expenses, travel cost, fees for consultation diagnosis and treatment till diagnosis.

4. Discussion

There exists delay in diagnosing tuberculosis both from the side of patients for reporting to health facility and at the side of the health facility for diagnosing them after they report. The delay for diagnosis taken by the system is more than that caused by the patient in reporting, which is highly unacceptable and is a barrier for TB control. Socio demographic factor are not seen affecting patient delay. Reported tobacco use or alcohol use of the patient or other co morbidities are also not a significant factor determining patient delay in our study. Presence of cough as a prominent symptom is seen reducing the delay and its absence is accompanied with delay. This may be because of the fact that the definition of TB suspect itself is cough >2 weeks which is well aware to patients and providers. The delay for diagnosis is higher in private institutions compared to government and unnecessary diagnostic tests are accompanied with. The cost incurred by the patient is un-acceptably high in a good proportion of cases and significantly higher in private institutions. When sputum testing facility is available at the centre of first consultation the delay can be significantly reduced.

4.1. *Factors associated with delay in diagnosis*

The Oslo review study mentioned show that some risk factors causing delay in diagnosis in some studies was a factor for

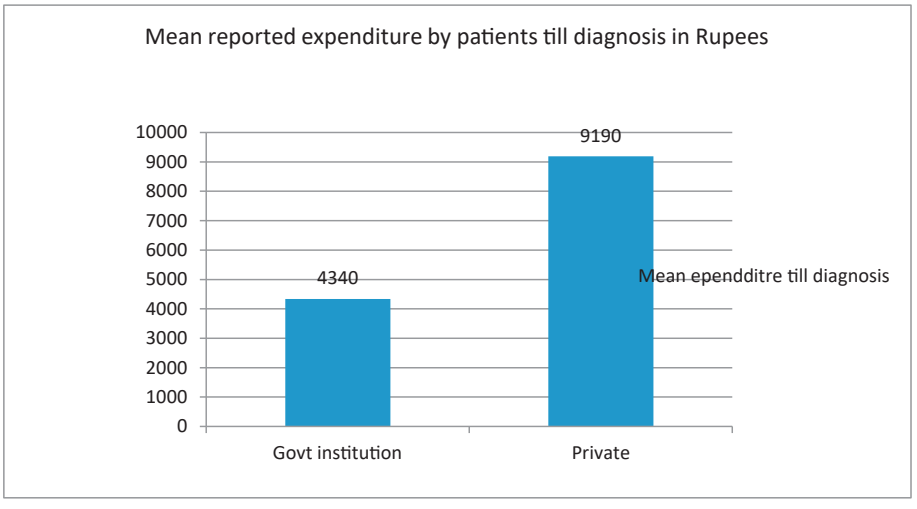

Fig. 2 – Comparison of expenditure till diagnosis incurred by patient in government and Private Facilities.

decreasing the delay in other studies, meaning that the risk factors for delay are different in different areas of the world.[5] For example existence of chronic cough or coexisting lung conditions was showing to cause delay in diagnosis in some studies while showing decrease in delay in other studies.[8,9] WHO study in Syria showed that HIV is a risk factor for delay where as studies conducted in Ghana and Thailand showed the opposite results.[10,11] Alcoholism was a risk factor showing delay in diagnosis in many studies.[12,13] Smoking also was a factor in one study.[14] In our study reported smoking or alcohol use showed no relation to delay. Absence of severe symptoms and general ill health was also shown to be causing diagnostic delay according to other studies.[15]

Poverty is another risk factor shown to be causing delay in many studies but not seen in our study.[14] Low awareness and knowledge were also causing delay in other studies.[13,15] Our study has shown no relation to delay with patients reported income or socioeconomic status. Many studies showed that delay is more in rural areas than urban which could not be studied in our study as the demarcation of urban and rural areas is vague in the district. Going to traditional healers or unqualified practitioners was another risk factor to cause delay.[5,16,17] In our study patients hardly any patients reported going to traditional healers. The first visit of the patient to private practitioners was seen causing delay other studies[14,15] which is similar in our study also. Generally better access to health care system, decrease the delay and in our case access to health facility not a problem for patients but access to sputum testing is not available in many private consulting facilities.

Socio demographic factors like old age, female gender and migrant population[5,14,13,15] were found causing delay in diagnosis in other studies which our study did not show. Another factor shown associated with delay is repeated visits to the same health facility or the same level facility [14, 17.] This was similar in our study also. Consulting traditional healers and quacks were seen causing delay in other studies.[5] In our study hardly any patient consulted such healers. Consulting Private practitioners has shown associated delay in our study also.

In a study conducted by R. Rajeswari et al in South India the awareness about chest symptoms by public was found to decrease delay in diagnosis[13] which is similar to our study finding which shows if cough is prominent symptom delay is less. In general, in this study, patient delay was more when government facility is visited and the system delay more when private facility is consulted.

5. Conclusions

There exists delay in diagnosis of Tuberculosis in a good proportion of cases in the District. The delay for diagnosis is more with Private hospitals and practitioners. There is also unacceptable high cost incurred by patients until diagnosing cases.

The study is conducted with 489 patients available over two quarters and so some factors which were studied in other studies referred could not be studied.

Conflicts of interest

The authors have none to declare.

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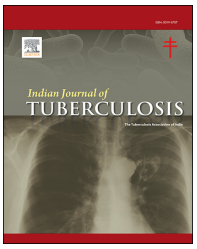

Original Article

Genitourinary non-tuberculous mycobacterial (GU-NTM) infections: A single institution experience in South India

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ABSTRACT

Introduction: Non-tuberculous mycobacterial (NTM) infections are rarely reported, and more so with genitourinary infections. This retrospective study was designed to understand the proportion and behaviour of genitourinary non-tuberculous mycobacterial (GU-NTM) infections compared with genitourinary mycobacterial tuberculosis (GU-MTB) treated at a tertiary care hospital in South India.
Materials and methods: The hospital records of every bacteriologically proved GU-MTB and GU-NTM infections treated at this centre from 2010 to 2016 were retrospectively reviewed.
Results: There were ten patients of GU-NTM and 15 patients of GU-MTB. There was no significant difference in presentation other than lesser frequency of irritative lower urinary tract symptoms (LUTS) among patients with GU-MTB. Urine smear for AFB was positive in 60% and 47% of GU-NTM and GU-MTB patients. 40% of GU-NTM patients had history of urinary tract instrumentation. *Mycobacterium abscessus* was grown in four patients and one had *Mycobacterium fortuitum/chelonae* complex; all the rest were rapid growers. No patient had multi-drug resistant tuberculosis. Imaging studies of GU-NTM patients were indistinguishable from GU-MTB with renal, ureteral and bladder involvements, and stone formation. The drug sensitivities varied among the NTM patients but all showed sensitivity to clarithromycin uniformly. Need for varieties of surgeries in the early and late phases were also comparable.
Conclusions: GU-MTB and GU-NTM infections are indistinguishable from their clinical presentation and imaging studies. All cases of suspected genitourinary mycobacterial infections must be subjected to nucleic acid testing. Treatments based on clinical and

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radiological features without culture studies may misdiagnose GU-NTM infections as MDR GU-MTB, thereby delaying the appropriate treatment.

1. Introduction

Non-Tuberculous Mycobacteria (NTM) or Mycobacteria other than tuberculosis (MOTT) describes those Mycobacterium species that are not members of the *Mycobacterium tuberculosis* or *Mycobacterium leprae* complex. NTM are ubiquitous organisms and can inhabit in soil, water, garbage, raw milk, vegetables, food, pipelines, dust, endoscopic instruments etc. As of March 2020, 190 different species of NTM have been identified,[1] of which only two or three dozen are familiar to clinicians and most microbiologists.[2] NTM are broadly classified by their rate of growth and pigment production in vitro using the Runyon classification. Rapid-growing mycobacteria include *Mycobacterium fortuitum* and the *Mycobacterium chelonae*-abscessus group and characteristically produce non-pigmented colonies on agar plates in less than seven days of incubation. Though infections of genitourinary tract due to *Mycobacterium tuberculosis* (GU-MTB) constitutes 27% (14%–41%) of extrapulmonary tuberculosis,[3] exact prevalence and incidence of genitourinary infections due to non-tuberculous mycobacteria (GU-NTM) are unknown.

NTM infections are generally resistant to the conventional anti-tuberculosis treatment (ATT). The prevalence of multidrug resistant tuberculosis (MDR-MTB) is reported as 2–6% in newly diagnosed cases and 12–35% among previously treated cases.[4–6] Diagnoses were based on clinical suspicion, smear positivity and/or radiologic findings. There is no mention regarding the possibility of including NTM among the so-labelled resistant cases since there are no distinguishing features for MTB and NTM. Reports of case series for genitourinary infections are scarce, and perhaps the largest series reported was of fifteen patients from Taiwan.[7]

This study was designed to analyse the clinical manifestations, imaging features, urine culture and sensitivity results and the outcomes of patients with GU-NTM infections compared with those of GU-MTB after the characterisation and/or speciation of the mycobacterium was made routine.

2. Materials and Methods

We collected the data retrospectively from the records of patients with genitourinary mycobacterial infections from 2010 to 2016 with positive NTM or MTB cultures of urine.

Urine samples were decontaminated with equal volumes of N-acetyl-L-cysteine and 3% sodium hydroxide, neutralized with phosphate-buffered saline, centrifuged, and processed for microscopy, culture and PCR analysis. Urine sediment smears were stained by the Gram and conventional acid fast smear (Ziehl-Neelsen) methods, and the resuspended specimens were inoculated into liquid media (MGIT 960; Becton Dickinson, Sparks, MD, USA). PCR analysis using *GeneXpert* MTB/RIF test (*Cepheid*, Sunnyvale, CA, United States) for *M. tuberculosis* complex was also carried out. Urine sediments were also cultured on blood agar, chocolate agar and MacConkey agar, incubated at 37 °C in air, and any significant growth of Gram positive bacilli was identified by biochemical tests and acid fast smear examination. Specific diagnostic properties of rapidly growing NTM included growth on MacConkey agar within seven days, nitrate positivity, urease positivity, catalase positivity at 68 °C, NaCl tolerance positivity in Lowenstein–Jensen medium and tellurite positivity.

3. Results

There were 25 patients of bacteriology confirmed genitourinary mycobacterial infections among which ten patients had GU-NTM and fifteen patients had GU-MTB, making the proportion of patients with GU-NTM to GU-MTB as 40%–60%. Among the GU-NTM patients, seven were males and three

Table 1 – Comparison of clinical features in GU-NTM and GU-MTB.

Clinical Features	GU-NTM (n = 10)	GU-MTB (n = 15)	P Value
Mean age in years (range)	57.1 (31–79)	54 (21–77)	
Male/Female	7:3	10:5	
Associated Conditions			
Chronic renal disease	2 (20%)	1 (7%)	0.3
Type 2 diabetes	4 (40%)	3 (20%)	0.2
Old pulmonary tuberculosis	1 (10%)	–	
Old GU tuberculosis	1 (10%)	3 (20%)	0.1
CLD	1 (10%)	–	
Prior urinary tract instrumentation	4 (40%)	2 (13%)	0.2
Recurrent stone former	1 (10%)	1 (7%)	0.03
Signs and symptoms			
Irritative LUTS	10 (100%)	10 (67%)	0.03
Fever	4 (40%)	15 (100%)	0.6
Haematuria	4 (40%)	2 (13%)	0.2
Anorexia	2 (20%)	8 (53%)	0.3
Laboratory Parameters			
S. Creatinine >1.5mg/dL	5 (50%)	3 (20%)	0.3
S. Creatinine <1.5mg/dL	5 (50%)	12 (80%)	0.3
Proteinuria	7 (70%)	8 (53%)	0.16
Microscopic haematuria	9 (90%)	8 (53%)	0.36
Pyuria	8 (50%)	15 (100%)	0.2
Mean Urinary pH (Range)	5.8 (5–5.6)	5.7 (4–6.5)	
AFB smear positivity	6 (60%)	7 (47%)	0.13
Abnormalities on Imaging studies			
X-Ray Chest	1 (10%)	3 (20%)	0.1
Abdominal sonography			
Hydronephrosis	4 (40%)	4 (26%)	0.13
Contracted UB	5 (50%)	3 (20%)	0.3
Ureteric stricture	1 (10%)	5 (33%)	0.2
Distorted PCS	1 (10%)	5 (33%)	0.2
Urolithiasis	1 (10%)	3 (20%)	0.1

Table 2 – Diagnosis, Imaging and Treatment of GU-NTM patients.

Case No.	Age/ Sex	Urine AFB Smear	Urine PCR/ culture	Pathogen	Imaging	Anti-NTM Therapy	Duration of treatment	Surgery	Outcome
1	56/F	Positive	PCR positive	*M abscessum*	NA	Levofloxacin, as patient was not keen on anything else	Lost to follow up		
2	79/F	Positive	Culture positive	Rapid grower	Normal CT	Isoniazid, Ethambutol, Ofloxacin	9 months	Nil	Stopped treatment as urine sample became negative; lost to follow up afterwards
3	36/M	Positive	Culture positive	Rapid grower	CT: Bilateral hydroureteronephrosis due to stricture involving ureterovesical junction; small stones right ureterovesical junction and right lower calyx; contracted urinary bladder (Fig. 1)	Levofloxacin 750mg OD, Clarithromycin 500 BD, Ethambutol 1000mg OD, Doxycycline 100mg BD	2 years	Augmentation cystoplasty	Completed 9 months treatment: became symptom-free
4	59/M	Negative	Culture positive	Rapid grower	NA	Levofloxacin 750mg OD, Clarithromycin 500mg BD, Ethambutol 1000mg OD, Doxycycline 100mg BD.	1 year	Nil	Completed 6 months treatment: became symptom-free
5	62/M	Negative	Culture positive	*M abscessum*	Normal CT	Levofloxacin 500mg OD, Amikacin 750mg OD, Linezolid 600mg BD, Doxycycline 100mg BD, Ethambutol 1000mg OD x 5 months; then Amikacin, Linezolid, Doxycycline, Clarithromycin	1 year	Nil	Repeat culture positive after 5 months' treatment: Resistant to quinolones 2nd time
6	56/F	Positive	Culture positive	Rapid grower	CT: Left pyonephrosis	Kanamycin, Isoniazid, Ethambutol, Clarithromycin, Ofloxacin	6 months	Nephrectomy	Completed NTM treatment
7	63/M	Negative	Culture positive	Rapid grower (*M fortuitum/chelonae* complex)	Bilateral hydroureteronephrosis and shrunken kidneys with lower ureteral strictures (Fig. 2)	Azithromycin, Doxycycline, Levofloxacin x 3 months; then as per repeat culture, Clarithromycin, Linezolid, Amikacin x 9 months.	1 year	Nil	Took 1 year treatment; became symptom-free
8	69/M	Positive	Culture positive	*M abscessum*	MRI: Stricture mid- and distal left ureter with upstream hydroureteronephrosis	Clarithromycin, Linezolid, Ofloxacin	1 year	Nil	Repeat culture was negative after 1 year treatment

(*continued on next page*)

Table 2 – (*continued*)

Case No.	Age/ Sex	Urine AFB Smear	Urine PCR/ culture	Pathogen	Imaging	Anti-NTM Therapy	Duration of treatment	Surgery	Outcome
9	31/M	Negative	Culture positive	Rapid grower	IVU: Right gross hydroureteronephrosis with cortical thinning; MCU: Left grade I vesicoureteric reflux; CT: focal pyelonephritis left mid-segment	Clarithromycin, Levofloxacin	9 months	Nil	Symptom-free after 7 months
10	54/M	Positive	Culture positive	*M abscessum*	Bilateral hydroureteronephrosis and contracted urinary bladder; bilateral tiny renal stones and calcifications (Fig. 3)	Clarithromycin, Linezolid	1 year and continuing	Nil	Imipenem could not be given due to financial constraints. Left PCN + Right DJ stenting. Left PCN > 1year. Serum creatinine stabilized at 2.1mg/dL

were females and their mean age at diagnosis was 57.1 ± 10.3 years. Twelve among the GU-MTB patients were male and three, females and the mean age at diagnosis was 52.6 ± 10.2 years. They were followed up for a mean of 5.6 ± 2.2 years and 6.3 ± 2.9 years respectively.

All ten patients of GU-NTM had irritative lower urinary tract symptoms (LUTS) of varying duration (mean nine months, ranging from one to 36 months), while haematuria and fever were observed in less than half of the patients and loss of weight in two patients (Table 1). Irritative LUTS was observed in only two-third of the patients with GU-MTB ($p = 0.03$).

The most common underlying comorbidity of patients with GU-NTM was diabetes mellitus which was noted in four patients, while another one had medical renal disease. One patient had pulmonary tuberculosis 30 years ago. Four patients gave a history of urinary tract instrumentation for unrelated causes. Four patients were treated with ATT for the current symptoms for varying periods. Urinalysis revealed microhaematuria in nine patients, pyuria in eight and proteinuria in seven; none of the patients had aciduria on their routine urinalysis. Though HIV infections are increasingly reported associated with mycobacterial infections, none of our patients in either group were found having this infection, which was done nine out of ten GU-NTM patients and 14 out of 15 GU-MTB patients.

AFB smear was positive in six patients (60%) of GU-NTM compared with seven patients (47%) with GU-MTB ($p = 0.13$). *Mycobacterium abscessus* was isolated from the urine in four patients and *M. fortuitum/chelonae* complex from one. Five patients had rapidly growing mycobacteria and further speciation could not be carried out by the available biochemical tests (Table 2). Nine patients received adequate prescribed regimens of medication. One patient was lost to follow up. Five patients responded to medical treatment alone. All patient received clarithromycin during their treatment. Two patients underwent definitive surgeries in the form of nephrectomy for non-salvageable kidney in one and augmentation ileocystoplasty for low capacity bladder with severely disturbing irritative LUTS in the other. One patient had NTM on repeat urine culture even after the completion of medication for the recommended duration, and is on continued medication even at two years after making the diagnosis. One patient is on percutaneous nephrostomy with anti-NTM treatment. There was no mortality associated with NTM infection. The management adopted and the outcome are summarised in Table 2.

Fifteen patients were positive for MTB on culture though smear was positive in seven patients only. None of them were identified with MDR-TB. Ten patients underwent one or more surgeries, besides initial ureteral stenting and some stone surgeries, which included six nephrectomies or nephroureterectomies for very poor function and other reasons (one asymptomatic non-functioning kidney is left in situ for the last 8 years in one patient), augmentation cystoplasties in two, ureteric re-implantation in one, cutaneous ureterostomies in two and open pyeloplasty in one. One patient died of sepsis following stroke with thalamic bleed two years after bladder augmentation.

Histology was not helpful in identifying any specific mycobacterial infections. Pre-treatment biopsies were

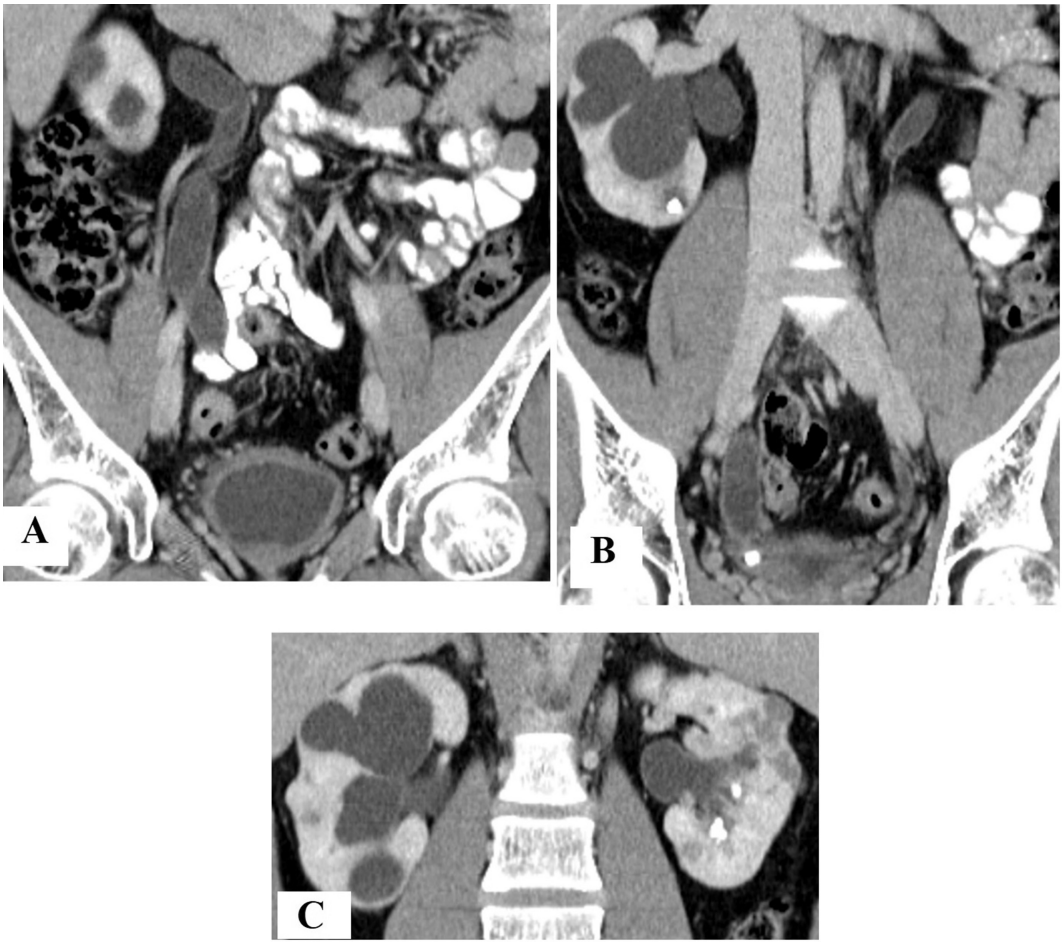

Fig. 1 – CT abdomen and pelvis: Rapid grower mycobacterium (speciation not done). (A) Dilated right calyces, ureter, shrunken and thick walled bladder. (B) Bilateral PCSdilatation, cysts, stones and calcification. (C) Right ureteropelvic and left lower calyceal stones, bilateral ureteral dilatation.

obtained seven patients: three each from the bladder of both GU-MTB and GU-NTM patients, and one prostate by transrectal ultrasound guidance from GU-MTB patient. One GU-NTM patient in the bladder and three GU-MTB patients, two in the bladder and the one in the prostate patients showed granulomatous changes with epithelioid cells, histiocytes and multinucleated giant cells including Langhans giant cells. Caseous necrosis was seen only in the prostate specimen in a GU-MTB patient. Rest of the patients and four additional operated patients after the initiation or completion of treatment showed varying degrees of inflammatory changes and fibrosis only, and nothing typical of any kind of mycobacterial infection.

4. Discussion

NTM infections were identified more than a century ago.[8] Pinner coined the term atypical mycobacteria in 1935.[9] Various terminologies were used to describe them such as atypical mycobacteria, non-tuberculous mycobacteria (NTM), mycobacterium other than tuberculosis (MOTT) or potentially pathogenic environmental mycobacteria (PPEM). In immunocompetent humans it constitutes 0.5%–35% of all mycobacterial infections while 50% of immunocompromised patients can harbour NTM.[10] Furthermore, it affects more frequently the elderly population and those having other medical comorbidities.[11] Four patients with NTM infection in our study had diabetes. In one study, prevalence of NTM was 14.1 per 100,000 population in North America.[12] It was first identified in India by Paramasivan et al in 1985.[13]

NTM includes various species of which the common human pathogenic species are *M. abscessus, M. fortuitum, M. chelonae, Mycobacterium marinum, Mycobacterium ulcerans, Mycobacterium kansasii, Mycobacterium avium intracellulare and M. avium complex*. We had *M. abscessus* as the commonest species in our study. They are classified according to Runyon criteria.[14] Runyon classification[15] is based on whether the mycobacterium is a slow grower (takes more than 20 hours to multiply) or rapid grower, and according to their ability to form pigments in the presence or absence of light or not at all (photochromogen, scotochromogen or non-chromogen respectively). Since MTB is a slow grower and non-chromogen, speciation may be of benefit in slow growers to distinguish NTM from MTB and to initiate early appropriate treatment. These species may vary in their prevalence

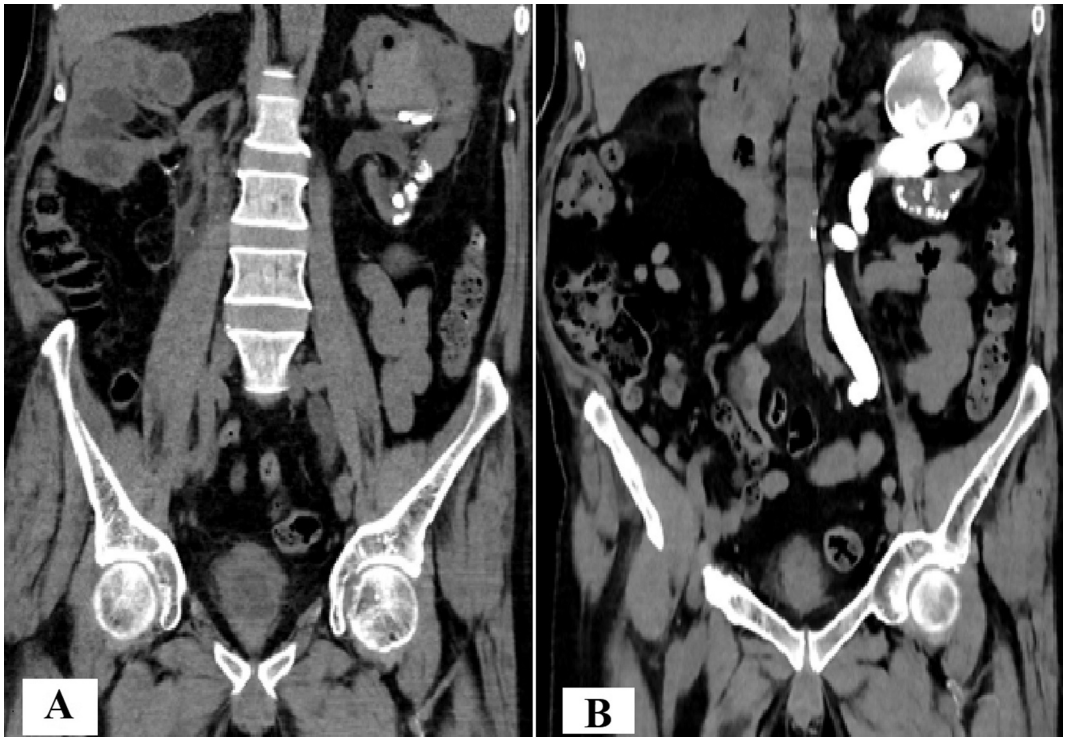

Fig. 2 – CT abdomen and pelvis: Rapid grower M Fortuitum/chelonae complex. (A) NCCT. (B) Left antegrade pyelogram.

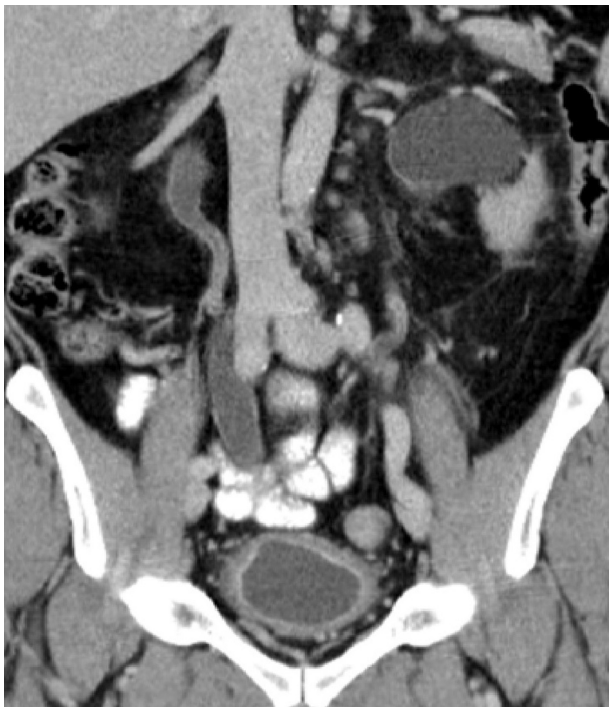

Fig. 3 – NCCT abdomen and pelvis: Rapid grower M abscessum.

according to geographical area.[16] Unlike the classic GU-MTB, animal to human or human to human transmission of NTM is not proven yet and therefore they may be considered as non-contagious.[17]

Most common site infected by NTM is lungs from which disease may be transmitted to genitourinary system by haematogenous spread. In our study, amongst the GU-NTM there was only one patient each with history of pulmonary tuberculosis and GU-MTB, while three patients with GU-MTB also had history of GU-MTB involving genitourinary tract (ureter, prostate and bladder) other than the sites noted in the current study. After invading the tissue, these microorganisms colonize and lead to granulomatous inflammation but classical coagulative necrosis seen in GU-MTB is absent in GU-NTM infection.[16] It is reported that NTM can inhabit in endoscopic instruments. Notably, four patients in this study had history of genitourinary tract instrumentation though the cause–effect relationship is not possible to be established from this history alone.

The clinical manifestations of GU-NTM infections ranged from lower urinary tract symptoms like urgency, frequency, dysuria and haematuria to renal failure. Urgency was the commonest presentation in our study, which was present in every patient. One patient had renal failure with serum creatinine of 2.1 mg/dL (normal-0.6 to 1.2 mg/dL). Not all patients had constitutional symptoms like fever and/or anorexia. Huang et al observed anorexia only in 27% and fever in 67% of their patients.[7] Persistence of symptoms despite adequate conventional ATT should raise the suspicion of NTM infection. Initial investigation of choice is acid-fast bacilli (AFB) smear of urine. It may detect microorganisms rapidly but it has high false negative and false positive rate in diagnosing GU-MTB.[14] Identification of the species is done by growing microorganisms on culture followed by phenotyping and/or genotyping. BACTEC MGIT 960 liquid culture has shown superiority as compared to egg-based or solid agar

media for isolating the species.[18] In presence of adequate growth on culture, various nucleic acid probes (e.g. Accuprobe) are used for identifying the species. In patients with positive AFB smear but negative nucleic acid detection test (*GeneXpert* MTB/RIF test), strong suspicion of the presence of NTM should be considered.[14] We had six GU-NTM patients with urine AFB smear positive.

Imaging is not helpful in distinguishing GU-MTB from GU-NTM. It is helpful in diagnosing the structural damages and complications borne out of these infections and healing processes such as ureteric stricture, contracted bladder, hydronephrosis, ulcerocavernous lesions of renal parenchyma, abscess formation, calcifications, etc. Commonest radiological finding we identified was contracted urinary bladder. Figs. 1–3 show the extensive involvement of genitourinary tract caused by different species of NTM infections that were indistinguishable from typical MTB infections. The imaging findings of our patients of GU-NTM are summarised in Table 2.

There is no standard treatment protocol defined for GU-NTM infections. Commonly used treatment includes rifampicin, clarithromycin, azithromycin, amikacin, linezolid, levofloxacin and isoniazid. Dosage and duration of the treatment depends upon the patients' general condition, creatinine clearance, culture and sensitivity and the response to treatment.

Clarithromycin was the most commonly used drug in our study, and treatment duration ranged from 6 months to 2 years. Outcome of patients with for GU-NTM infection cannot be predicted. It depends upon multiple factors like the immune status of patient, underlying comorbidities, severity of infection, structural damages and response to the treatment. Only 50% of patients in our study responded adequately to the recommended treatment.

Surgical intervention is required for managing complication, as with GU-MTB, which can vary from ureteric stenting, through ablative procedures like nephrectomy, to complex reconstructive procedures like pyeloplasty, pyelocalicostomy, ureterocalycostomy, ileal ureter, ileocystoplasty and other methods of urinary diversion.

The incidence and recognition of GU-NTM infection are showing rising trend over the last few decades.[11] Increasing awareness among treating physicians, improved follow up due to increasing social acceptance and national activities and facilitated access to diagnostic services could be the reasons of enhanced reporting of NTM infections. The morbidity is still significantly high due to the delay in making the diagnosis, mistaken labelling as MDR-MTB, reduced or lack of governmental support to complete the treatment for NTM, and, in certain cases, increased overall cost of the treatment compared with the conventional ATT. The diagnosis and thereby the treatment are compounded by the fact that the presentations of NTM infections are quite varied and 30% of MTB infections are multidrug resistant.[17] Patients not showing the anticipated response should be investigated for NTM infections. In cases where bacteriology cannot be confirmed, empirical ATT is generally started. However, if favourable response is not evident in an anticipated timeframe, judicious administration of clarithromycin may be worth a trial considering the possibility of NTM rather than resistant MTB infection.

5. Limitations of the study

Though mycobacterial infections are quite frequently encountered, bacteriological diagnosis is often not made before initiating treatment. The number of patients in this study is small but the distribution of GU-MTB versus GU-NTM is different from what is generally believed. This could be partly because the patients reaching this tertiary care centre or the number of patients reaching bacteriological confirmation is a skewed population. Increasing reporting of pulmonary and extra-pulmonary NTM points to the possibility of a significantly high under-reporting of GU-NTM as well, emphasising the need for further elaborative surveys.[19]

6. Conclusion

About 40% of mycobacterial infections affecting the genitourinary tract were found to be NTM in this study. GU-MTB and GU-NTM infections are indistinguishable from their clinical presentation and imaging studies. Treatments based on clinical and radiological features without culture studies may misdiagnose GU-NTM infections as MDR-MTB, thereby delaying the appropriate treatment potentially leading to increased morbidity or even patient loss. All cases of suspected genitourinary mycobacterial infections must be subjected to nucleic acid testing like *GeneXpert* MTB/RIF and liquid culture using BACTECT MGIT to rule out NTM infection. When starting empirical ATT in the absence of conclusive nucleic acid tests or culture studies, addition of clarithromycin may be considered along with ATT when the response is inadequate, preferably repeating the bacteriological studies.

Conflicts of interest

The authors have none to declare.

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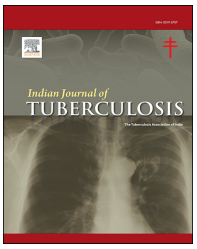

Original Article

Consumption of spine by tuberculosis in the era of directly observed treatment, short-course and genomic diagnosis

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ABSTRACT

Background: Extra Pulmonary Tuberculosis (EPTB) is a significant health problem in both developing and developed countries. Spinal tuberculosis (STB) is one of the significant forms of EPTB lacking epidemiological data. The present study was conducted to study the clinical, radiological, microbiological and histopathological features, treatment and outcome of Spinal tuberculosis.

Methods: This study was conducted for a duration of 19 years, from 2000 to 2018 at the department of Neuromicrobiology, NIMHANS, Bengaluru. It comprised of 252 patients with STB. All patients were diagnosed with the clinical features and confirmed by radiological, microbiological and histopathological findings.

Results: Results were tabulated and statistically studied. The most common age group is 30–40 years with male preponderance. Most patients presented with motor paraplegia/para paresis (99.6%). Thoracic spine was the most common vertebra affected (47.62%). The commonest imaging feature is soft tissue collection (81.74%). Most common histopathological feature was necrotising granulomatous inflammation (65.87%). Microbiology reports showed growth of *Mycobacterium tuberculosis* (MTB) in 29.76%, Ziehl Neelsen (ZN) smear showed acid fast bacilli (AFB) in 25.79%. Anti tubercular drugs and surgery were advised in 55.55% patients and only anti TB drugs for 39.28%. The entire course of anti tubercular treatment (ATT) was completed in 60.71% and 4.76% were defaulters.

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Conclusion: Spinal tuberculosis is a global disease, timely diagnosis with clinical, imaging, microbiological, histopathological features and complete course of anti-tubercular treatment along with symptomatic treatment appears to be safe and effective.

1. Introduction

Spinal tuberculosis (STB) is a destructive form of tuberculosis. It is characterised as clinical and imaging manifestation of a progression of generalised weakness, malaise to symptom free period and sudden bounce of vertebral body destruction, collapse to kyphotic deformity with or without neurological encroachment.[1]

India is the country with highest burden of Tuberculosis (TB). As per the India Tuberculosis report 2019, the estimated incidence of TB in India was approximately 27,00,000 accounting for about a quarter of the world's TB cases.[2] Extra Pulmonary Tuberculosis (EPTB) being a significant health problem in both developing and developed countries accounts for 17% among new TB cases in India.[3] There are very few literatures available from India regarding the relative contributions of extrapulmonary disease to the total number of tuberculosis cases due to lack of reliable epidemiological data.[4]

A push has been made to fight the extrapulmonary form of tuberculosis from the country. Revised National Tuberculosis Control Program (RNTCP) is a large-scale implementation of the Indian government was started in 1997. RNTCP uses the Directly Observed Treatment Short Course (DOTS) strategy recommended by World Health Organisation (WHO).[5] Diagnosis of EPTB is not covered by RNTCP, and for treatment, these cases are forwarded to the DOTS regimen. Tertiary care centres appear to be an excellent place for medical education and operational research in this regard.[6]

The objective is to study, the clinical and imaging features were documented to elucidate the morphological spectrum of spinal tuberculosis. An effort was also made to include microbiological and histopathological spectrum of the disease, the impact of past history of tuberculosis and outcome of anti-tubercular drug therapy.

1.1. *Ethical statement*

Since this is a record based retrospective study that uses re-identified data, the study is exempted from Ethical review.

2. Materials and methods

This is a record based retrospective study traversing a period of 19 years (2000–2018), reviewing all the confirmed cases of Koch's spine at the Department of Neuromicrobiology, National Institute of Mental Health and Neurosciences, Bengaluru. The diagnosis was confirmed radiologically, histopathological and microbiological investigations (as per the criteria modified from Ching-Yun Weng, et al).[7] The details of data collection has been depicted in Fig. 1. The socio-economic status was classified based on modified B G Prasad classification.

- *Inclusion criteria:* Patients with clinical, radiological, pathological and microbiological evidence of active spinal tuberculosis.
- *Exclusion criteria:* Disorders of spine other than spinal tuberculosis and patients without clinical confirmation of TB, incomplete clinical details, imaging and histopathological findings

A total of 252 cases during the study period fulfilling the inclusion criteria formed the study material. Pus aspirated from vertebral abscess and tissue samples excised from the spine were received in the Neuromicrobiology laboratory and were subjected to various methods described in Fig. 2. The sample was processed in Bio safety cabinet. Screening and grading of Ziehl Neelsen (ZN) smears and culture was performed and inspected using standard protocol.[8]

The clinical features, microbiological and histopathological features of the lesions resected by CT guided biopsy or surgery and neuroimaging findings {computed tomogram (CT) and magnetic resonance imaging (MRI)} were reviewed. The past TB status and family status were also reviewed.

2.1. *Statistical analysis*

Descriptive statistics were presented in the form of numbers and proportions as appropriate using IBM SPSS ver. 20 software.

3. Results

A total of 252 confirmed spinal tuberculosis cases fulfilling the inclusion criteria were included in the study. The demographic details of the patients are compiled in Table 1. Most of these, i.e. 120 (47.61%) presented in the third and fourth decades (age ranged from 1 to 80 years) with a male preponderance (male: female – 1.4:1). The median age was 35 years. One hundred and forty-seven patients belonged to lower socio-economic status. The data on duration and manifestation of illness is summarised in Table 1. Clinically most of the patients presented with paraplegia/para paresis (99.6%), followed by local spinal pain (94.84%) and sphincter involvement (40.87%). A total of 51.58% of the patients presented to the hospital within 1–6 months. Forty-three out of

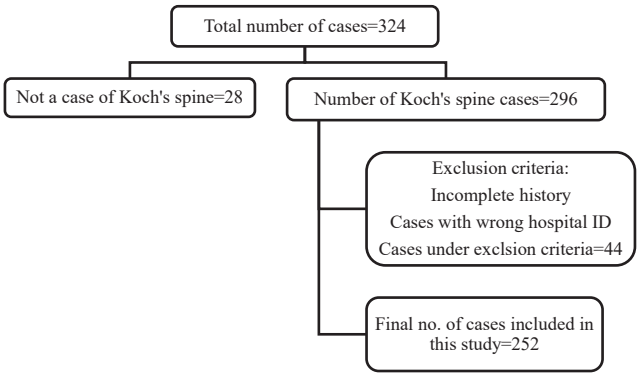

Fig. 1 – Details of data collection.

252 cases had past history of pulmonary tuberculosis, 17 had family history of tuberculosis, 3 had TB meningitis and 6 were screened positive for Human Immune deficiency Virus (HIV).

Site of involvement and imaging features are summarised in Table 2. Thoracic spine was the most common site of affection (47.62%) followed by cervical (18.25%). Thoracolumbar junction involving lower thoracic and upper lumbar vertebrae was the most common vertebral junction (7.93%). In 91.66% cases, 1–5 consecutive vertebrae were typically affected. In 6 cases, multiple vertebral levels were involved. Cold abscess and Kyphosis were noted in 81.74% and 28.57% of cases respectively. The commonest radiological parameter is soft tissue collection (prevertebral, paravertebral, epidural, psoas and retroperitoneal abscess) noticed in 81.74%, complete vertebral body collapse in 45.23% followed by cord compression in 29.76% cases.

Microbiology and Histopathological findings are summarised in Table 3. Most common histopathological feature was necrotising granulomatous inflammation observed in 65.87% cases. In four percent of the cases, there was only chronic inflammation with variable fibrosis and no definite granulomas. Microbiology reports showed growth of *Mycobacterium tuberculosis* (MTB) in 29.76%, ZN smear showed acid fast bacilli (AFB), *Mycobacterium tuberculosis* in 25.79%, both ZN smear and culture were positive in 9.92%.

Treatment and outcome are compiled in Table 4. Treatment modalities included anti tubercular treatment (ATT) and surgery in 55.55% patients, only ATT was advised for 39.28%. Thirteen (5.15%) patients got discharged against medical advice. The entire course of ATT was completed in 60.71% and 4.76% of them were lost for follow up. Complete recovery was noticed in 60.71%. Residual symptoms like musculoskeletal and neurological dysfunction after treatment were noticed in 9.52%, one patient died during the course of treatment and in 29.36% of patients follow up was not possible due to reference to local general hospital (GH).

4. Discussion

Spinal tuberculosis is a secondary infection from the primary site of tuberculosis. It spreads to spine mainly through haematogenous route. It is a delayed hypersensitivity reaction, initially starts with inflammatory reaction with lymphocytes, epithelioid cells and Langhan's giant cells constituting a granulomatous inflammatory response with granulation tissue.[9] Proliferation of granulation tissue takes place producing thrombosis of vessels. Tissue necrosis and breakdown of inflammatory cells result in a paraspinal abscess. The pus may be localized, or it may track along tissue planes. Kyphotic deformity results from progressive necrosis of bone. Typically, anterior aspect of the vertebral body adjacent to the disc is infected first. The infection then spreads to the adjacent

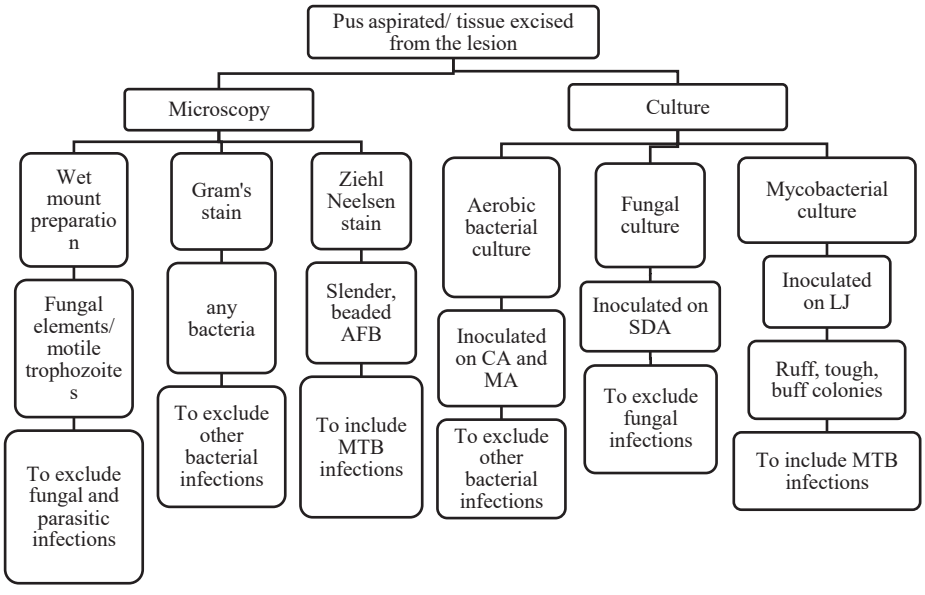

Fig. 2 – Methodology for sample processing.

Table 1 – Demography, presenting symptoms, signs and other history.

Characteristics	No. of cases (252)	Percentage (%)
Gender		
Male	148	58.7
Female	104	41.2
Age		
0–20	48	19.0
20–40	120	47.6
40–60	77	30.5
60–80	07	2.7
SES[a]		
Lower	147	58.3
Middle	27	10.7
Upper	08	3.1
Upper middle	0	0
Lower middle	0	0
SES not known	70	27.7
Symptoms		
Motor paresis/paralysis below the level of lesion	251	99.6
Local spinal pain	239	94.8
Constitutional symptoms	50	19.8
Duration of illness		
1–6m	130	51.5
<1m	60	23.8
7m-1y	32	12.6
1.5-2y	12	4.7
2-10y	08	3.1
Not known	07	2.7
1y-1.5y	03	1.1
Autonomic		
Sphincter involvement	103	40.8
Dysphagia	06	2.3
Past history of tuberculosis	43	17.0
Family history of tuberculosis	17	6.7
TB meningitis	3	1.1
HIV	6	2.3

[a] SES: Socioeconomic status.

vertebral bodies under the longitudinal ligaments.[10] It is a serious threat in developing countries as it goes unnoticed or misdiagnosed due to less awareness among the people which has resulted in delay in visit to the doctor and also initiation of treatment.

The diagnosis was based on modified criteria by Ching-Yun Weng, et al.[7] The criteria are as follows (Table 5):

According to WHO Global tuberculosis report, 10.0 million (range, 9.0–11.1 million) people fell ill with TB globally in 2018, a number that has been relatively stable in recent years. India (27%) is one among the eight countries accounting for two thirds of the total global cases.[11] The percentage of EPTB cases among all TB cases in developing countries such as India, is between 15% and 20%.[12] In this study, 252 confirmed STB cases were included. The prevalence of STB in the third and fourth decades of life and of a slight male preponderance was similar to that reported by Patel VK et al.[1]

TB affects people of both sexes in all age groups but the highest burden is in men (aged ≥15 years). The male preponderance may be due to cultural practices among women belonging to lower SES which acts as a barrier to access the healthcare leading to under reporting in women. Majority of them 147 (58.3%), belonged to lower SES as per modified B G Prasad classification. The above data is in accordance with Alam et al[13] indicates that malnutrition, overcrowding, illiteracy, poor sanitation, health ignorance and poor reachability to health facilities among the lower SES people contributes to the disease[14]

STB is a chronic disease with majority of patients presenting between 1 and 6 months of initiation of symptoms (51.5%) which is similar to Patel et al[1] and Ahmed et al.[15] The commonest symptom is motor paresis/paralysis accounting 99.6%, followed by local spinal pain in 94.8% similar to Zheng Liu et al[16] which is typically localized to the site of involvement, most commonly the thoracic and lumbar spine. Sphincter involvement was seen in 40.8%. Constitutional symptoms were present in 19.8% of patients. The less prevalence of constitutional symptoms when compared to other studies may be due to retrospective nature of study and no one bothers to document constitutional symptoms with neurological deficits.[17] The reasons for these being: Ours is a tertiary care centre and the patients would have probably gone to GH when they were suffering from constitutional symptoms.

The primary infection site is a pulmonary lesion. Spread occurs either via the arterial or the venous route. 43 (17%) patients had past history of pulmonary tuberculosis and 17 (6.7%) patients had family history or history of contact with tuberculosis. 6 (2.3%) patients had been co-infected with HIV.

STB usually has an extraspinal source and spreads by haematogenous route. It manifests as a combination of osteomyelitis and arthritis that involves more than one vertebra. The anterior aspect of the vertebral body adjacent to the subchondral plate is commonly affected and may spread from

Table 2 – Imaging features and number of vertebrae involved.

Characteristics	No. of cases (252)	Percentage (%)
Imaging features		
Vertebral body collapse	114	45.2
Cord compression	75	29.7
Disc destruction	56	22.2
Pedicle involvement	20	7.9
Gibbus	2	0.7
Kyphoscoliosis	75	29.7
Soft tissue collection (204)		
Pre and paravertebral	139	55.1
Psoas	36	14.2
Epidural	29	11.5
Retroperitoneal	02	0.7
Vertebrae involved		
Thoracic	120	47.6
Cervical	46	18.2
Lumbar	41	16.2
Thoracolumbar	20	7.9
Cervicodorsal	13	5.1
Lumbosacral	06	2.3
Sacral	00	0.0
Multiple levels	06	2.3
No. of vertebral levels		
1–5	231	91.6
5–10	18	7.1
11–15	02	0.7
15–20	01	0.3

Table 3 – Laboratory findings.

Characteristics	No. of cases (252)	Percentage (%)
Histopathological features		
Necrotising granulomatous inflammation	166	65.8
Ill formed/vague granulomas	75	29.76
Chronic inflammation with fibrosis	11	4.36
Microbiological findings		
Source of material		
Open surgical material	145	57.5
CT guided aspiration	107	42.4
ZN stain		
AFB seen	65	25.7
AFB not seen	94	37.3
Data not available	93	36.9
L J Culture		
MTB grown	75	29.7
MTB not grown	169	67.0
Data not available	08	3.1
ZN+ culture positive	25	9.9
ZN+ culture negative	69	27.3
ZN-culture positive	20	7.9

Table 4 – Treatment and outcome.

Characteristics	No. of cases (252)	Percentage (%)
Treatment modalities		
ATT with surgery	140	55.5
ATT alone	99	39.2
Duration of treatment		
• Completed for 18 months	153	60.7
• Lost for follow up	12	4.7
DAMA[a]	13	5.1
Outcome:		
Well[b]	153	60.7
No follow up[c]	74	29.3
Residual symptoms[d]	24	9.5
Death	1	0.3

[a] Discharge Against Medical Advice.
[b] No pain, deformity, neurological symptoms or signs.
[c] Due to referral for General hospital.
[d] Musculoskeletal and neurological dysfunction present.

that area to adjacent intervertebral discs. In adults, vertebral body is affected first and then spreads to the disc. In children, the disc can be the primary site because it is vascularised.[18] There is peculiar tendency of the disease to localize in the bodies of the lower thoracic and upper lumbar vertebrae. The two reasons being: the close relationship of the thoracic duct to the bodies of the vertebrae and cancellous tissue showing marrow degeneration is peculiarly liable to become infected.[19]

In our study, most of the patients (47.6%) had thoracic vertebral involvement followed by cervical (18.2%), lumbar vertebrae (16.2%) and thoracolumbar junction (7.9%). Lumbar and thoracic spine were the commonest regions involved universally,[20,21] which is noted in this study as well. About 1-5 adjacent vertebrae were involved in 231 patients. The reason for the above thoracic and lumbar vertebrae may be due to dense vasculature of cancellous bone of the vertebral bodies by Batson's paravertebral venous plexus.[22]

CT and MR imaging are useful for delineating the features of tuberculous spinal disease, but MRI is recommended as it is highly accurate in detecting disease at distant sites and for assessment of soft tissue components of spinal tuberculosis. CT is useful in accessing the type and extent of bone destruction. MRI is especially important in the evaluation of spinal cord and the nerve root integrity in the asymptomatic patient.[23] We found that on MRI and CT scan, findings in patients were soft tissue collection, cord compression, vertebral body collapse, disc or bone or pedicle destruction. Vertebral body collapse was the most common (45.2%) radiological feature followed by cord compression. Moorthy et al[24] found that cord compression is the serious radiological signs seen in patients with STB which is similar to our study with 29.7% of cord compression which is one of the most common radiological feature. 75 (29.7%) had clinically evident kyphoscoliosis, with two of them having gibbus deformity.

CT guided aspiration was performed in 107 (42.4%), 145 (57.5%) were open surgical material, which were the sources for microbiological and histopathological diagnosis. ZN smear from the purulent contents of the abscess or biopsy material showed AFB in 25.7% (Fig. 3D). Mycobacterial (MTB) culture was positive in 29.7% (Fig. 3E and F). Both smear and culture were positive in 9.9%. Histopathological evidence of tuberculosis was noticed in 166 (65.8%) and 03 (1.1%) did not. Inconclusive results were noted in 7 (2.7%) cases. The percentage of smear positivity is less when compared to culture is due to less concentration of acid-fast bacilli in the biopsy sample sent which has to be screened meticulously or due to improper processing.

In our study, the AFB positivity in ZN smear is 25.7% which is higher when compared to Nassaji et al.[25] Our study is among the few studies were ZN smear is used as a major tool for diagnosis of STB. The reasons are: rapid method of diagnosis and little material is required when compared to automated methods. Despite low sensitivity, this method should be performed in patients suspected of STB especially in developing counties where newer modality is not routinely available.

Pathological processes encountered in the human spine due to tuberculosis are: first, a destructive lesion directly due to the infection with caseation of bone and soft tissue, second, a vascular phenomenon occasioned by loss of blood supply from thrombosis or endarteritis, or occlusion or destruction of blood vessels by the presence of large dissecting abscesses – sclerosis of bone. In this study, the most common histopathological feature was necrotising granulomatous inflammation

Table 5 – Ching-Yun Weng et al. Diagnostic criteria for spinal tuberculosis.

1. Symptoms exceeding one-month duration
2. Specific imaging features on MRI/CT spine
3. Exclusion of alternative spinal disease
4. Raised ESR/Mantoux positivity (or both)
5. Paraspinal aspirates showing acid-fast bacilli
6. Histology of tissue biopsy demonstrating granulomatous inflammation or caseation.

Definite STB fulfils all criteria 1–4 and 5 or 6
Probable STB fulfils criteria 1–4 only
Possible STB fulfils criteria 1–3 only

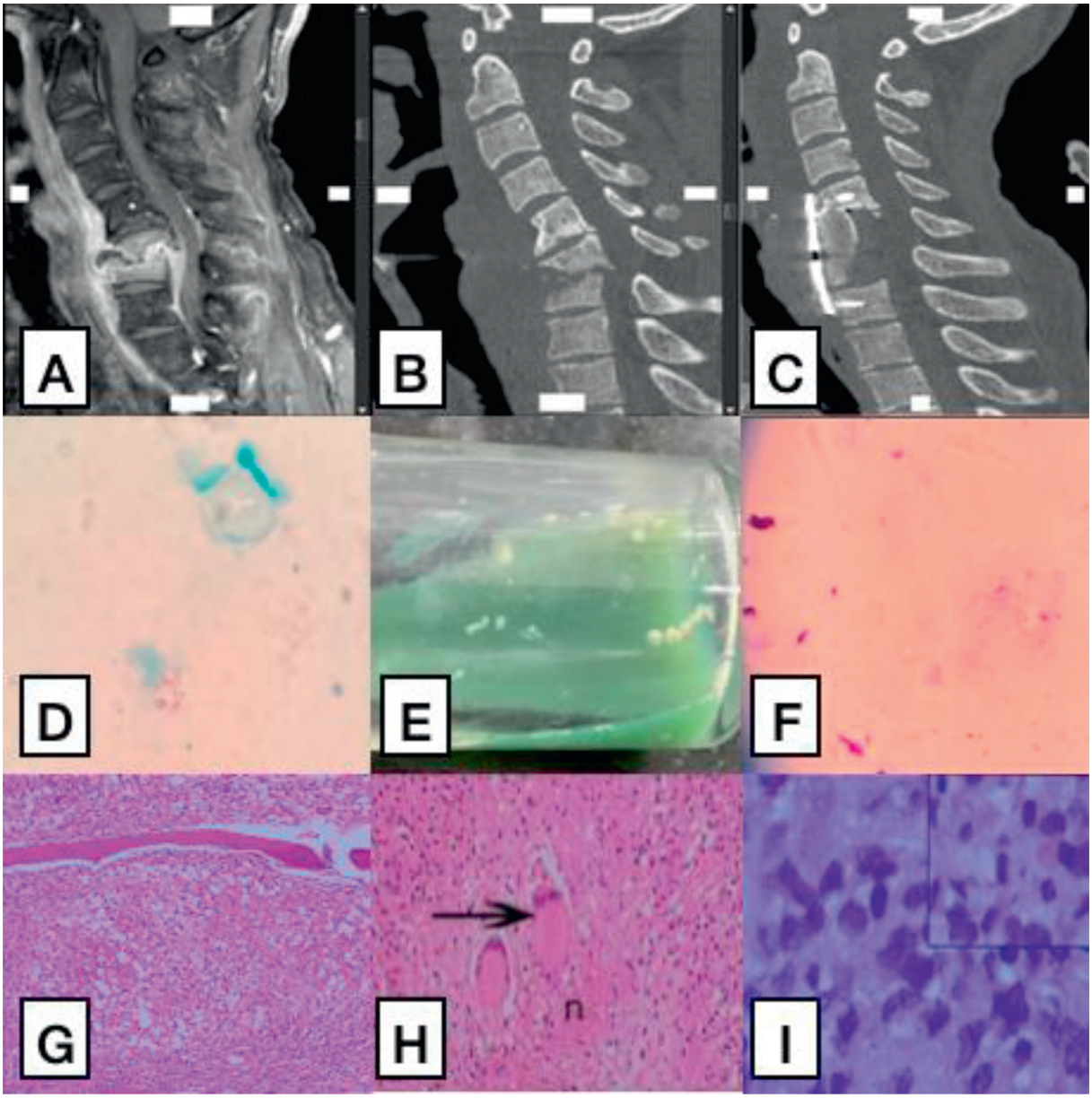

Fig. 3 – Images of a 40-year-old male who presented with a chief complaint of fever for 2 months with generalized weakness, neck pain for 25 days, bilateral upper and lower limbs weakness for 15 days, and urinary retention for 7 days. A. MRI T1W post-contrast study showing C6–C7 vertebral body destruction with enhancement and epidural collection causing compression of cervical cord. B. CT spine showing C6–C7 vertebral body paradiscal destruction with mild kyphosis. Elements not involved. He underwent anterior cervical approach C6–C7 corpectomy and fusion using right iliac crest graft, plates and screws. C6 and C7 vertebral bodies were destroyed with necrotic material within disc space C. Postoperative CT spine showing correction of kyphosis. After surgery he received antitubercular drug therapy for one year. D. AFB in ZN smear from paraspinal abscess sample. E. Ruff, tough, buff coloured colonies of *Mycobacterium tuberculosis* on LJ medium. F. AFB in ZN smear of culture smear from MTB growth on LJ medium. G. Microphotograph showing granulomatous inflammatory response involving the intertrabecular area of the bone. H & E. X 100. H. Microphotograph showing a well-defined, distinct epitheloid cell granuloma with Langhan's giant cells (arrow) and necrosis (n). H & E X 200. I. Microphotograph showing scattered acid-fast bacilli. Inset also shows acid fast bacilli. ZN stain x 1000 Oil immersion.

(Fig. 3G and H) observed in 166 (65.87%) of cases which is similar to the above explanation.[26]

As to distribution of treatment, 140 (55.5%) were treated surgically along with ATT and 99 (39.2%) with ATT only. 153 (60.7%) completed 18 months of treatment, 12 (4.7%) were lost for follow up. Simple aspiration or CT-guided percutaneous catheter drainage of the abscesses, anterolateral extra pleural approach (Menard) and debridement of diseased tissues,

mechanical decompression of the cord, and bone grafting for anterior spinal fusion, Posterior spinal fusion (Albee and Hibbs) and lateral decompression (Alexander) are the surgical treatment options.[27] The key aspects in the treatment of STB is the systemic treatment with ATT before and after the surgical debridement, the careful debridement of the entire focus of infection, and the successful method to reconstruct for spinal stability[28] (Fig. 3A–C).

Combination of rifampicin, isoniazid, ethambutol, and pyrazinamide for two months followed by combination of rifampicin and isoniazid for a total period of 6–18 months is the most frequent protocol used for treatment of spinal TB. For ease of management of spinal TB, treatment has been broadly divided into two groups: those with or without neurological deficits. For those without neurological deficit, medical therapy is the treatment of choice sometimes surgical intervention may be needed. In cases with neurological deficit, medical therapy is the treatment of choice but medical therapy along with surgical treatment yields best results.[29]

As to distribution of prognosis, 153 (60.7%) patients gradually achieved cure within 18 months after hospital admission and initiation of treatment. 24 (9.5%) patients continued to have musculoskeletal and neurological dysfunction. Follow-up data on the other 74 patients (29.3%) were incomplete. They included patients who were transferred to GH, those with lost contact, those not cured, and those who died. One death was due to systemic infection.

5. Conclusion

STB remains a severe problem that cannot be ignored. Even in the absence of Gene-Xpert or culture growth, a combination of clinical, radiological, histopathology and ZN smear findings can be used to diagnose TB especially in resource poor countries. Timely and complete course of ATT along with symptomatic treatment appears to be safe and effective.

Conflicts of interest

The authors have none to declare.

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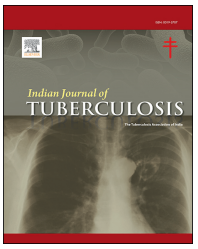

Original Article

To study the impact of active case finding (ACF) among the TB patients detected in South Delhi

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ABSTRACT

Background: TB is one of the top 10 causes of death worldwide. The WHO adopted the End TB Strategy with ambitious goal of ending the global TB epidemic by 2030. The targets for this were 95% reduction in number of TB deaths, 90% reduction in TB incidence rate between 2015 and 2035 and to ensure that no family is burdened with catastrophic expenditure due to TB. Enhanced case detection is one of the components of End TB strategy adopted by WHO and within this Active Case Finding has an important place. However, its role in the Indian context needs to be assessed.

Aims and objectives: To study the impact of Active Case Finding (ACF) in National Tuberculosis Elimination Program (NTEP) implementing area of National Institute of TB and Respiratory Diseases New Delhi in terms of case detection and treatment outcome.

Materials and methods: The TB patients detected during ACF through house to house survey in vulnerable population were identified, evaluated and followed up. Data from ACF records and TB treatment cards were filled in a pretested proforma and compared with passive case detection in the previous month from same area.

Results: In December 2017 a total 8600 vulnerable population (living in slums, camps and night shelters) were screened over two weeks of whom 85 were found to have symptoms suggestive of TB of whom 19 were PTB that gives a case detection rate of 220 per lakh population. PTB case detection rate by passive case finding (PCF) in November 2017 from the same area of our study was found to be 63 per lakh population. This difference between the detection rate in ACF and passive case findings was statistically significant with Z proportion test and p value <0.00001. Treatment success rate was 75% and lost to follow up rate was 25% patients among the PTB patients detected in ACF. In passive case detection from the same area in November 2017 treatment success rate was 81.8% and lost to follow up rate (LTFU) was 18% in PTB patients. Even though LTFU rate was slightly higher but was not statistically significant.

Conclusion: ACF is an effective way to find additional cases of TB. ACF is more labour intensive than PCF but if judiciously used under national programme to target specific vulnerable population of society it can produce additional number of TB cases which otherwise would have gone undiagnosed.

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However, treatment outcome for these patients is below the target and hence to get the maximum impact of ACF there is a need to enhance the adherence to treatment through different methodologies. Poor treatment adherence will lead to increase transmission risk in communities and greater chance of developing drug resistance. Further studies with larger representative population should be undertaken in order to get more conclusive.

1. Introduction

National Tuberculosis Programme (NTP)[1] initiated in 1962 in India gave way to Revised National Tuberculosis Control Programme (RNTCP) in 1997 to cover entire nation by march 2006 in phased manner. In 2006 STOP TB strategy[2] was announced by WHO which was adopted by RNTCP. RNTCP name changed to National Tuberculosis Elimination Program (NTEP)[3] in 2020. Under NTEP passive case detection strategy was followed.

Initially under RNTCP Case notification rates increased, but then plateaued and rather started decreasing in many parts of the country despite increasing efforts of symptomatic examination in public sector. National Sample Survey Office (NSSO) prevalence surveys also suggested that not all chests symptomatic sought care and many ignored the symptoms.[4] This necessitated that the programme and health services needed to make special efforts for reaching unreached. India accounts for about a million 'missing' cases that are not notified under national tuberculosis control programmes.[5] The reason for these huge number of missing cases are primarily due to under diagnosis, misdiagnosis, and diagnosis and treatment of TB patients in the vast private sector.

The NTEP is dynamic and evolving public programme. Thus in order to address these challenges, NTEP has formulated several strategies, including active case finding (ACF), among clinically vulnerable and socially marginalised populations.[6]

Primary objective of ACF was detecting TB cases early in targeted groups and to initiate treatment promptly. Increased coverage can be achieved by screening and focussing on clinically, socially and occupationally vulnerable population within the capacity of the health system, and the availability of resources.[4]

In this study the strategy of house to house survey was adopted and the impact of ACF in terms of case detection and treatment outcome was analysed. Ethical approval was taken prior to initiation of study.

2. Methods

This Observational, Cross-sectional study was conducted at NITRD in areas (Tigri, Bersarai, Khanpur) having vulnerable population (slum, camp, night shelters and J J colonies) in South Delhi.

The mapping of vulnerable population area was done by state and district programme officers. The field activities were done by at least two members either STS/STLS/TB-HV or Partner organization (NGO outreach worker) staff or the General health services staff, ASHA or community volunteer. Vulnerable population included people living in camps, slum areas, night shelters. ACF was conducted for 2 weeks from 4th to 18th December 2017. Field activities by staff included: Conducting household visit to target population, symptom screening of individuals, offering 2 sputum containers to symptomatic and explain how to produce and collect sputum sample which they gave to nearest Designated Microscopy Centre. Screening the target population eligible for sputum examination included: Persistent cough for $\geq$2 weeks, fever for $\geq$2 weeks, significant weight loss (>5% weight loss over last 3 months), presence of blood in sputum any time during last 6 months, chest pain in last one month, history of anti-TB treatment (previous/current).

Sputum smear microscopy and CBNAAT was done for all symptomatic persons. The people who were sputum positive were initiated on treatment. The persons who were sputum negative but symptomatic were further followed up and evaluated using X-ray and CBNAAT as per NTEP Technical & Operational Guidelines 2016 and initiated on appropriate treatment. All children, extra pulmonary patients and PLHIV were offered upfront CBNAAT. Additionally, the team looked for other symptoms/diseases also. If person was having any symptoms or other ill health, she was referred for evaluation by a Medical Officer for further management, if needed.

The TB patients detected during ACF activities were started on treatment and followed until a final outcome was ascertained as per NTEP guidelines. Monthly follow up was done telephonically. Counselling was done at every stage to ensure that patient was continuously taking TB treatment till the end and till the outcome was available after treatment initiation. The patients were interviewed as per a predesigned structured questionnaire that enquired into several clinical, socio-economic and demographic variables. Treatment outcome for Pulmonary TB were analysed as per RNTCP measures. Similar data was also collected for the newly diagnosed TB patients notified passively from same area where ACF was conducted for the month NOV17 for comparison. We converted this data for per lac population. This data formed the basis for our PCF (passive case finding) which we then compared with the ACF yield to find out the efficacy of the ACF.

3. Results

Total population which was to be covered by ACF team was 17,350, but actually total vulnerable population screened in

ACF was 8600 (5700 population was screened in Bersarai, 2500 population in Tigri, and 450 population in Khanpur area of South Delhi) because the rest of the population was already under routine surveillance by a charitable trust and NGO located in Bersarai.

In ACF total 8600 vulnerable population were screened, 85 out of them found to have symptoms suggestive of TB. About 1% of population screened was symptomatic and 34.1% of symptomatic had TB disease. Total 29 out of 85 were diagnosed to have TB. Out of 29 patients 19 were PTB and rest 10 were EPTB.

Out of 19 PTB patients 17 were microbiologically confirmed and 2 were clinically diagnosed by CXR and detailed clinical evaluation. Out of 17 microbiologically confirmed cases, 3 were DRTB and 14 were DSTB. All 29 patients were initiated on ATT. In 10 EPTB cases diagnosed, 5 were pleural effusion, 4 were TB lymphadenitis and 1 patient was diagnosed having Abdominal Koch's.

In this ACF study for PTB patients, 15/19 (79%) patients had age distribution 15–40 years with median age 25 years. 12/19 (79%) were males and 7/19 (21%) were females. 47% of the PTB patients were married. The entire patient belonged to lower middle and lower class. Camps were most common (63%) site for vulnerable population who got PTB disease. 14/19 (73.7%) were newly diagnosed PTB. Cough (100%) and fever (89%) were two most common presentations. None of our patient was HIV positive who were tested. 17/19 (89%) were microbiologically confirmed and 2/19 (11%) were clinically diagnosed. Only 1/19 (5%) PTB patient was diabetic.

18/19 (94.7%) of the PTB patients were referred to respective DOTS centre within 7 days of diagnosis. 16/19 (84%) were initiated on ATT within 7 days of diagnosis. In 3/19 (15.7%) patients, treatment initiation was delayed for more than 7 days. Reason for delay for them as 2 patients were daily wage worker who did not get leave from employer and rest 1 patient had lack of family support to bring them to health centres. 14/19 (73.7%) were given CAT 1 ATT, 2/19 (10.5%) of patients took CAT 2 ATT and treatment regimen was changed to DRTB regimen in 3/19 (15.8%) patients.

Total evaluated = 16 and treatment regimen were changed for 3 patients. Treatment success rate was 75% and lost to follow up rate was 25% for PTB patients during ACF.

Sputum smear test could not be done in 7/19 (36.8%) patient as 4 were lost to follow up, 2 were on DRTB treatment and 1 patient died during treatment.

Out of 17 microbiologically confirmed TB, 14 were DSTB and 3 were DRTB. Treatment outcome was analysed for DSTB 14 cases and 2 clinically diagnosed PTB (N = 16) only. Treatment success rate was 75% for PTB. Lost to follow up rate was overall 25% in ACF.

In this study data was also collected from NTEP dept of NITRD for the month of NOV17 for those cases notified passively (PCF) from the similar vulnerable population of 17,350 where ACF was done. No case was reported to DRTB centre from this population passively in the month NOV17. Then whole data was normalized to per lac population for comparison.

Total TB patients notified to NTEP in month NOV17 i.e. PCF were 12 (PTB = 11 and EPTB = 1). 58% (7/12) were male and 42% (5/12) were female. 58% of TB patients were less than 35 years. Median age was 27.5 years. Total evaluated PTB patients in PCF were 11.

None of them found to be drug resistant TB (DRTB). Treatment success rate was 9/11 (81.8%) and lost to follow up (LTFU) rate was 2/11 (18.2%).

On comparing for PTB cases in terms of case detection rate, success rate and LTFU rate for ACF and PCF for same vulnerable population.

- Case detection rate for PTB was (19/8600) 220 per lac population for ACF while it was (11/17,350) 63 per lac population in PCF. This difference between the detection rate in active (ACF) and passive case finding (patient themselves reporting to health clinic and hospitals) was statistically significant with Z proportion test and p value 0.00001.
- Success rate for ACF was 75% while it was 81.8% for PCF (p Value- 0.115 = not significant).
- LTFU rate was 25% for ACF while it was 18.1% for PCF (p value-0.12 = not significant).

4. Discussion

The Active Case Finding was able to find a greater number of cases and this became a useful tool for enhanced case detection specially in selected population. We found that there was a statistically significant difference in yield for PTB cases between ACF and PCF in terms of case detection with Z proportion test and P value 0.00001. The modest increase in the yield of PTB cases was also supported by other studies done by **Nhung et al**,[7] **Fukushi Morishita and Eang et al**.[8] In this study we had unfavourable results for ACF in terms of lower treatment success rate and higher LTFU rate when compared from PCF but statistically not different. The same was supported by study of **Hemant Deepak Shewade et al**.[9] Higher LTFU rate in ACF despite regular follow up home visits by DOTS provider was due to the fact that these patients belonged to the lower socioeconomic status and being daily wage earners, they could not afford a day spent in getting medicine from the DOTS centre. They were also prone to relocate more often in search for jobs which interrupted their treatment. So, it can be inferred from our data that even though ACF is a superior case

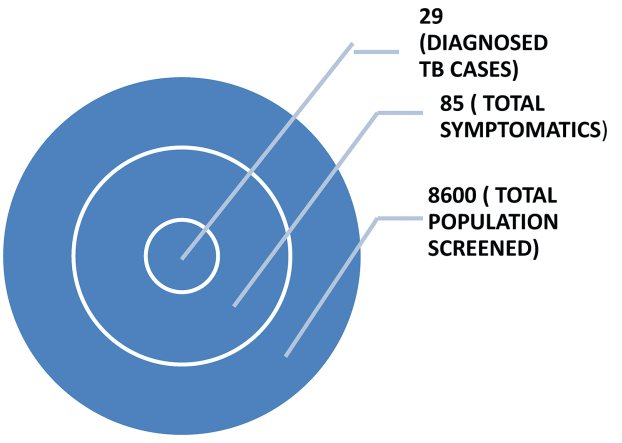

Fig. 1 – Overview of ACF.

finding strategy, for it to be truly effective adherence of the patient to the treatment plan must be ensured.

In our study we had lesser number of symptomatic patients but a greater number of TB patients detected out of symptomatic when compared to study conducted by **V Anand Kumar Kalaiselvan G et al**[11] and **Mridul Gupta et al**.[12] This was probably due to our strict questionnaire criteria for defining TB symptoms during house to house survey which yielded less symptomatic but higher TB patients(Figs. 1–2).

Diagnostic tool of study included robust questionnaires and molecular microbiological test for TB which are now widely available under NTEP. We believe that having a good questionnaire like that was used in our study increases the positive prediction of diagnostic tool. Hence efficient ACF should include a thorough questionnaire which also should be easy to implement in field condition.

ACF is more labour intensive than PCF but if judiciously used under national programme to target the vulnerable

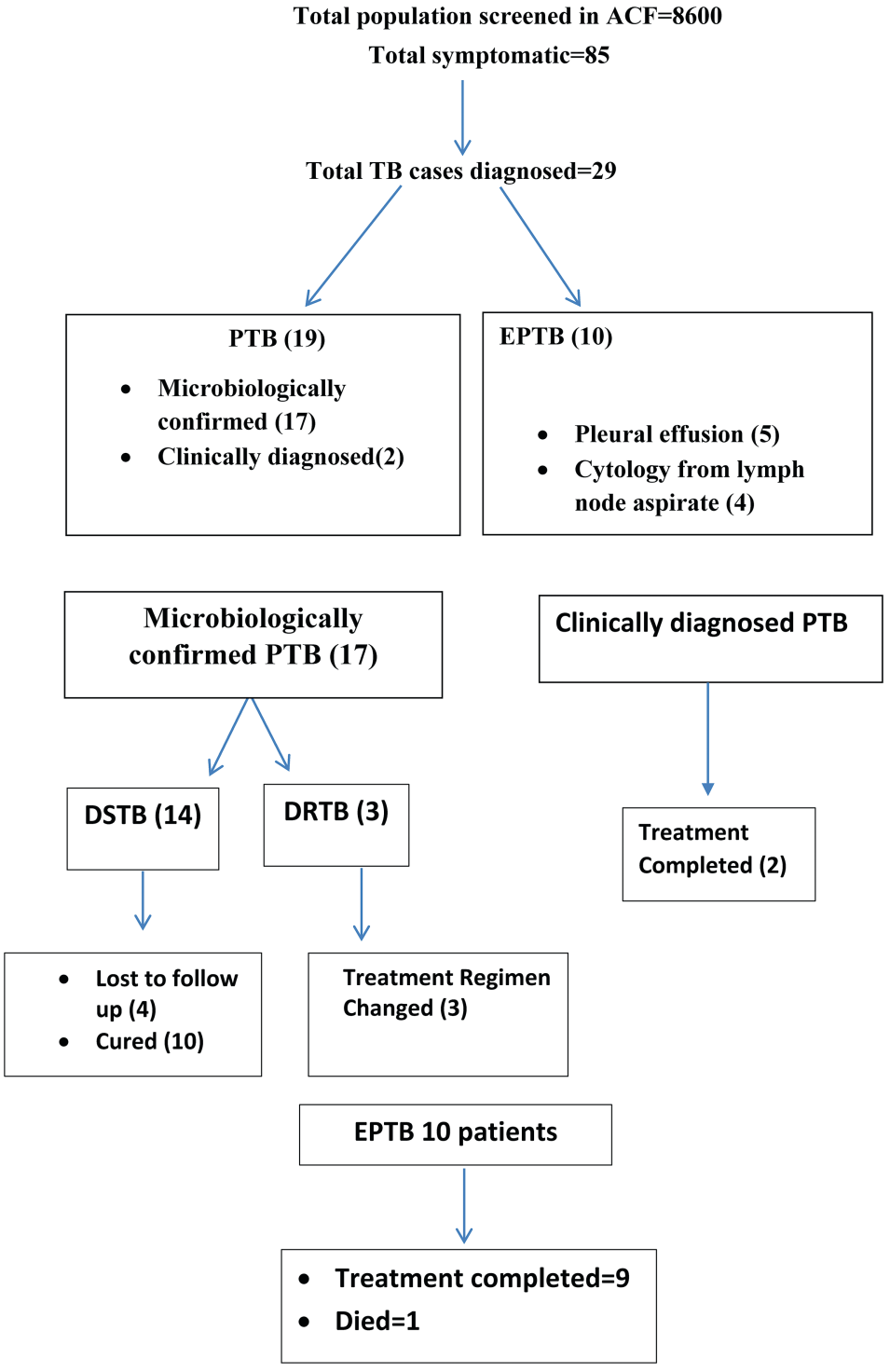

Fig. 2 – Overview ACF continued.

Table 1 – Treatment outcome of PTB patients detected during ACF (N = 19).

Treatment outcome	No. of patients	Percentage
Cured	10	62.5%
Treatment completed	02	12.5%
Lost to follow up	04	25%
Died	0	0%
Treatment regimen changed	03	15.8%
Treatment failure	0	0%
Not evaluated	0	0%

Table 2 – Treatment outcome of PTB patients reported through PCF (N = 11) in Nov 17.

Treatment outcome	No. of patients (N = 11)
Cured	7
Treatment completed	2
Lost to follow up	2
Died	0
Treatment regimen changed	0
Treatment failure	0
Not evaluated	0

population of society it can yield additional number of TB cases which otherwise would have gone undiagnosed. ACF is useful provided that adherence to treatment can be ensured in all detected TB patients otherwise it will be detrimental in the interest of national program if treatment is inadequate(Tables 1–2).

5. Conclusion

ACF strategy achieved good yield though early loss to follow up was high. There was no significant difference in treatment outcome of ACF done in vulnerable population and PCF from the same area. To achieve the objective of END TB STRATEGY 2035, we need to detect cases of TB which otherwise would get lost in the community and keep on spreading this deadly malady. ACF is an effective way to find these additional cases and useful specially when vulnerable population is targeted provided that adherence to treatment can be ensured. Poor treatment adherence will lead to increase transmission risk in communities and greater chances of developing drug resistance. The number being small this doesn't give a direction and cannot be conclusive stated. To get the full benefit of ACF detection it is important to focus on ensuring treatment adherence through different mechanism. Further studies with larger representative population should be undertaken in order to get a better quality of evidence to guide the concerned bodies to better incorporate this strategy in the main framework of NTEP.

Conflicts of interest

All authors have none to declare.

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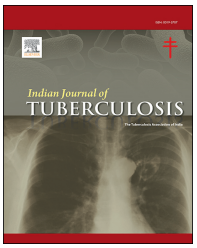

Original Article

Detection of genital tuberculosis among women with infertility using best clinical practices in India: An implementation study

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ABSTRACT

Background: Diagnosis of genital tuberculosis (TB) as a cause of infertility still remains a diagnostic dilemma for clinicians, as no standard guidelines exist. The recently proposed best practices for genital TB diagnosis have not been evaluated yet in India.

Objectives: To implement best practices to diagnose and treat likely genital TB as a cause of infertility.

Methods: Between April 2016 and June 2018, consenting women seen at a tertiary hospital infertility clinic were assessed by thorough TB related clinical history, ultrasonography, tuberculin skin test (TST), and ESR. Those with suspected genital TB underwent laparohysteroscopy. Clinical and laboratory characteristics were compared between likely (microbiologically confirmed or probable TB) and unlikely (possible and no genital TB) genital TB. Fertility outcome was assessed among women initiated on anti-TB treatment (ATT).

Results: Of 185 women seeking infertility care, likely genital TB was identified among 29 (15.7%) women, with 6 (21%) confirmed and 23 (79%) probable genital TB. Compared to unlikely genital TB cases, the likely genital TB group were found to have past history of TB ($p < 0.001$); positive TST ($p = 0.002$) and elevated ESR ($p = 0.001$). Among the likely genital TB group, all 6 confirmed genital TB were started on ATT and 2 (33.3%) conceived. Of 5 probable genital TB started on ATT, 3 (60%) conceived.

Abbreviations: TB, Tuberculosis; ATT, anti-TB treatment; HIC, high-income; LMIC, low-and middle-income countries; EPTB, extra pulmonary TB; BCG, Bacille Calmette-Guerin; BJGMC, Byramjee-Jeejeebhoy Government Medical College; IGRA, interferon gamma release assay; IQR, interquartile range; TST, Tuberculin skin test; ESR, erythrocyte sedimentation rates; USG, ultrasound; RNTCP, Revised National Tuberculosis Control Program; PCR, Polymerase Chain Reaction; ICH, International Conference on Harmonization (ICH E6); IEC, Independent Ethics Committee; IRB, Institutional Review Board; BMI, body mass index; MKS, Modified Kuppuswami Score; H/O, History of; PCOS, Polycystic Ovarian Disease.

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Conclusion: Approximately 1/6th of women seeking infertility care met the criteria for likely genital TB. Conception among over-half of treated probable genital TB cases provides preliminary evidence that best clinical practices can be utilized, but needs further confirmatory studies.

1. Introduction

Female infertility is rising globally, with variation in etiology between high-income (HIC) and low-and middle-income countries (LMIC).[1] While anovulation is common in HICs, infectious etiology remains prevalent in LMICs where tuboperitoneal damage affects fertility.[2] Genitourinary tuberculosis (TB) is a common form of extra pulmonary TB (EPTB) worldwide, accounting for 9% of EPTB.[3] Genital TB is a known cause of infertility in women where endometrial damage, tubal obstruction, ovarian and cervical affection can lead to infertility.[4,5] In the infertility clinics worldwide, an estimated 5% of the women presenting with infertility have genital TB, with prevalence rates ranging from less than 1% in HICs to as high as 3–26% in LMICs.[6,7,8,9] In India, reported annual EPTB burden was 20–25%of which 4% of EPTB cases were reported to be urogenital TB (urinary tract and genital TB).[10,11] Prior studies have attempted to define genital TB cases using individual criterion, i.e. microbiological, ultrasound (USG) and laparohysteroscopy. However, a comprehensive definition of probable or possible genital TB using all the criteria: clinical presentation, USG, laboratory and laparohysteroscopy findings, are not available.[4,13] Since genital TB is a paucibacillary disease, the yield of the newer diagnostics such as GeneXpert, known to have high diagnostic sensitivity and specificity, may still be lower. This poses a diagnostic challenge to the clinicians.[2,4,14] Therefore, similar to other EPTBs, most genital TB would likely be diagnosed based on clinical, radiologic and histopathologic findings.[14] Importantly, there is a lack of standard guidelines for diagnosis of genital TB. Recent Revised National Tuberculosis Control Program guidelines recommend treatment for laboratory confirmed genital TB cases.[12] However, these guidelines do not specify any algorithm which can be used as best practice for diagnosing and treating clinical (probable) genital TB.

Recently, an algorithmic best practice approach was proposed to diagnose genital TB among infertile women.[16] However, it has not yet been evaluated in India. Employing best clinical practices in diagnosing and treating genital TB may help optimize fertility rate.[1,4] Therefore, we aimed to evaluate this approach to identify likely genital TB (confirmed and probable), and unlikely genital TB (possible and no TB) among female infertility cases accessing care at a tertiary level teaching hospital in India, a country with the world's largest TB burden.[16]

2. Methodology

2.1. Study design

A prospective cross-sectional study was conducted between April 2016 and June 2018 among patients visiting the weekly infertility clinic at Byramjee-Jeejeebhoy Government Medical College and Sassoon General Hospital, Pune, India, a tertiary referral center. Consenting female infertility patients between 18 and 40 years of age were eligible and enrolled in the study. Women with male partner infertility and congenital anatomical abnormalities were excluded.

After enrolment, clinical and socio-demographic characteristics, including an in-depth medical history including history of smoking, alcohol, diabetes and HIV were recorded in the case report forms designed for the study. Standard of care clinical history including menstrual history such as irregular menstrual cycles, flow, and duration of infertility, prior pregnancy outcomes and prior infertility treatments was recorded as per routine practices. Clinical examination like per abdominal, per speculum and per vaginal examinations and USG were performed as part of standard of care.

Based on the extensive literature review, we derived the best practices to identify confirmed and probable cases of genital TB as cause of infertility as shown in Fig. 1. Our best clinical practices included screening for TB symptoms, obtaining history of prior TB and recent TB contacts, erythrocyte sedimentation rates (ESR) and tuberculin skin test (TST). Those with positive TST (>10 mm induration) and/or ESR (>20) underwent further investigations such as ultrasound if not already done. In addition, endometrial TB culture or PCR and laparohysteroscopy were performed in suspected cases. At laparohysteroscopy, the uterine cavity, uterine surface, tubes, ovaries, ovarian fossa, utero sacral ligaments and peritoneal findings were assessed and tissue samples were taken if any abnormality was detected or genital TB was suspected, for both microbiological and/or histopathological diagnosis. Using this approach, genital TB case definition (confirmed, probable) was established cumulatively from clinical history, radiology, microbiology and/or laparohysteroscopy. Those categorized as confirmed and probable genital TB were referred for anti-TB treatment (ATT) initiation.

2.2. Study definitions

Primary infertility was defined as those women who are unable to conceive after one year of unprotected intercourse.[17]

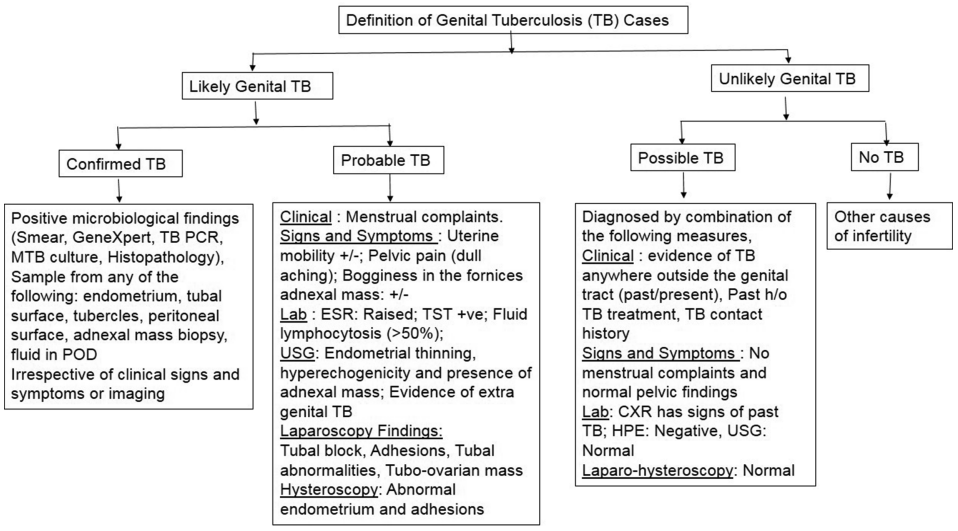

Fig. 1 – Figure showing the best clinical practices to diagnose genital tuberculosis among women seeking care for infertility. Note: POD: Pouch of Douglas. TST: Tuberculin Skin Test. ESR:Erythrocyte Sedimentation Rate. USG: Ultra Sonography. H/o: History of. +/–: Positive or negative. CXR: Chest X-ray. HPE: Histopathological Examination. PCR: Polymerase Chain Reaction. MTB: Mycobacterium Tuberculosis.

Secondary infertility was defined as inability to conceive after previous conception irrespective of the obstetric outcome. Genital TB was categorized as likely and unlikely TB. Likely TB was defined as microbiologically confirmed and probable TB. Unlikely genital TB was defined as possible or no TB (Fig. 1).

2.3. *Ethical considerations*

The study was conducted in accordance with internationally recognized standards for ethical research and the International Conference on Harmonization (ICH E6). The protocol was reviewed and approved by the Independent Ethics Committee (IEC) of BJGMC and Institutional Review Board (IRB) of Johns Hopkins University, respectively. Written informed consent was obtained for each participant prior to entry into the study.

2.4. *Statistical analysis*

Data were analyzed using Stata version 14.2 (Stata Corp). Continuous variables were compared across likely and unlikely genital TB groups using Mann–Whitney (Rank-sum) test, and categorical variables were compared using Fisher's exact test. P values < 0.05 were considered significant.

3. Results

Of 246 infertile women accessing care during the study period, 185 were eligible and enrolled. Overall, the median age was 26 years (interquartile range (IQR), 24–30) and the median body mass index (BMI) was 22.96 (IQR, 21.5–25.1) (Table 1). Primary infertility was found in 155 (84%) women and secondary in 30 (16%) women (Table 1). Using the best clinical practices, 29 (15.7%; 95% CI: 11%–22%) met the definition of likely genital TB and 156 (84.3%; 95% CI: 78%–89%) met the definition of unlikely genital TB (Fig. 2). Of the 29 likely genital TB cases, 26 (89.7%) were primary infertility cases and 3 (10.3%) were secondary infertility. All 6 confirmed cases had primary genital TB and all 3 secondary infertility cases were probable genital TB. Of the 29 with likely TB, 6 (20.7%) had microbiologically confirmed TB and 23 (79.3%) had probable TB. Of the 156 unlikely genital TB group, 12 (7.7%) had possible TB and 144 (92.3%) had no TB. Overall, 14 (8%) reported a past history of TB.

Demographic and clinical characteristics were comparable between the likely and unlikely genital TB groups with a few exceptions (Table 1). Those with likely genital TB were more likely to be older (28 vs. 26 years, $p = 0.05$), less educated ($p = 0.03$), lower BMI (22.21 vs. 23.23 kg/m^2, $p = 0.02$), past history of TB (64% vs. 36%, $p < 0.001$), and past history of infertility treatments (34% vs. 17%, $p = 0.04$). In addition, those with likely genital TB were more likely to have >20 mm of ESR ($p = 0.001$), and positive TST (defined as >10 mm induration, $p = 0.002$). Furthermore, likely genital TB group were subjected to laparohysteroscopy more often (75% vs. 5%, $p < 0.001$).

The laparohysteroscopy findings among likely genital TB group is shown in Table 2. Peri-tubal and tubo-ovarian adhesions were seen in 10 (66.7%), hydrosalphinx in 4 (26.7%), tubal block in 3 (20%), and other tubal abnormalities in 3 (20%) women (Figs. 3 and 4). Tubercles on the fallopian tube was seen in one woman. Hysteroscopy revealed normal endometrium in 12 (80%) and pale oligemic endometrium in 3 (20%) women (Table 2).

Of the likely genital TB group, 2 (33.3%) of the 6 confirmed genital TB cases who initiated and completed ATT conceived (Fig. 2). Among 23 probable genital TB cases, 5 (21.7%) were initiated on ATT and 3 (60%) conceived. Of 18 patients who did

Table 1 – Characteristics of women seeking care for infertility by likely and unlikely genital tuberculosis in Pune, India.

Variable	Overall (N = 185)	Likely Genital TB (N = 29)	Unlikely Genital TB (N = 156)	p-value
Age, median (IQR**)	26 (24–30)	28 (25–30)	26 (24–29)	0.05*
Education, n (%)				
≥Diploma/intermediate	5 (3%)	2 (7%)	3 (2%)	
High-school	65 (35%)	5 (17%)	60 (39%)	0.03*
≤Middle school	114 (62%)	22 (76%)	92 (59%)	–
Occupation, n (%)				
≥Semi-skilled worker	50 (19%)	7 (24%)	43 (28%)	
Unskilled worker	56 (30%)	8 (28%)	48 (31%)	–
Unemployed/housewife	79 (43%)	14 (48%)	65 (42%)	0.85
MKS* Scale, n (%)**				
Upper	2 (1%)	1 (3%)	1 (1%)	0.26
Upper middle	4 (2%)	0	4 (3%)	
Lower middle	68 (37%)	8 (28%)	60 (38%)	
Upper lower	111 (60%)	20 (69%)	91 (58%)	
Duration of marriage (IQR)	5 (3–8)	7 (4–10)	5 (3–7)	0.03*
BMI[+], median (IQR) Scale	22.9 (21.5–25.0)	22.2 (20.0–23.8)	23.2 (21.6–25.1)	0.02*
Underweight (<18.5)	8 (4%)	1 (3%)	7 (5%)	0.05*
Normal (18.5–24.9)	125 (68%)	25 (86%)	100 (65%)	
Overweight (>24.9)	51 (28%)	3 (10%)	48 (31%)	
BCG[††] scar, n (%)				
Yes	184 (99%)	29 (100%)	155 (99%)	>0.95
No	1 (1%)	0	1 (1%)	
Infertility, n (%)				
Primary	155 (86%)	24 (86%)	131 (86%)	≥0.95
Secondary	25 (14%)	4 (14%)	21 (14%)	
Prior t/reatment for infertility, n (%)				
No	149 (80%)	19 (66%)	130 (83%)	0.04*
Yes	36 (20%)	10 (34%)	26 (17%)	
Past H/o[†††]TB, n (%)				
No	171 (92%)	20 (69%)	151 (97%)	–
Yes	14 (8%)	9 (31%)	5 (3%)	p < 0.001*
Pelvic Pain, n (%)				
No	182 (98%)	28 (97%)	154 (99%)	0.40
Yes	3 (2%)	1 (3%)	2 (1%)	
Per Vaginal: Uterus size, n (%)				
Bulky	2 (1%)	1 (3%)	1 (1%)	–
Normal	181 (98%)	28 (97%)	153 (98%)	0.5
Small	2 (1%)	0	2 (1%)	–
Mobility, n (%)				
Normal	109 (59%)	16 (57%)	93 (60%)	–
Present	71 (39%)	10 (36%)	61 (39%)	0.17
Restricted	4 (2%)	2 (7%)	2 (1%)	
Adnexal mass, n (%)				
Present	4 (2%)	2 (7%)	2 (1%)	–
Absent	181 (98%)	27 (93%)	154 (99%)	0.12
ESR**, Median (IQR)**				
≤20	129 (70%)	12 (41%)	117 (75%)	–
>20	56 (30%)	17 (59%)	39 (25%)	0.001*
TST[††††], Median (IQR)				
≤10	108 (58%)	9 (31%)	99 (63%)	–
>10	77 (42%)	20 (69%)	57 (37%)	0.002*
Evidence of PCOS***, n (%)**				
No	127 (70%)	24 (86%)	103 (67%)	0.05*
Yes	55 (30%)	4 (14%)	51 (33%)	
Diagnostic Hysterolaparoscopy (n = 22)¥	22 (12%)	15 (68%)	7 (32%)	p < 0.001*
TB PCR Positive (n = 13) ¥	13 (7%)	6 (46%)	7 (54%)	>0.95

*Statistically Significant; **IQR: Interquartile Range; ***MKS: Modified Kuppuswami Score Socioeconomic status in India. MKS class I-Upper, class II - Upper middle, III -Middle/lower middle, IV- Lower/upper lower),V (Lower); [+]BMI:Body Mass Index; [††]BCG: Bacillus Calmette–Guérin; [†††] H/O:History of; ¥ for specific invasive procedures, the percentages are based on total number of testing done shown in the variable column. **** ESR: Erythrocyte Sedimentation Rate; [††††] TST: Tuberculin Skin Test; *****PCOS: Polycystic Ovarian Syndrome.

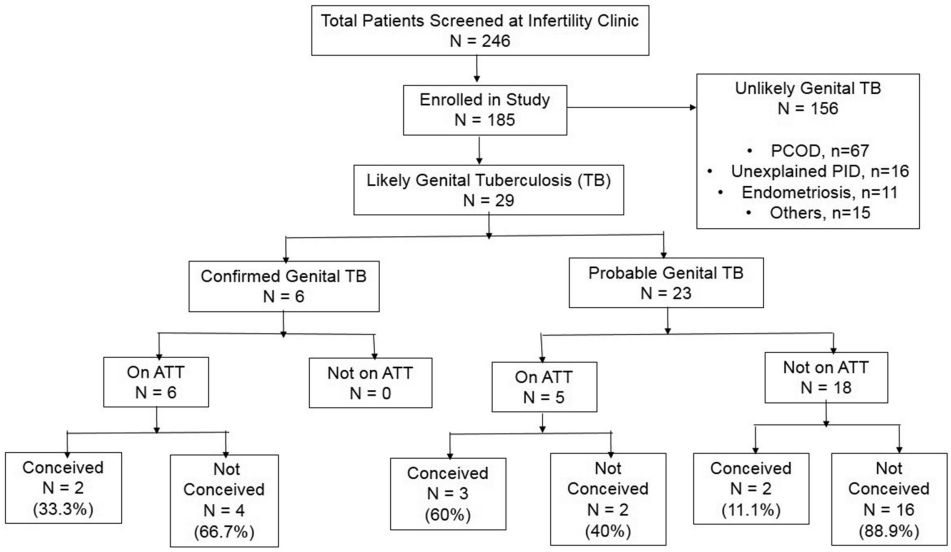

Fig. 2 – A flow-diagram showing women with likely and unlikely genital tuberculosis and their pregnancy outcomes. Note. PCOD: Polycystic Ovarian Disease. PID: Pelvic Inflammatory Disease. ATT: Anti-Tuberculosis Treatment.

Table 2 – Laparohysteroscopy findings among women with confirmed and probable genital tuberculosis presenting with infertility.

	Total n (%)	Confirmed n (%)	Probable n (%)
Total likely GTB	29	6 (20.7)	23 (79.3)
Laparohysteroscopy	15 (51.7)	6 (40)	9 (60)
Laparoscopy findings			
Adhesions	10 (66.7)	4 (40)	6 (60)
Hydrosalphinx	4 (26.7)	3 (75)	1 (25)
Tubal block	3 (20)	2 (66.7)	1 (33.3)
Tuboovarian mass	2 (13.3)	1 (50)	1 (50)
Other tubal abnormalities	3 (20)	1 (33.3)	2 (66.7)
Hysteroscopy findings			
Normal	12 (80)	6 (50)	6 (50)
Abnormal (Pale endometrium)	3 (20)	0	3 (100)

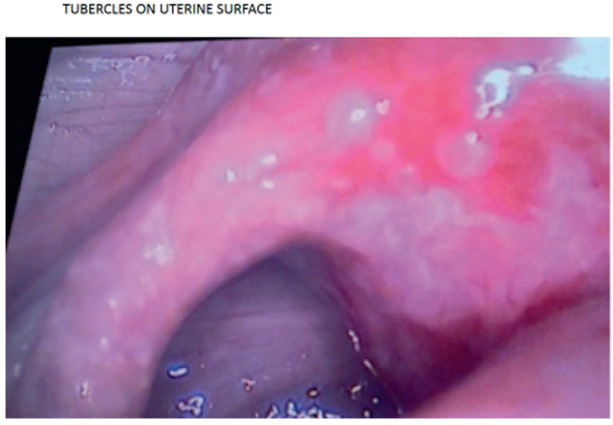

Fig. 3 – A laparoscopy picture showing tubercles in woman with likely genital tuberculosis.

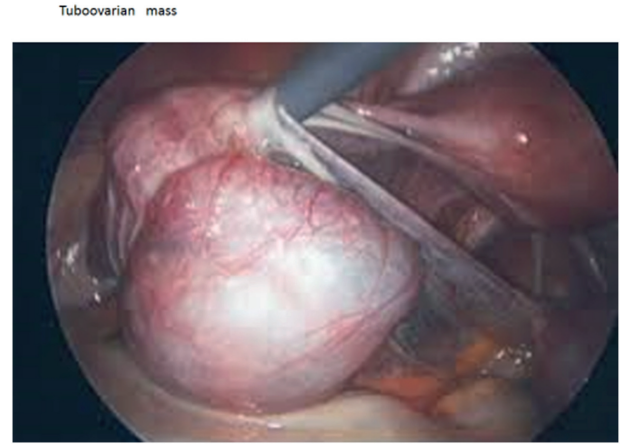

Fig. 4 – A laparoscopy picture showing tubo-ovarian mass in woman with likely genital tuberculosis.

not initiate ATT, 2 (11%) conceived and 16 (89%) did not. All those who conceived had no obstetric complications and delivered healthy babies at term.

In unlikely GTB group, the possible TB patients received routine care for infertility treatment. They were counselled regarding symptomatology of genital TB especially menstrual complaints and TB related symptoms. They were requested to follow up if they had any such complaint for further evaluation.

4. Discussion

Diagnostic delay of genital TB as a cause of infertility can lead to severe irreversible organ damage with poor fertility

outcomes.[17,18] Furthermore, assisted reproductive techniques may become the only option to have a biological child, which is very costly and burdens the health system.[19,20] Our study that employed best clinical practices to diagnose genital TB identified a 16% prevalence of likely genital TB among women reporting infertility. Importantly, though the numbers were very small, 3 out of 5 women with probable genital TB conceived after starting treatment.

The prevalence of genital TB found in our study is consistent with other studies in India but much higher than from the United States (<1%).[21] Similar to our findings, a study by Sharma reported 3–16% of genital TB among infertile patients in India, but extensive investigations were not used.[9] In contrast, a North Indian study reported a very high rate of genital TB (48.5%) among infertile women.[22] A nationwide survey by Indian Council of Medical Research reported an increasing prevalence of genital TB from 19% to 30% between 2011 and 2015[23,24] but noted region wise differences as well as a lack of standardized approach to diagnosing genital TB.[23,24]

Importantly, our study showed that 1/3rd of confirmed genital TB participants initiated on ATT conceived. Interestingly, though small numbers, much higher proportion of conception (60%) was found among those with probable genital TB started on ATT. A prospective study reported 19.2% conception rate among women treated for infertility with ATT, with a much lower live birth rate (7.2%),[8] in contrast to the 24.1% overall conception rate and 100% live births observed in our likely genital TB group. Using assisted reproductive technique after completion of ATT could further improve the conception rate in selected patients without endometrial damage.[25] However in our cohort, an assisted reproduction technique was unavailable in public sector tertiary level hospital. The observed improvement in fertility outcome could be related to successful TB treatment.

With India leading the world in the absolute burden of TB, our evaluation of best clinical practices to diagnose genital TB among infertile patient is timely and will provide guidance to clinicians on how to diagnose genital TB. Challenges to diagnose genital TB as an etiology of infertility exist due to several reasons. First, genital TB does not present with classic TB symptomatology. Furthermore, there is considerable overlap between presenting symptoms of genital TB and other infertility causes like pelvic inflammatory diseases, ovarian cyst, posing diagnostic dilemmas. In fact, our study found that 12% with likely genital TB had other gynaecological conditions, confusing the clinical picture. Second, the yield of microbiologic investigations has known to be suboptimal, even with Gene Xpert, as presence of blood in genitourinary biopsy specimens may interfere with GeneXpert tests. Finally, there are no standard approach to diagnose genital TB, which prompted our group to use the best practices to diagnose genital TB among infertile women.[16,24,26]

Our study has a few limitations. We did not have a comparative group. Our approach utilized the best tools and practices available at a public tertiary hospital. Furthermore, we did not uniformly apply some invasive components of the diagnostic approach to all infertile women, but used the clinical judgment of treating clinicians to avoid unnecessary procedures for those unlikely to have genital TB or whenever alternate diagnoses were available. Genital TB being a paucibacillary disease, the decision about treatment initiation for probable TB cases was as per the treating physician, based on the combined evidence for TB in the form of abnormal clinical findings, supportive laboratory evidence like raised ESR, raised TST, as well as abnormalities seen during laparohysteroscopy (suggestive of genital TB). Our sample size was small to provide definitive evidence for fertility rate among likely genital TB group, but provides preliminary evidence for future studies. Despite these limitations, our study provides important clinical, easily adoptable best practices to diagnose and treat genital TB, a likely treatable cause of infertility.

In summary, our study demonstrates that genital TB should be considered as a cause of infertility in high TB burden settings. Importantly, the best clinical practices helped identify probable genital TB, suggesting that the proposed best clinical practice can be used in high TB burden settings as ours in India.[15] Larger studies that are powered to confirm our observations, and standard application of diagnostic tools, are needed to confirm our findings.

Conflicts of interest

The authors have none to declare.

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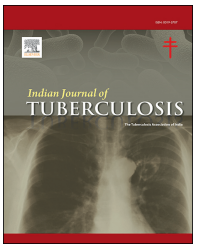

Review Article

A review: Epidemiology, pathogenesis and prospect in developing vaccines for novel Coronavirus (COVID-19)

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ABSTRACT

In December 2019, a large number of coronavirus cases were emerged in Wuhan, Hubei Province, China and rapidly spread to different countries and territories around the world within four months. The World Health Organization (WHO) declared this outbreak as a global health emergency. The spread of COVID-19 over globe is highly contagious; they transmitted from person-to-person through small droplets of infected person. Many diagnosis and treatment methods have been implemented to reduce and control the outbreak. Efforts have been made to develop coronavirus vaccine against S protein or spike glycoprotein of coronavirus. COVID-19 outbreak will affect the Gross Domestic Product (GDP) of the world. At the time of preparing manuscript, total number of active cases reaches to more than 8.9 million and confirmed death reaches to approx. 4.6 lakh. This article highlights the ongoing research and advances in designing vaccine and therapeutics against COVID-19 and also focusing on the epidemiology, transmission, future direction and control the spread of infectious diseases.

1. Introduction

Coronavirus is one of the most infectious pathogens that targets human respiratory system. In December 2019, a cluster of pneumonia patients was admitted in hospital, which were epidemiologically linked to a seafood market in Wuhan, Hubei Province, China.[1] The disease was first named as 2019 novel coronavirus (2019-nCoV) on 7 January 2020 and later renamed Severe Acute Respiratory Syndrome Coronavirus 2 (SARSCoV-2).[2] Number of cases was reported from all over countries and then WHO declared this outbreak as a global health emergency on 30 January 2020 and retitled coronavirus disease (COVID-19).[3] The most common symptoms of COVID-19 are fever, dry cough and tiredness.[4] Patients have different symptoms like aches, nasal congestion, running nose, sore throat while some patients have no symptoms but they act as a carrier for the diseases. About 80% of infected people recover without any special treatment and approximately 1.0 out of 6.0 patients is seriously ill and facing breathing difficulty.[5] People having weak immunity, diabetes, heart problem, and are infected with coronavirus, need extra attention and clinical care.[6] COVID-19 spread from person to person through

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small droplets, when infected person cough, exhale or speaks. This is why it is important to keep distance of at least 3–6 feet from a person who is ill.[5] On 11th March 2020, WHO declared COVID-19 as a pandemic disease.[7] All the country are doing their best and implementing the appropriate control and preventive strategies. In the absence of specific medicines for treatment of COVID-19, drugs that might be effective include remdesivir, ritonavir, chloroquine (CQ) and hydroxychloroquine (HCQ) alone or in combination with convalescent plasma, monoclonal antibodies and Interferons.[8–12] Many efforts have been made to develop vaccine against CoV infection but there are certain limiting factors such as degree of cross-protection and their sequence diversity which prevent the development of suitable and effective vaccine.[13] According to WHO guideline, the infected patients must be provide with proper oxygen therapy, fluid therapy, medicine and also recommends proper isolation system.

2. Structure and origin of Coronavirus

Coronavirus are enveloped virus, with single stranded, non-segmented, positive sense RNA belongs to the family *Coronaviridae*, subfamily *Coronavirinae* and order *Nidovirales*. Genome size of coronavirus is approximately 26–32 Kb and is the largest known genome of RNA virus.[14] Its size ranges from 60 nm to 140 nm in diameter having club-shaped spike projections (Fig. 1). Under electron microscope, spike looks like crown and hence named coronavirus.[15] Coronavirus have helically symmetrically nucleocapsids, which is very rare among positive sense RNA virus. On the basis of phylogeny, subfamily *Coronavirinae* consist of four genera: *Alphacoronavirus* (α-CoV), *Betacoronavirus* (β-CoV), *Gammacoronavirus* (γ-CoV) and *Deltacoronavirus* (δ-CoV). α -CoV and β -CoV usually causes respiratory problems in human, whereas γ -CoV and δ -CoV infect birds. In human two highly pathogenic viruses SARS-CoV and MERS-CoV, causes severe respiratory syndrome, whereas four human coronavirus HCoV-NL63, HCoV-OC43, HCoV-229E and HKU1 induced mild respiratory syndrome in immunocompetent person. According to current sequence database HCoV-OC43, HKU1 have originated from rodent and HCoV-NL63, HCoV-229E, SARS-CoV and MERS-CoV have originated from bats.[14,16] Through sequencing, it was found that nCoV-2019 belongs to β –coronavirus.[17]

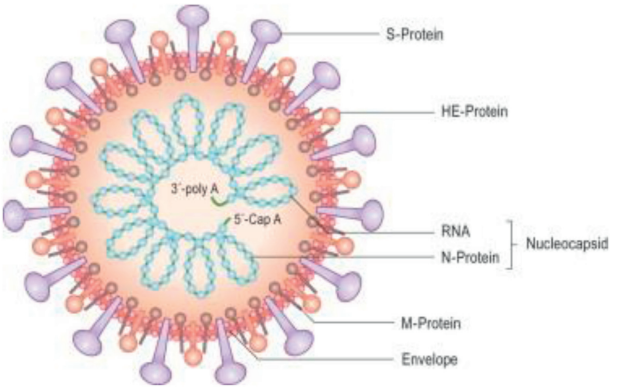

Fig. 1 – Skeleton of coronavirus; inside and outside morphology.[19]

In 2003, coronavirus of beta genera having bat origin transmit to human via civet cat as an intermediate host in the Guangdong province of china. This virus causes acute respiratory syndrome and nearly 8422 people were affected in China and Hong Kong. Another outbreak occur in 2012, Middle East respiratory syndrome coronavirus (MERS-CoV) emerged in South Arabia in which 2494 people were affected and fatality rate was reported as 34%.[18]

3. Transmission

A novel β-coronavirus was first identified in December 2019, in Wuhan, Hubei province, China. This outbreak in China is the third epidemic in 21st century, which already surpassed SARS and MERS. Currently, large number of pneumonia patients were reported, who had exposed to seafood market, which is a hub for many species of live animal. In January 10, 2020, full genome sequences of COVID- 19 were released in public database, and were found that sequence has some similarity with SARS. 2019-nCoV was renamed as SARS-CoV-2 by International Committee on Taxonomy of Viruses. Genetic sequence of COVID-19 shows more than 80% similarity with SARS-CoV and 50% sequence identity with MERS-CoV.[21] Extensive study from the phylogenetic analysis revealed that the COVID-19 belongs to *betacoronavirus* genus. Binding of receptor is the first step of viral infection followed by fusion with the cell. It is reported that COVID-19 binds to angiotensin-converting enzyme 2 (ACE2), as the sequence of receptor binding domain of coronavirus spikes is similar to that of SARS-CoV.[22]

The number of coronavirus cases increases exponentially in Wuhan, China and first case was reported on November 17, 2019. The coronavirus spread rapidly from China to other countries that include Thailand, Nepal, Malaysia, Sri Lanka, Singapore, United Arab Emirates, United States, India, Australia, Finland, Germany, Combodia, Vietnam, Taiwan, Canada, France, The Philippines, Japan, Republic of Korea (Fig. 2).

WHO declared novel Coronavirus outbreak as pandemic and reiterated the call for all countries to take immediate action to detect, treat and reduce the transmission to save people's lives. At the time of preparing manuscript 8.9 million coronavirus cases and approximately 4.6 lakh death cases were reported by WHO.[23] Several reports suggest that person-to-person transmission via direct contact; through droplets by coughing or sneezing from infected person and indirect contact such as surface contamination are the routes for the transmission of COVID-19 infection. Other studies conducted on pregnant women, who were in third trimester of pregnancy and confirmed for COVID-19 infection, but the transmission from mother to child was not confirmed. Pregnant women are more susceptible to infection by respiratory pathogens.[24]

4. Symptoms and diagnosis

The common symptoms of this disease are fever, cough and tiredness.[4] Some patients may have different symptoms like aches, nasal congestion, sputum production, haemoptysis, running nose, sore throat, diarrhoea, dyspnoea and

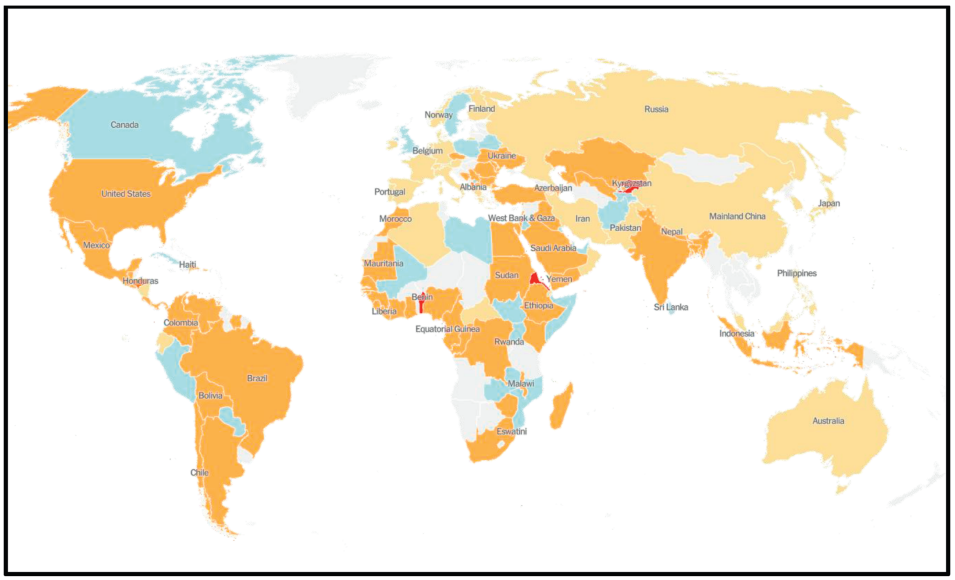

Fig. 2 – Map of spread COVID-19 global outbreak as on June 28, 2020.[20] Blue colour indicates decrease in coronavirus cases where as orange and red colour indicates the increasing number of coronavirus cases.

lymphopenia.[22,18,25] The symptoms appear after incubation of approximately 5.2 days.[26] The total period from onset to death of coronavirus disease ranges from 6 to 41 days with a median of 14 days.[27] The period of infection is dependent on patient's immunity and age. Infection period is shorter in patients with age >70 years than compared to those under the age of 70 years. Clinical features revealed by Chest CT scan presented as pneumonia, Acute Respiratory Distress Syndrome (ARDS), acute kidney injury, cardiac injury and even death may occur in severe cases.[28,18] In some patients, multiple ground glass opacity observed in subpleural region of both the lungs which induced both localized and systemic immune response that leads to inflammation.[29] Chest radiology of some patients shows an infiltrate in upper lobe of lungs which is associated with dyspnea and hypoxemia.[30] Patients infected with COVID-19 also developed symptoms like diarrhoea, so faecal and urine sample test is important to include an alternative route of transmission of coronavirus.[31]

Patients infected with coronavirus shows increased level of pro-inflammatory cytokine, high leukocyte numbers, and abnormal respiratory function. The main pathogenesis of COVID-19 infection is severe pneumonia, incidence of ground glass opacities RNAaemia and acute cardiac injury. Blood sample of COVID-19 patients shows high level of cytokine and chemokine such as TNFα, IL7, IL8, IL9, IL10, VEGFA, GCSF, GMCSF, PGF2, etc.[18]

The respiratory samples (nasopharyngeal swab, sputum, throat swab, bronchoalveolar lavage, endotracheal aspirates) taken from the infected person both symptomatic and asymptomatic and sent to laboratory for diagnosis. The specimen were diagnosed by real-time reverse transcription polymerase chain reaction (RT-PCR) using the protocol published by WHO. As the numbers of patients were increasing on daily basis, it leads to shortage of laboratory based molecular testing capacity and reagents. Thus rapid and easy to use device were manufactured to test outside the laboratory settings in a couple of minutes. Antibody based testing kit is generally harder to get correct result, as the antibody present in the strip can detect antigens of virus other than COVID-19 which cause common cold. To overcome this problem antibody detecting rapid diagnosis test for patients care was developed. This rapid kit detect the antibody present in the blood of infected person. The strength of antibody response were depend on severity of infection, patients age, nutritional status, HIV patients having certain medication etc.[32] The most widely used diagnostic kits were included in Table 1.

5. Therapeutics

Therapeutic options that can be used for COVID-19 includes siRNA, anti-sense RNA, monoclonal antibodies targeting host receptor, host cell protease inhibitors, targeting specific enzymes involved in viral replication and transcription, antiviral peptide targeting S2 and natural product.[11,35] Neither any antiviral drugs nor vaccines are available for the treatment of COVID-19. Efforts have been made by scientist to develop vaccine against coronavirus, but a degree of cross-reactivity is the limiting factors.[26] For developing a new vaccine, at least a year or 18 months will required said by Dr. Anthony Fauci, Director of the National Institute of Allergy and Infectious Diseases, US. Johnson & Johnson said human test for experimental vaccine will begin by September 2020. So in the absence of specific medicines for treatment of COVID-19, many low-cost available drugs have been tried like chloroquine (CQ) and hydroxychloroquine (HCQ) which are used as antimalarial along with several other antiviral drugs such as remdesivir, ribavirin, oseltamivir, lopinavir, darunavir, cobicistat and favipiravir are in phase III trial for COVID-19.[8,36] *In vitro* chloroquine and hydroxychloroquine (HCQ) have antiviral activity against severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) and some other viruses such as influenza.[37] As of April 2020, remdesivir (GS-5734) was comes into light as the most promising treatment for COVID-19 and

Table 1 – Diagnostic test kits used for the diagnosis of COVID-19.[33,34]

Product name	Manufacturer
cobas SARS-CoV-2 Qualitative assay for use on the cobas 6800/8800 Systems	Roche Molecular Systems, Inc.
Primerdesign Ltd COVID-19 genesig Real-Time PCR assay	Primerdesign Ltd
Abbott Realtime SARS-CoV-2	Abbott Molecular Inc.
PerkinElmer® SARS-CoV-2 Real-time RT-PCR Assay	PerkinElmer Inc.
Real-time fluorescent RT-PCR kit for detecting 2019-nCoV	BGI Europe A/S
Detection Kit for 2019 Novel Coronavirus (2019-nCoV) RNA (PCR- Fluorescence Probing)	Da An Gene Co., Ltd. Of Sun Yat-sen University
RealStar SARS-CoV-2 RT-PCR kit 1.0	Altona Diagnostics
Patho Detect	MY LAB
Allplex 2019-nCoV assay	Seegene
nCoV Real-Time Detection kit	SD Biosensor
TRUPCR SARS-CoV-2RT-qPCR kit version 2	KILPEST (BLACKBIO)
Quantiplus CoV detection KIT Ver 2.0	Huwel Lifesciences Pvt. Ltd.
TaqMan 2019-nCoV Control Kit v1	ABI (Applied biosystems)
BIO COVID ID/COVID-19 qualitative PCR detection Kit version 2	Biogenomics (India)
qSARS-CoV-2 IgG/IgM Rapid Test	Cellex.Inc
Quest SARS-CoV-2 rRT-PCR	Quest Diagnostics Infectious Disease, Inc.
Everlywell COVID-19 Test Home Collection Kit	Everlywell,Inc.
COVID-19 RT-PCR Test	Laboratory Corporation of America (LabCorp)
Panther Fusion SARS-CoV-2 Assay	Hologic, Inc.
TaqPath COVID-19 Combo Kit	Thermo Fisher Scientific,Inc.
Xpert Xpress SARS-CoV-2 test	Cepheid

included for evaluation of four stage treatments under European Discovery trial and international Solidarity trial.

S protein of coronavirus is considered as target for designing therapies such as RBD-ACE2 blocker, protease inhibitor, S protein inhibitor etc.[38] All therapeutic strategies show potential activity *in vitro* and *in vivo*, but due to insufficient support of animal and human trial, they are not properly used against COVID-19. In order to develop pre- and post-prophylaxis against coronavirus diseases, there is urgent need for the establishment of animal model to replicate the severe disease observed in human. Scientists were continuously and rigorously working for developing potential vaccines to providing a better understanding of virus–host interaction.

6. Vaccine and plasma therapy

S-protein based strategies such as S1 receptor binding domain (S1-RBD), DNA, viral vector, full length S protein etc. have been used for developing vaccine against COVID-19.[39–41] S1-RBD interact with angiotensin-converting enzyme 2 (ACE2) and S2 domain of S protein mediate fusion of virus and host cell membrane for releasing viral RNA into the cytoplasm. The S protein plays a major role for induction of immunity during COVID-19 infection, which elicits antibodies and T-cell response.[38] Hence the S-protein based vaccine blocks not only viral binding receptor but also prevent viral genome uncoating.[42] Therefore full length or may be the appropriate part of S protein are most promising candidate for vaccine production. The Coalition for Epidemic preparedness Innovation (CEPI) is continuously working with global health authorities for the development of vaccine against COVID-19. As on April 8, 2020, 115 vaccines were developed, of which 73 are at preclinical stage and most advanced vaccine such as mRNA-1273 from Moderna, INO-4800 from Inovio, pathogen specific aAPC (artificial antigen-presenting cell) from Shenzhen Gene-Immune Medical Institute, Ad5-nCoV from CanSino Biologicals moved to clinical stage (Table 2).

Table 2 – Clinical-phase vaccine for COVID-19.[43,44]

Candidate	Vaccine Characterization	Lead Developer	Status
Ad5-nCoV	Adenovirus type 5 vector that expresses S protein	CanSino Biologicals	Phase I (NCT04313127)
mRNA-1273	LNP- encapsulated mRNA vaccine encoding S protein	Moderna	Phase I (NCT04283461)
LV- SMENP- DC	DCs modified with lentiviral vectormexpressing synthetic minigene based on domains of selected viral proteins; administered with antigen-specific CTLs	Shenzhen Geno- Immune Medical Institute	Phase I (NCT04276896)
Pathogen specific aAPC	aAPCs modified with lentiviral vector expressing synthetic minigene based on domains of selected viral proteins	Shenzhen Geno- Immune Medical Institute	Phase I (NCT04299724)
INO-4800	DNA plasmid encoding S protein delivered by electroporation	Inovio Pharmaceuticals	Phase I (NCT04336410)

aAPC, artificial antigen-presenting cell; CTL, cytotoxic T lymphocyte; DC, dendritic cell; LNP, lipid nanoparticle; S protein, SARS- CoV-2 spike protein.

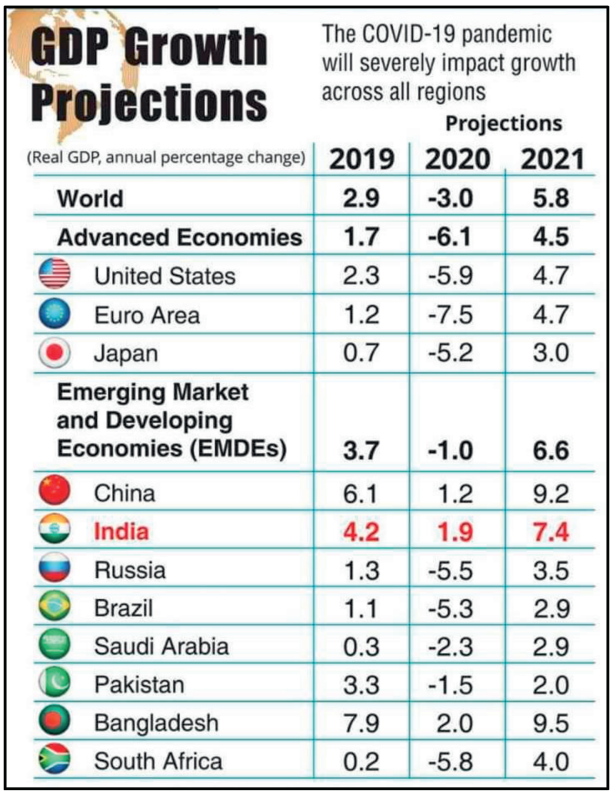

Fig. 3 – Impact of COVID-19 on GDP growth rate; according to World Economic Growth Projection.[50]

Convalescent plasma transfusion (CPT) is an immune based treatment against COVID-19. Plasma from the patients recovered from COVID-19 has been potent and last resort to increase the survival rate of COVID-19 patients.[45] Several studies shows shorter hospital stay and decreased mortality in patients who are treated with plasma than those who are not treated with plasma. This technology was also previously used in case of MERS, 2009 pandemic influenza A H1N1 or in 2014 against Ebola virus disease.[46,47] Recently it has been suggested by Food and Drug Administration that administration of CPT may provide an effective treatment against COVID-19 during public health emergency.[48] According to WHO, COVID-19 management is primarily focus on preventing infection transmission, early detection and proper health care support system.

There are some limitation such as along with CPT, patients receive antiviral drug, thus there is a possibility that these antiviral drugs may also contribute in the recovery of patients. Some patients also administered with glucocorticoids, which might interfere with immune response. Duan et al[49] concluded that CPT shows a potential effect with low risk against COVID-19 treatment. Single dose of CPT with high antibody concentration can rapidly reduce the virus load and improve patient's condition. A definitive conclusion cannot be drawn against CPT, as the optimal dose and treatment time point can be further investigated. Clinical studies are further needed to control this pandemic situation.

7. Prevention and control

- Individual with respiratory symptoms, advised to meet medical health care for proper treatment.
- Regular hand wash with disinfection or soap and use of alcohol (at least 70%) based sanitizer.
- Use of face mask, and avoid direct contact with infected person.
- Safe distance of at least 1 meter should be maintained.
- Health care are recommended to use N95 mask and FFPE kit while handling suspected or confirmed cases of coronavirus.
- Avoid touching nose, eye and mouth without proper hand sanitization.
- Patients with pre-existing medical condition such as diabetes, asthma, heart disease etc. may continuously be in contact with their medical supervisor.

8. Effect of COVID-19 on global GDP

Global economy will suffer the worst financial crisis, said the International Monetary Fund as the planet is struggling with the COVID-19 pandemic. IMF has estimated that in 2020 the growth for global GDP is estimated to fall to −3% (Fig. 3) and will rebound to 5.8% in 2021. The cumulative global loss due to COVID-19 in year 2020 and 2021 is expected to be around 9 trillion dollar.[50] IMF has projected that GDP of China will be around 1.2% in 2020 and will grow to 9.2% in 2021. India is expected to grow in 2020 and 2021 at GDP of 1.9% and 7.4% respectively. The UN 'Economic and Social Commission for Asia and the pacific (ESCAP) 2020 said that COVID-19 having a great impact over economic, tourism, aviation sector and financial linkages. According to the SBI Ecowrap report, the extension of the lockdown would result in economic loss of 6% of the nominal Gross Value Added (GVA). If we talk about the positive growth, the emerging Asia is projected to be the only region with positive growth rate expected in 2020.

9. Conclusion and future prospect

Person-to-person contact was minimized to control the spread of COVID-19 infection. Guideline was published by WHO for healthcare workers, medical staffs, public and researchers those who are handling COVID-19 samples. There are no specific drugs or effective vaccine for COVID-19, so we have to rely exclusively in prevention and control measures such as social distancing, wearing mask whenever go outside. Various research conducted *in vitro* against COVID-19, that shows drug remdesivir and chloroquine are highly effective in controlling the infection. At present, it is important to control infection and cut off the transmission route. S protein is considered as an important viral antigen for developing vaccine. We should promote research to develop vaccine and reduce mortality for the safety of human lives and also to maintain the economic growth rate of the world.

Conflicts of interest

The author has none to declare.

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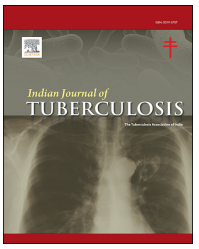

Review Article

Social determinants of multidrug-resistant tuberculosis: A scoping review and research gaps

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ABSTRACT

Tuberculosis is a prime example of a *social disease* that requires social, economic and environmental interventions. However, research on social determinants of Multidrug-Resistant (MDR-TB) is limited. The five-stage scoping review showed the most common association of MDR-TB with multidimensional poverty (income, nutrition, education and social support) both as a contributing factor and a consequence of it. The review also found that physical environment (inadequate housing, overcrowding, poor physical environment, and smoking), health care needs, cultural determinants (race, ethnicity and gender), comorbidities had a strong influence on the development and transmission of MDR-TB. Since, epidemiology and care for MDR-TB are greatly influenced by socioeconomic factors, social, environmental and economic actions are needed in addition to the implementation of novel diagnostic techniques and treatments.

1. Introduction

Multidrug-resistant tuberculosis (MDR-TB) is TB infection that is resistant to both rifampicin and isoniazid, the two most commonly prescribed anti-TB drugs available. Globally, in 2017, an estimated 558,000 (range, 483,000–639,000) developed TB that is resistant to rifampicin (RR-TB); 82% of these cases had MDR-TB.[1] 2017 WHO surveillance data reveal that globally, 3.5% of new and 18% of previously treated TB cases have MDR/RR-TB.[1] Low- and middle-income countries (LMICs), where the world's most vulnerable and impoverished people live, have the highest burden of the disease.[2,3]

1.1. Social determinants of TB vs MDR-TB

Current national tuberculosis control programs (NTP) mainly focus on breaking the chain of transmission through early case detection and treatment using quality assured diagnostics and drugs, putting medical interventions at the core of the End TB strategy. However, despite global efforts, in 2017, only 28% of the incident cases of MDR-TB were notified and

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just one-fourth of the estimated cases received treatment.[1] The global NTPs endorsed by the WHO has decreased the overall mortality and morbidity attributable to the disease, but the impact of the strategy on decreasing the incidence has been minimal. To reduce high incidence rates of diseases, there is a need to address the social determinants of diseases. A key message from the WHO's Commission on Social Determinants of Health (CSDH) is that public health achievements will largely depend on actions outside the health care sector (CSDH, 2008).[4] The CSDH defines determinants of health as conditions that influence the social stratifications in society that give rise to an unequal distribution of the living conditions, psychosocial circumstances, and behavioral and biological risk factors of certain diseases.[4] Improved living conditions are often identified as a key component of TB control.[5]

There is growing evidence on the impact of the social determinants of health on TB. TB is a prime example of a ''social disease'' that requires social, economic and environmental interventions.[5] Strategies to improve the social determinants of health and increase social protection have been associated with decreased rates TB in high-income countries.[1] Yet, research on the impact of social determinants on MDR-TB is limited. Most studies address only one or a few determinants. A scoping review would serve the purpose of mapping the current literature on the topic in terms of the size, nature and characteristics of the research. This review aims to collate and synthesize evidence on the social determinants of MDR-TB and examine the relationship between the social determinants of MDR-TB for possible pathways of impact. This review also aims to identify research gaps.

The objectives of the study are

1) to synthesize the existing literature on the social determinants of MDR-TB and identify what is known.
2) to map the interrelations among the social determinants of MDR-TB.
3) to identify gaps in the existing literature on the social determinants of MDR-TB and identify what is not known.

2. Methods

This study applied Arskey and O'Malley's five-stage scoping review methodology, which includes developing the research questions, identifying the relevant studies, formulating exclusion and inclusion criteria, charting the data, and summarizing the results.[6] The review started with a research question: What does the existing literature say about the relationship between the social determinants of health and multidrug-resistant TB? The search terms were comprised of a combination of 'social determinants' or 'determinants of health' or 'socioeconomic conditions', terms often used to refer to social determinants of health, AND 'multidrug resistant tuberculosis' or 'multi drug resistant tuberculosis' or 'multidrug resistant TB' or 'multi drug resistant TB' or 'MDR-TB' or 'MDR TB'. We searched SCOPUS, MEDLINE, and CINAHL as the primary databases to retrieve citations of peer-reviewed literature, covering research topics from all scientific disciplines, including medicine and the social sciences.[7] We used different search criteria (see Table 1) to search for research articles. The search strategy was based on title/keyword search. The keywords used in the search strategy were obtained from the WHO documents on MDR-TB and determinants of health for TB as well as CDC and PHAC documents on the determinants of health or social determinants of TB. In the search strategy, the quotation marks in the keywords were used to limit the search to the exact phrase mentioned, while the asterisks were used to retrieve other possible related keywords. We started the search for the documents with the keywords 'multidrug resistant tuberculosis' or 'multi drug resistant tuberculosis' or 'multidrug resistant TB' or 'multi drug resistant TB' or 'MDR-TB' or 'MDR TB' and obtained 15,684 documents. We added 'social determinants' with the unifier 'AND' to the previous search term and got 615 documents. Subsequently, we included all 18 determinants of health ('socioeconomic*', 'poverty', 'income', 'overcrowding', 'housing', 'nutrition', 'smoking', 'healthcare access', 'cost', 'education', 'stigma', 'gender', 'race', 'ethnicity', 'social support', 'physical environment', 'health services', 'comorbidity) to the previous search term and retrieved 162 documents.

The review of those literature increased our familiarity with the concept and helped us define the term 'social determinants of MDR-TB' and formulate the exclusion and inclusion criteria (Table 2). We limited the search term for language (only English) and study period (1998–2018) and obtained 158 documents. 1998 was used as the first year because the World Health Organization (WHO), Centre for Disease Control (CDC) USA and other partners for the first time conceived a strategy for MDR-TB diagnosis and management. This study period was set to capture the maximum number of documents on the topic. The online search was performed on August 29, 2018. References of the included articles were appropriately scanned to identify the additional literature that were included in the review articles and were of our topics of interest.

Out of the total 158 articles, 14 were excluded based on titles screening, and 109 were excluded following abstract review because the subject matters of the documents were not directly related to our topic. A total of 35 articles underwent full screening. No additional articles were identified by hand searching references of included articles. Finally, 15 documents (original research and review articles) were selected for review (Fig. 1). Two reasons dropped the number to 15: we excluded all the articles with a primary focus on any other types of TB, except for MDR-TB; we included articles with primary focus on social determinants of health as a broader concept rather than individual determinants. That is why this list is not exhaustive. Document citations were transferred to Refworks for further analysis.

A data extraction tool was developed in Excel. We applied a qualitative approach of open coding and inductive reasoning to obtain themes from the research articles and to formulate categories for sorting the necessary information. The extracted datasheet contained general information on the articles including the title, authors' names, year and country of publication, keywords, methodology, list of social determinants mentioned and type of association among different social determinants and MDR-TB.

Table 1 – Research strategy and keywords used to retrieve documents.

Search method	Keywords used	Constrains
Title search	*multidrug* AND *resistant* AND *tuberculosis* OR *multidrug* AND *resistant* AND *tb* OR *multi* AND *drug* AND *resistant* AND *tb* OR *mdr* AND *tb* OR *mdr-tb* OR *multi* AND *drug* AND *resistant* AND *tuberculosis* AND *social* AND *determinants* OR *determinants* AND *of* AND *health* OR *socioeconomic** OR *poverty* OR *income* OR *overcrowding* OR *housing* OR *nutrition* OR *smoking* OR *healthcare* AND *access* OR *cost* OR *education* OR *stigma* OR *gender* OR *race* OR *ethnicity* OR *social* AND *support* OR *physical* AND *environment* OR *health* AND *services* OR *comorbidity*	None
Title-abstract search	*multidrug* AND *resistant* AND *tuberculosis* OR *multidrug* AND *resistant* AND *tb* OR *multi* AND *drug* AND *resistant* AND *tb* OR *mdr* AND *tb* OR *mdr-tb* OR *multi* AND *drug* AND *resistant* AND *tuberculosis* AND social AND determinants OR determinants AND of AND health OR socioeconomic* OR poverty OR income OR *overcrowding* OR *housing* OR *nutrition* OR *smoking* OR *healthcare* AND *access* OR *cost* OR *education* OR *stigma* OR *gender* OR *race* OR *ethnicity* OR *social* AND *support* OR *physical* AND *environment* OR *health* AND *services* OR *comorbidity*	None
Limit	Language-English, Duration-1998-2018	

For a better understanding of the social determinants and to describe their relationships with the different stages of TB epidemiology, we have categorized the social determinants into the following: multidimensional poverty (inadequate income, poor nutrition, poor education, and lack of social support), physical environment (inadequate housing, overcrowding, poor physical environment, and smoking), health care services (inadequate healthcare access, inadequate health care services, health cost), comorbidity, and cultural determinants (gender, race, ethnicity, and stigma).

3. Results

A bibliographic summary of the included articles is reported in Table 3. Of the social determinants, health services were frequently mentioned in the documents (73%, n = 11), followed by comorbidity (e.g. HIV/AIDS, depression, diabetes) (60%, n = 9). All the articles included in the review indicated some kind of association between many different social determinants and MDR-TB. Based on their impact, we have grouped the determinants into multidimensional poverty, physical environment, health care services, comorbidity, and cultural determinants. The pathway of association was at different phases: development and transmission of MDR-TB, healthcare-seeking behavior of the affected population, diagnosis and treatment initiation, and treatment completion and outcome. (Fig. 2).

Table 2 – Inclusion and exclusion criteria for literature review.

Inclusion criteria	Exclusion criteria
- Articles published from 1998 to 2018	- Articles published before 1998 to 2018
- Articles that address MDR-TB and social determinants of health	- Articles that do not address MDR-TB and one or more determinants of health
- Articles published in English language	- Articles published in other than English language
- Articles with their full texts could be obtained	- Articles with their full texts could not be obtained

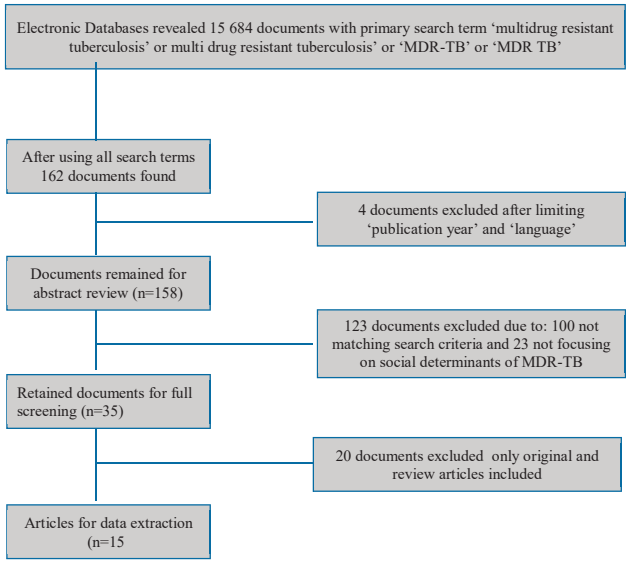

Fig. 1 – Flow diagram of the Scopus review.

Table 3 – General Information of the studies.

Variables	Results
Publication year (top three)	
2018	2
2017	3
2015	2
Document Type	
Empirical Research	11
Review	4
Source of article (top three)	
Intl. Journal of Tuberculosis and Lung Disease	2
Tuberculosis	2
Clinical Infectious Disease	2
Country (top three)	
United States	5
United Kingdom	4
Spain	3

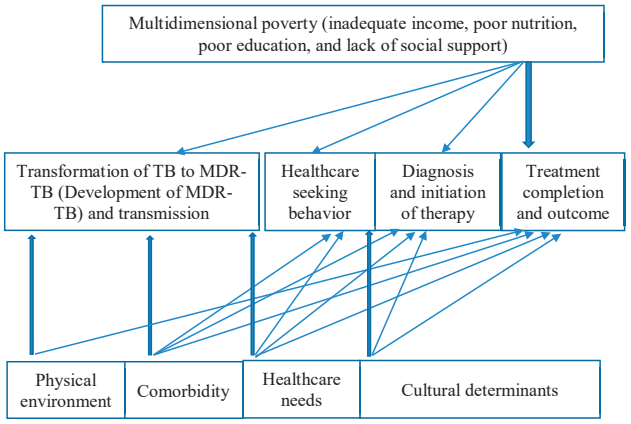

Fig. 2 – Dynamic relationship between social determinants and MDR-TB Epidemiology. N B: Thick lines means evidence from the most number (more than three) articles and thin lines means evidence from the least number (one to three articles).

3.1. *Multidimensional poverty*

The WHO's 'End TB Strategy' states that no TB-affected families should face catastrophic hardship due to tuberculosis.[8] Therefore, the removal of financial hardships to facilitate access to quality diagnostics and treatment to avoid catastrophic expenditures is essential. Also, the 'Sustainable Development Goals' (SDGs) share a conceptual vision with the WHO's End TB Strategy in that both are linked with determinants of human health. The End TB Strategy aims to reduce tuberculosis incidence by 90%, deaths by 95%, and catastrophic expenditures by 100% by 2035. Thus, TB elimination will require progress on SDG 1 sub-targets towards the reduction of poverty and expansion of social protection coverage.[9]

The most common association of MDR-TB was with multidimensional poverty (income, nutrition, education and social support) both as a contributing factor and a consequence of it. The association of multidimensional poverty was most frequently mentioned with treatment completion, followed by the development and transmission of MDR-TB, and healthcare-seeking behavior of the affected population.[10–21] MDR-TB is associated with a loss of daily income and increased out-of-pocket health costs, as the treatment regimens for MDR-TB are usually longer than those of drug-sensitive TB.[1,15,17] Studies have shown that MDR-TB can cause catastrophic direct and indirect economic costs, which in turn hampered patients' ability to access continued healthcare and complete treatment.[10–15,17,18,21] Poor adherence to treatment due to economic constraints and the high cost of second-line anti-TB drugs affects all phases of both acquired and primary MDR-TB.[10,14,15,17,18] The cost of MDR-TB treatment put an extra burden on the families of the affected people, as more than half of the yearly income could be spent on TB management.[12,13,16,22]

Studies demonstrated a strong negative association between adverse outcomes of TB such as drug resistance and the Gross Domestic Product (GDP). Most laboratory tests for MDR-TB are costly, making early detection of MDR-TB difficult in countries with limited resources.[21]The treatment regimen for second-line drugs is several times more costly than that of drug-sensitive TB. The national tuberculosis control programs of low-income countries struggle to provide proper care for all identified MDR-TB cases. Poorly resourced national TB programs concomitant with household poverty force patients to seek cheap, inappropriate treatment from untrained medicine practitioners (quacks), medicine retailers, and other private health care providers.[12]

Many primary and previously treated MDR-TB cases had been attributable to undernourishment.[10,14,15,17,18] Poverty leads to a lack of access to sufficient, affordable, nutritious food and eventually malnutrition, which was also found to be associated with increased susceptibility to drug-resistant bacteria as a result of lowering the body's immunity level[10,22] and also poor treatment outcomes.[17]

Weak or absent social support was found to be a barrier to access to TB care, poor health-seeking behavior, poor adherence and incomplete treatment.[10,14,15,17,18]

Multiple papers suggested that the elimination of extreme poverty and the provision of social protection could significantly reduce the incidence of MDR-TB.[2,23] Vocational training, providing nutrients, and cash transfer were identified as significant components of integrated poverty-reduction interventions.[7,12,13,22] Studies suggested that TB patients in low-and middle-income countries receiving financial support during treatment were more likely to have better clinical outcomes and decreased drug resistance than their peers.[7,12]

3.2. *Physical environment*

The review found that physical environment (inadequate housing, overcrowding, poor physical environment, and smoking) had a strong influence on the development and transmission of MDR-TB and poor treatment outcomes.[10,24] Overcrowding was commonly cited as a crucial risk factor for MDR-TB transmission, as it facilitates close contact and easy transmission in communities with high TB

prevalence.[10,24] Exposure to smoke in a poorly ventilated houses can increase the risk of the transmission of drug-resistant bacteria.[17] A notable point often raised in the literature was that confined spaces and inappropriate penitentiary system practices may lead to poor living conditions, which in turn increases the risk of the acquisition of MDR-TB and its transmission among prisoners.[13,14,19,20,25]

3.3. *Healthcare needs and TB epidemiology*

Evidence showed that healthcare substantially affected all aspects of MDR-TB including the development of drug resistance, the diagnosis of MDR-TB, treatment initiation, treatment completion and outcomes.[7,12–20,22,24,25] Insufficient infection control measures led to an estimated 3.1% of all new MDR-TB cases in 2007.[17] Poor case detection and improper patient management were identified as critical reasons for the high number of MDR-TB cases.[16,17] An ineffective surveillance system was reported as a reason for the failure to identify existing MDR-TB cases, which could increase the transmission of the resistant bacteria to others. Resource-constrained countries with limited laboratory and diagnostic capacity had an increase in MDR-TB cases.[12–14,17] Studies mentioned that a lack of universal health coverage and insufficient health financing were critical causes of the development of drug resistance. Most of the high MDR-TB burden countries have limited financial, technical and human resources for the implementation of the standard MDR-TB management protocol, which leads to inadequate health care access and improper treatment. As the patients have to carry a substantial financial burden, a lack of complementary economic support in the TB care program results in poor health care-seeking behavior and incomplete treatment.[16,17] A significant proportion of the TB cases occurred in countries with a private healthcare system that is not properly integrated into the national TB control program nor effective in the diagnosis and treatment of MDR-TB.[16,17,22]

Migrants have a substantially high rate of MDR-TB. The inability of the health system to cope with mass immigration during complex emergency situations leads to poor access to healthcare services and poor living conditions. Refugees mostly come from countries with a high prevalence of MDR-TB and contribute to the MDR-TB burden of low incidence countries.[18,19,24] Currently, in most resource-limited countries, not all susceptible people are under surveillance, and drug-susceptibility testing (DST) is not done in most cases. Most of the time, DST is only done in retreatment cases. This practice leads to a large number of primary and secondary MDR-TB cases going undetected.[12,13,16,22]

3.4. *Cultural determinants and TB epidemiology*

Cultural determinants based on race, ethnicity and gender are found to have an influence on TB incidence, the healthcare-seeking behavior of the affected population, health services, and treatment completion and outcomes. A fear of being discriminated against combined with stigma due to MDR-TB can impact the healthcare-seeking behavior and cause delays in diagnosis. MDR-TB patients experience extreme social isolation.[26] Stigma might lead a patient to hide their symptoms, delay or even avoid seeking care, hide their diagnosis and avoid treatment. This stigmatization has been mentioned as a cause of high rates of suicide attempts in certain groups of people.[12] The stigma was worse in the presence of comorbidities such as HIV/AIDS.[12] Studies have also mentioned that the stigmatization of MDR-TB among health care workers prevents them from availing of protective measures and results in transmission of the resistant bacteria to vulnerable populations.[12] Gender-based vulnerabilities of female patients such as financial dependency and limited mobility may discourage them from seeking care for TB, which eventually may lead to the development of MDR-TB.

3.5. *Co-morbidities*

Comorbidities including HIV/AIDS, diabetes and depression were also suggested as a strong risk factor for MDR-TB development, inadequate treatment completion and poor outcomes.[7,11,12,16,17,25] People with having HIV/AIDS were identified to be more than 30 times at risk of developing MDR-TB than others. TB was mentioned as the most common primary illness and a major cause of death of people with HIV/AIDS and being drug-resistant increases the risk several-fold.[17,20,25] HIV coinfection was identified as increasing the development and progression of MDR-TB, as the immunocompromised state increases the bacterial load and enhances the evolution of drug-resistance.[17] Reliable diagnoses of drug-sensitive TB in HIV-affected populations are difficult through conventional diagnostics, so the failure of countries with a high burden of HIV to utilize more healthcare resources contributes to the development of MDR-TB.[17]

Diabetes was recognized as an important risk factor for poor adherence and treatment failure for TB cases leading to the development of MDR-TB. Evidence showed that TB cases with diabetes as a comorbidity had an almost four times greater risk of MDR-TB compared to their peers without diabetes.[11,22] Diabetes was also found to delay smear conversion during the treatment process, which affected the DST results and might increase the risk of transmission.[11] Diabetes was also linked to adverse treatment outcomes of TB due to hyperglycemia, which led to poor adherence to treatment and the development of MDR-TB.[11]

Studies showed that a substantial proportion of MDR-TB patients had some forms of depression.[10] Conversely, depression was mentioned as an important factor regarding the treatment completion of MDR-TB, as it affected patient adherence.[10] It was stated that MDR-TB increased the risk of depression, as the treatment duration was prolonged, and there was a higher possibility of adverse drug reactions.[10] Moreover, depression was found to negatively affect HIV-infected patients, which was mentioned as an important risk factor for MDR-TB development.[1,10]

4. Discussion

The idea that social determinants influence health and disease is nothing new. Identifying the determinants of specific diseases and pathways of impact can be useful for designing interventions. This review highlights that issues related

health care services such as inadequate and inappropriate health care and increased out-of-pocket health care costs have more explicit pathways of influence on the incidence of MDR-TB, treatment completion, and the outcomes of the disease compared with other social determinants. Physical environment such as housing and overcrowding and cultural determinants such as gender, race, ethnicity and stigma are shown to impact TB infection and transmission and healthcare-seeking behavior. Multidimensional poverty has associations with all aspects of the disease without any explicit and direct mechanism of action.

To our knowledge, this is the first scoping review to collate and synthesize relevant existing literature on determinants of health/socioeconomic determinants and MDR-TB. The determinants were grouped based on their area of impact on MDR-TB.

The TB strategies based on Directly Observed Treatment, Short-Course (DOTs) are medical interventions that despite having a significant impact on preventing mortality due to TB have not been effective in reducing global incidence and prevalence. In fact, inappropriate medical interventions have contributed to the increased incidence of MDR-TB. Comprehensive TB strategies need to address determinants of MDR-TB transmission, diagnosis and treatment beyond health services and include interventions to improve physical environment, address cultural determinants, and alleviate multidimensional poverty.

4.1. *Research gaps*

The review has identified a number of gaps in knowledge.

1. The complex process that links multiple determinants to many different aspects of MDR-TB can be better understood through network analyses that identify central actors and relationships. Previous studies have isolated determinants and aspects of MDR-TB, providing a snapshot for a better understanding of the complexity.
2. Many studies suggest broader socioeconomic interventions, yet there is little empirical knowledge on the effectiveness of actions to address the social determinants of MDR-TB and identify best practices. Case studies of locally adapted and culturally accepted interventions that meet the needs of at-risk and underserved populations can be a good start. Some national TB programs (NTPs) that have adopted the provision of economic support to cover the cost of treatment, travel and time off work due to treatment could make suitable natural experiments.
3. Some patients preferred consistent psychosocial support rather than targeted economic interventions.[1] Unlike economic support, psychosocial support does not have any global indicator and thus could easily be overlooked. Comparative studies of psychosocial interventions versus economic support also represent a knowledge gap.

5. Conclusions

It is evident from the scoping review that MDR-TB epidemiology and care are greatly influenced by socioeconomic factors, so a biosocial approach including social, environmental and economic actions are needed in addition to the implementation of new and improved diagnostic techniques and treatments to provide a sustainable solution to the TB epidemic. The biosocial approach will not only target the morbidity and mortality of TB but also would contribute substantially to address the social inequality to help susceptible populations achieve better health. This will require a multi-sectoral approach involving governmental sectors, health organizations and civil society.

Author contribution

MN supervised research project and conceptualized and edited the manuscript, **AR** reviewed online sources, analyzed data and wrote initial draft of the manuscript, **QT** edited the manuscript, **AS** co-supervised the research, conceptualized and edited manuscript, and coordinated the team.

Conflicts of interest

The authors have none to declare.

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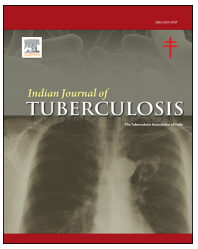

Review Article

Pretomanid: A novel therapeutic paradigm for treatment of drug resistant tuberculosis

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ABSTRACT

Tuberculosis is currently an anticipated driver of pandemic diseases. It remains an imminent issue accounting for about 1.4 million deaths annually across the world. Since the evolution of human entity drug susceptible tuberculosis was managed through potent first line therapies. Unfortunately, the emergence of newer multitude strains refractory amongst available drugs in Drug resistant TB has led to an emergence MDR-TB and XDR-TB. Moreover, the increasing incidence of drug susceptible TB in developing countries paved way to development of new guidelines for treating various form of tuberculosis. Furthermore, newer regimens are warranted to combat resistance that preferably cause a reduction in mortality. Until now, various ongoing trials are being carried in order to potentially evaluate the suitable novel drug candidates, repurposed drugs and host directed therapies that will optimistically be safe, easy to tolerate, cost effective and non-toxic that will modify the prospects for treating drug resistant TB and latent TB. In context, the current scenario seems to impose a significant challenge on health care researchers in the field of drug discovery owing to complexities, prolong treatment duration, and is cumbersome. Pretomanid is a novel drug with potent bactericidal properties emerging a key advancement used in combination along with other drug therapies This review details the role of pretomanid in treating tuberculosis and the clinical trials in adultsd.

1. Tuberculosis: An ongoing context

Tuberculosis is a persisting pandemic disease that has been prevalent since evolution of human existence, wherein primarily caused by mycobacterium tuberculosis a complex bacterial pathogen, ultimately accounting for millions of deaths every year.[1–3] However, it still erodes to impose a significant threat worldwide as it outpaces Human immune deficiency virus (HIV). As stated by World health organization (WHO) report, In 2018 around 10 million adults appear to be

Abbreviations: WHO, world health organization; TB, multi-drug resistant tuberculosis; XDR, TB-extensive drug resistant tuberculosis; FDA, food drug, and Administration; GATB, Global Alliance for tuberculosis drug development.

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infected with tuberculosis globally, wherein incidence is 132/100,000 mankind concurrently causing 1.2 million deaths, 251,000 deaths in those with tuberculosis associated with HIV negative, HIV Positive subjects.[4,5] Geographically, it is widespread across the world in both economically developed and underdeveloped nations, wherein Drug-resistant tuberculosis has appeared to be prevailing in countries such as China, India, Africa, and Europe.[6] Over the decades, current standard first line agents used for the treatment of tuberculosis were Isoniazid, Rifampicin, Ethambutol, Stretomycin.[7,8] Further no significant resistance to these agents is classified as drug susceptible tuberculosis.[9] Morever, In the recent years another alarming issue is the advent of unprecedented resistance strains, probably caused due to genetic mutations. Furthermore based on emergence of resistance it is further classified as multi drug resistant and extensive drug resistant tuberculosis[10] wherein multidrug resistant tuberculosis is a condition that emerges as a threatful challenge notably caused due to attributable resistance to isoniazid and rifampicin, along with concomitant HIV infection, whereas extensive drug resistant tuberculosis measurably lead to resistance to fluoroquinolones and other second line injectable agents.[11–16] Even though since 2008 studies suggest a steady declinement in mortality rates, the expected favourable outcome is only 54% therein imposing a significant burden on clinicians and researchers.[6,17]

Treatment of multi drug resistant tuberculosis is a complex task due to various attributes such as prolonged duration, high costs of drugs administered, unfavourable adverse events and depleting health care system.[18,19]

Surprisingly, other than unintentional compliance, the foremost contributing pathways that are significantly involved in development of Multi drug resistant tuberculosis are primary and acquired resistance [20,21] Nonetheless, Drug resistant tuberculosis needs to be addressed rapidly, as it is critically associated with increased mortality thereby amplifying antimicrobial resistance across the world.[22] Owing to its complexity of increase infinitude strains, notoriously leading to patient adversity, therefore newer research on anti -TB drugs is an essential requisite. Henceforth, in order to reduce mortality, newer potent anti -TB regimens are required which are not toxic, cost effective tolerable, effective and are of shorter duration.

Until now, diverse clinical trials are presently underway in order to paramount several antimicrobial drug candidates that conclusively arbitrate the possibility of counteracting TB.[23,24] Despite introduction of newer shorter regimens such as bedaquiline, delamanid, clofazimine as armaments against TB, yet emergence of resistance to bedaquiline in various trials is a major issue of concern[25]

2. Overview of current TB drugs in pipeline

Currently, standard first line therapies claimed to be effective in bacillary clearance used exclusively for a period of 6–9 months, it is sustained to marginal lapses in compliance.[5,26] In the core of this widespread epidemic, the End TB Strategy promptly elucidated that the world would be freed of tuberculosis probably by 2035.[27,28] However, the treatment of MDR tuberculosis is thought to be complex, typically due to vigorous prolong duration ranging from 18 months extending upto 2 years. Further obscuring this outcome is concomitant HIV infections. Particularly various second line drugs such as aminoglycosides, fluoroquinolones, thioamides have been used for treatment of MDR-TB similarly for management of XDR -TB, there has been no therapeutic standard of care[7,29,30] Hence to combat MDR and XDR tuberculosis, preferably there is an urgent need of novel promising regimens with attributable properties of unique mode of action to lower resistance, minimal treatment duration through enhanced bactericidal activity, cost effective with fewer adverse events, also potentially effective in HIV patients without concomitant interactions and having a reliable safety criteria to be used in pregnant women and children.

In recent times, newer potential drug candidates were underway in various phase of clinical trials that demonstrates the efficacy of different new and repurposed drugs used alone or as cocktail likely intended for the treatment of MDR-TB and XDR-TB.[31,32] However, repurposed drugs use was limited due to high cost, increased antimicrobial resistance, reduced bactericidal activity and toxicity profile.[33] After a long span of time, nearly after 40 years, clinical trials led to development of two novel molecular entities such as Bedaquiline and delamanid latterly authorized by the United Stated Food and Drug Administration (FDA) in 2013 and the European Medicines Agency (EMA) specifically, suggested to be incorporated with combination regimens when other relevant therapies are not suitable.[34,35]

3. Pretomanid: A new therapeutic approach

Pretomanid (PA-824) is a nitroimidazole prodrug, bicyclic in nature originated by optimization of a nitroimidazofuran radiosensitizer apparently proposed by Stover et al notably manifested to especially treat MDR tuberculosis[36–38] In view of clinical perspective, pretomanid was first determined in animal models and eventually progressed to clinical trial development by GATB.[39] Various nitroimidazoles subgroups were inevitably imperative against Mycobacterium Tuberculosis. It has been demonstrated to exhibit robust antimycobacterial activity by disrupting and inhibiting the mycolic acid synthesis and simultaneously effective in killing bacilli in both replicating and hypoxi-static cultures by releasing toxic nitrogen species that damages intracellular proteins and cell wall lipids.[40–42] However, studies proposed that pretomanid notably acts on mycolic acid biosynthetic pathway resulting in depletion of ketomycolates and aggregation of hydroxymycolates.[36,43]

Various trials are performed using numerous combinations of bedaquiline (B), clofazimine (C), moxifloxacin (M), linezolid (L), and pyrazinamide (AAC-0090719). Recently, the Global Alliance for TB Drug Development following license by Novartis has established pretomanid as a newer therapeutic agent for treatment of TB. Successfully, On 14 August 2019, the US FDA authorized pretomanid under the Limited Population Pathway for Antibacterial and Antifungal Drugs (LPAD) pathway incorporated with BpaL regimen for the management of adults with pulmonary XDR TB.[44–46]

4. Clinical pharmacology

Pretomanid is nitroimidazooxazine antimycobacterial agent. It has the ability to act against both reproducing and non-reproducing forms of tuberculosis. Among the replicating bacteria pretomanid works by inhibiting the production of mycolic acid thereby stopping the cell wall synthesis. While in case of non-replicating bacteria pretomanid acts by producing reactive nitric oxide. However, to exhibit all these activities pretomanid gets reduced by enzyme deazaflavin-dependent nitro reductase, Ddn. This F_{420} dependent glucose-6-phosphate dehydrogenase causes reduction of co factor F_{420} which is essential for Ddn to cause nitro reduction of pretomanid in mycobacterial cell wall. The MIC of pretomanid is 0.005–0.48 mcg/ml.[41,43,47] The chemical structure of pretomanid is given in Fig. 1.

Absorption of pretomanid shows a relative dose relationship within applicable dosage ranging between 50 and 200 mg, achieving the desired serum drug levels within a period of 4–6 days. The $t_{1/2}$ of pretomanid is 16–20 hours and T_{max} is 4–5 hours. The plasma protein binding of pretomanid is 86.4%. Additionally, CYP3A4 (20%) displayed minor effect in metabolism and is mainly excreted through urine and faeces.[47–49] However, other factors such as age, hepatic impairment have no significant influence on pharmacokinetics (see Table 1).

5. Therapeutic efficacy in clinical trials

After 40 years of negligence, several studies have reported pragmatic results thereby demonstrating the effectiveness of pretomanid in cocktail with other regimens as a prominent scalable approach for treating multi drug resistant and extensive drug resistant tuberculosis. .Moreover, various evidence underpins the use of pretomanid.

In an Phase 2b randomised trial (NC-005) conducted in south Africa for 8 weeks in those patients who were smear positive in Drug susceptible and Multi Drug Resistant tuberculosis wherein subjected to combinations of bedaquiline (200 mg) and pretomanid (200 mg), moxifloxacin (400 mg) and pyrazinamide (1500 mg) (BPaMZ) in one cohort, comparatively standard first line therapy in another cohort. Interestingly, the results manifested that pretomanid containing regimen exhibited a significant higher bactericidal activity (5.302; 95% Bayesian credibility interval (BCI) 4.518–6.157) in comparison with standard treatment regimen, (4.016 (95% BCI) 3.52–4.499) invariably assessed by change in sputum culture positivity.[50]

Similarly, another phase 2b study was conducted in 207 patients for 8 weeks, wherein demonstrated the efficiency of pretomanid administered at a dosage of 100 mg along with other combination regimens, thereforth the results displayed that upon addition of pretomanid it resulted in higher bactericidal activity (0·155, 95% Bayesian credibility interval 0·133–0·178) in contrast with other standard regimen (0·112, 0·093–0·131). Henceforth, pretomanid use might shorten treatment duration hence is underway to be carried out in phase trials.[51]

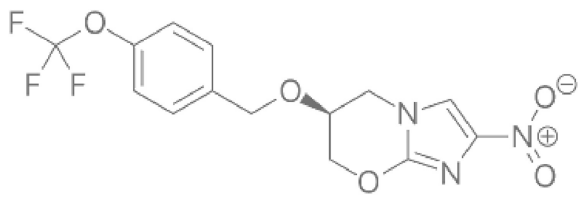

Fig. 1 – The chemical structure of pretomanid.

In 2015 a phase 3 randomised trial named as STAND trial was recruited, unfortunately due to evidence fatal hepatitis it couldn't be carried out further.[52]

In turn, a phase 3 trial commonly known Nix TB was conducted exclusively in Multi drug and extensive drug resistant tuberculosis exclusively for a treatment duration of 6 months which recruited 109 patients, wherein constitutes a BpaL regimen containing pretomanid 200 mg, bedaquiline 400 mg for the initial 2 week interval followed by 200 mg three times/week and linezolid 1200 mg/day. Microbiologic assessment of sputum cultures were regulated at baseline and week 1,2,4,6,8 followed by every month until results obtained till 26 weeks. Moreover, main goal was to determine the incidence of bacteriological failure, preferably any relapse during follow up mostly after completion of treatment, further, those who were sputum positive, surplus 3 months treatment was given. Surprisingly, after end of treatment 66 patients (89%) benefitted from the therapy, 11 patients experienced unfavourable outcomes. Henceforth, high cure rates, negative TB culture were obtained demonstrating the efficacy of pretomanid. Hence pretomanid can be used as a part of combination regimen for the treatment of Multi-Drug Resistant tuberculosis.[46] However, further clinical trials are underway to ascertain this conclusion.

Ongoing trials:Various ground-breaking phase 3 trials are being conducted in adults with Multi Drug Resistant tuberculosis to evaluate and assess the safety and efficacy of newer optimal regimens, therein such trials include the TB-PRACTECAL,Simplici-TB, (ZeNiX) etc.

6. Therapeutic use of pretomanid in patient care

Pretomanid is a novel drug candidate significantly used along with combination therapies in treatment of those with multidrug resistant (MDR), extensively drug resistant (XDR), and treatment intolerant TB of adults. However, its use is limited in those forms of tuberculosis who are not tolerant or non-responsive as in case of MDR-TB, Drug -sensitive TB, lastly in subjects with Latent or Extra-pulmonary infection.[45,47]

7. Adverse event profile

Despite having a unique entity with accountable properties, pretomanid is still characterized by unprecedented adverse events. Uncertainly with cocktail regimens some of the reported events in Nix-TB trial were peripheral neuropathy, acne, rash, pruritus, anaemia, headache, gastrointestinal symptoms, dyspepsia, abdominal pain, pleuritic pain,

Table 1 – Various clinical trials with pretomanid included in combination regimens.

Trial Identifier Sponsor, Type of study	Intervention	Study duration	Key notes	Results, conclusion/ Primary Objective
NiX-TB (NCT02193776), Sponsor: GATB Phase-3[46]	Bdq, Pa, Lzd (6 months) +option of 9 months for those still culture positive at 6 months.	Recruitment of Subjects: 2015 Full results: Feb 2019	Includes children ≥14 yrs, wherein has an adaptive design to incorporate new treatment if they become available during the study period.	**Results:** Interestingly, In the ITT analysis.98% of patients had a positive favourable outcome at the end of 6 months. However, significant adverse events associated with linezolid. **Conclusion:** Henceforth, with adequate safety management, BpaL regimen is a best suitable alternative for highly resistant type of TB.
NC-0005 (NCT02193776), Sponsor: GATB Phase 2b[55]	(1). 180 patients with drug-susceptible Tuberculosis assigned any of the following $B_{(load)}$PaZ. $B_{(200)}$PaZ; HRZE (2). 60 patients with rifampicin-resistant Tuberculosis: assigned to BpaMZ.	Recruitment of patients: 2014 Results: 2019	Those aged ≥18 with sputum smear grade greater than 1, (GeneXpert or MTBDRplus) was used to confirm and differentiate the diagnosis of tuberculosis.	**Results:** $B_{(200)}$PaZ produced the highest daily percentage change in TTP (5·17%), followed by $B_{(load)}$PaZ (4·87%) and HRZE group (4·04%). However more no of patients in the B_{load}PaZ and B_{200}PaZ groups discontinued the study drug than in the HRZE group because of adverse events. **Conclusion:** B_{200}PaZ + pretomanid is an efficacious promising therapy in the management of drug susceptible TB.
ZeNiX (NCT03086486) Sponsor: GATB Phase 3[54]	1.1200 mg Lzd, Pa, Bdq (26 weeks) 2.1200_0mg Lzd (9 weeks) +Pa & Bdq for 26 weeks 3.600 mg Lzd, Pa & Bdq for 26 weeks.	Recruitment of patients: 2018 Results expected: 2022	Those aged ≥14 years. Further, if sample shows culture positive at 16 weeks treatment may be increased to 39 weeks.	**Primary objective:** A continuation trial of NiX-TB to determine various characteristics such as effectiveness, safety of linezolid along with 6-month regimens that also constitutes bedaquiline and pretomanid.
TB-PRACTECAL (NCT02589782) *Sponsor: MSF* Phase 2–3[53]	1. Bdq, Pa, Mfz, Lzd (6 months) 2. Bdq, Pa, Lzd, Cfz (6 months) 3. Bdq, Pa, Lzd (6 months)	Enrollment of subjects; 2017 Results expected: 2021	Includes adults ≥18 yrs All oral investigation arms.	**Primary objective:** To examine the safeness and effectiveness of three 24-week regimens besides moxifloxacin or clofazimine, in association with standard care of WHO.

(*continued on next page*)

Table 1 – (continued)

Trial Identifier Sponsor, Type of study	Intervention	Study duration	Key notes	Results, conclusion/ Primary Objective
SimpliciTB (NC-008) (NCT03338621) Sponsor: GATB Phase- 3[53]	Bdq, Pa, Mfz, Pza (6mths)	Recruitment of subjects: 2018 Results expected: 2022	Those adults ≥18 yrs Includes an oral only study arm.	**Primary objective:** (1) In Drug-susceptible and Rifampin resistant TB main goal is to assess the effectiveness, robustness and endurability of a 4-month 4-drug therapy versus standard 6-month therapy for comparison.
STAND (NCT0234886) Sponsor: GATB Phase 3[56]	DS-TB: Mfz + pretomanid (100/ 200 mg) + Pza for 4/6 months. MDR-TB: Mfz + PA-824 (200 mg) + Pza for 6 months	Enrollment of Subjects: 2015 Results: 2019	Includes < 18 yrs, all oral study arms.	**Results:** Pretomanid exhibited promising results in the DS-TB, unfortunately, reported hepatotoxicity and 3 deaths, therefore was put on hold wherein recruitment was ceased by FDA.

Listing of studies constituting pretomanid in the treatment regimen. GATB-Global alliance for TB development; DS-TB-Drug susceptible TB; MDR-TB-Multidrug resistant TB; Bdq-Bedaquiline; Pa-Pretomanid; Mfz-Moxifloxacin; Lzd-Linezolid; Cfz-Clofazimine; TTP-Time to sputum culture positivity; MSF-medicine sans frontiers; WHO-World health organisation; HRZE-Isoniazid, rifamicin, pyrazinamide, ethambutol; BpaL-Bedaquiline,pretomanid, linezolid; BpaZ-Bedaquiline,pretomanid, pyrazinamide; BpaMz-Bedaquiline, pretomanid, moxifloxacin.

haemoptysis with or without cough, lower respiratory tract infection, increased gamma-glutamyl transferase increased transaminases, amylases, visual impairment, hypoglycaemia and abnormal loss of weight while QT prolongation has been observed when used in combination with bedaquiline, and linezolid. In Contrast, the unusual adverse events in the Nix-TB regimen is primarily due to high dose of linezolid, henceforth numerous efforts are being undertaken by ZeNiX trial to test lower dosage of linezolid in the regimen. However further trials are underway to rule out the cause.[44,46,47,57]

8. Resistance

In tuberculosis, drug resistance renders to be a deterrent cause thought to be intervened mainly due to chromosomal mutations which ultimately targets intrinsically or bacterial enzymes eventually leading to activation of prodrugs.[58] Moreover, drug resistance remains a persisting intimidating issue which needs to be addressed urgently. Most importantly, pretomanid has been associated with mutations in genes mainly ddn, fgd1, fbiA, fbiB, and fbiC, wherein caused either due to prodrug activation or inevitably linked with F420 biosynthetic pathway.[42,59] However, it has shown the presence invitro resistance ranging within 10-7 to 10-5 at 2 to 6 times of MICS. Strangely enough, not all genes isolate exhibit resistance. Most importantly, the data obtained from murine model presents almost similar activity in comparison with isoniazid and rifampicin.[60,61]

9. Future prospects

In view of clinical perspective, currently the universal standard regimen to combat drug

susceptible tuberculosis is generally comprised of four drug regimen namely Isoniazid, Rifampin, Pyrazinamide, Ethambutol which is constantly used for 2 months in an intensive phase pursued by extensive continuity phase as recommended by WHO guidelines. However, due to unprecedented resistance to Isoniazid, paradoxically new anti tb dugs are warranted. On the other Hand, numerous combination regimens are concurrently used for treatment of Drug Resistant tuberculosis. Not long ago, newer repurpose drugs and various shorter regimens have been identified and used along with standard drugs. However, use of repurposed dugs is ambiguous.

Until now, emergence of threat due to tuberculosis is a looming issue worldwide, it remains a bottleneck in the era of drug discovery. It is thought to be acceptable vague, where a tailored therapeutic approach is urgently needed to halt transmission of resistance strains to significantly reduce morbidity and mortality. Neverthless, to our knowledge the therapeutic rationale drugs are prerequisite that further prevent amplification of drug resistance which potentially improve patient outcomes, improves adherence, minimizes adverse events, shortens duration of treatment, economically cost effective, easily tolerable.

However, with the rapid advancement of clinical development process it led to introduction of newer promising drugs, newer advance diagnostic tools, newer emerging public health strategies, and is thought to be encouraging. Furthermore, the main goal of WHO is to eradicate tuberculosis by 2050, henceforth, paved way to newer therapeutic molecules with numerous ongoing trials.

Not long ago, pretomanid a novel chemical entity was recently approved by FDA in 2019, whereas conditionally, approved by European medicine agency (EMA),interestingly the preliminary results indicated its effectiveness in Multi Drug Resistant tuberculosis. In addition, it does not exhibit cross resistance with other anti -tb regimens hence it can be extensively used along with combination regimens to treat MDR-XDR tuberculosis. Furthermore, recently completed Nix TB trial constituting BpaL regimen, illustrates clinically significant results, though some adverse events were reported prolongation is minimum with pretomanid.

Additionally,ZeNix-trial is a new ongoing trial which is the descendant of Nix-TB trial is conducted in Multi Drug Resistant tuberculosis or Extensive drug Resistant tuberculosis patients in order to evaluate the effectiveness, acceptability, diverse dosage of BpaL regimen wherein numerous efforts are being undertaken to test lower dosage of linezolid in the regimen.

However further clinical trials are needed to ascertain its therapeutic efficacy, tolerability and safety data. Furthermore, various ongoing trials are being recruited to collectively present the evidence of safety data in the following years. Hopefully, in future if results are favourable pretomanid will be nurtured as a fallible hope against Drug Resistant tuberculosis.

10. Conclusion: Conferring a way forward

Although drug-resistant Tuberculosis threatens by its resisting characteristics, with changing landscape, anticipated advent of new molecules and expertise led to the development of promising agent like pretomanid that can be effectively used in the treatment against multidrug resistant, extensively drug resistant TB. Pretomanid has immense bacteriostatic activity against *Mycobacterium tuberculosis* and has an ability to reduce the duration of treatment and enhancing treatment outcomes. In future after careful evaluation of safety profile as well as other aspects such as antimicrobial stewardship, which are yet to be addressed pretomanid can be used in addition to DOT therapy and can be of great support in eradication of tuberculosis.

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Author's contributions

This work was carried out in collaboration among all authors. All authors contributed in data collection, data compilation and drafting of the paper. All authors read and approved the final manuscript.

Conflicts of interest

All authors have none to declare.

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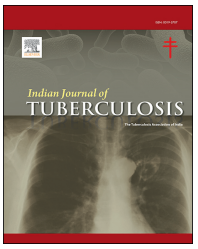

Review Article

Understanding the gaps in elimination of tuberculosis in India

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ABSTRACT

Tuberculosis (TB) is a highly infectious disease, and it has the highest global burden on India with 21% prevalence rate and 27% of patients who do not receive pertinent medical treatment. Although India spends 23 billion dollars annually towards medical expenses for TB, India still ranks among the top 2 countries with the highest incidence and prevalence rates with more than 300,000 deaths excluding the patients with HIV and TB calling for prompt consideration. India faces a great challenge socially and economically. They lack a uniform health care system, making it burdensome to use effective surveillance techniques for prevention of TB. Currently, India is working on resolving the issue meticulously through the web-based application program 'Nikshay' with other strategies like Revised National Tuberculosis Control Program (RNTCP) and World Health Organization's The End TB Strategy. India's cardinal goal is to make advanced diagnostic tools made available and public-private healthcare sector collaboration. India needs to focus more on primary prevention by effective policy formation and campaign which promote proper sanitation and vaccine administration while educating the layman.

1. Tuberculosis in India

Tuberculosis (TB) is a highly infectious bacterial disease caused by *Mycobacterium tuberculosis*, which was first isolated by Robert Koch in 1882.[13] The disease dates back to around 150 million years ago yet the incidence rate is 10.4 million cases annually.[2] In 2004, TB accounted for 2.5% of deaths worldwide with 95% of cases occurring in India and China.[6] India accounts for one fifth or 21% of the global burden of TB[10] and a total of 27% of the patients that do not receive appropriate medical attention and are active reservoirs of infection.[24] The current statistics show that India accounts for 24% of TB prevalence, 23% of incident cases, and 21% of TB related deaths globally.[21] India spends around 23 billion dollars on

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medical expenses for the treatment of TB yet has an incidence rate of approximately 2.2 million cases per year, more than 300,000 deaths excluding the patients with HIV and TB.[26] The high statistics illustrate that TB is not only submerging India in a chronic health crisis but also an economic crunch.[26] This paper focuses on why TB still persists as a major public health concern with the prevention strategies pursued in the past and present and the future goals embarked upon India.

2. Multi drug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis

Tuberculosis (TB) which has resistance towards drugs like isoniazid and rifampicin (first-line drugs) is defined as MDR-TB.[7] Pre–XDR is resistance against multiple TB drugs along with resistance to injectable second-line drugs and fluoroquinolone.[7] XDR-TB causes resistance to multiple drugs like fluoroquinolone and at least one of three injectable second-line drugs like capreomycin, kanamycin, and amikacin7,20. More emerging strains like totally drug-resistant (TDR) TB or extremely drug-resistant (XXDR) TB have resistance towards the first as well as the second line of drugs.[20] This is concerning considering TB is treated using only the first line and second line drugs, and resistance to viable treatment options makes it arduous to treat.

3. Increasing incidence

One of the main reasons why the incidence of Tuberculosis (TB) is increasing is because of the increased emergence of Multi-drug resistant (MDR) TB and Extensively drug-resistant (XDR) TB.[7] A study conducted by[14]; states that the incidence rates for MDR-TB were 30.8%. In 2015, about 480,000 cases for MDR-TB were reported worldwide with 79,000 cases reported in India, the Russian Federation, and South Africa which were resistant to drugs like isoniazid and rifampicin. In India, only 46% of patients with MDR-TB have been reported to achieve successful treatment with 20% lost to follow-up or death.[7] Another important factor that causes an increase in the incidence of MDR-TB and XDR-TB is incomplete treatment regimen, as the treatment for TB can last up to 6 months some patients quit the treatment making themselves more susceptible to the drug-resistant TB.[25] Also, TB with HIV co-infection increases the chances of contracting MDR or XDR.[3] Some other leading causes of drug-resistant TB are nosocomial exposure to MDR-TB or living in an area with a high prevalence.[25] Thus, the emergence of drug-resistant strains, co-infections and lack of motivation to complete the drug regimen are leading causes for the increased incidence.[7,25,3]

4. The role of antibiotics in drug-resistant tuberculosis

The first-line drugs like isoniazid and ethionamide work via directly affecting the Nicotinamide-Adenine Dinucleotide (NADH) oxidation by producing the highly toxic free radicals that contribute to the mutations in *M. tuberculosis* strains during the tricarboxylic acid cycle (TCA) which causes increased likelihood for MDR TB.[22] The newer *M. tuberculosis* strains are becoming more and more resistant towards antibiotics, and these bacteria can even advance via compensatory mutations which only enhances their virulence making it even more difficult to treat and thus contributing to the increasing incidence.[22]

5. Social determinants responsible for tuberculosis

The social determinants such as poverty, literacy rate, overcrowding, unsanitary surroundings, and malnutrition are among the top contributors for Tuberculosis (TB).[5,10,8] The impoverished sector of society is more likely to acquire TB, this sector receives a poor quality of health care and are prone to drug-resistant TB as they are least likely not to complete the treatment regimen.[4,10] The benighted sector of the society who contract a cough first seek care in the informal private sector, like the drug stores and unqualified practitioners, then from private medical practitioners, and later on end up in a government funded health care facility.[18] This entire pathway takes weeks to months, during which that patient is an active carrier for TB and a potential source of infection.[18] TB has a compelling correlation with social determinants, thus keeping in mind health equity while designing any framework for the provision of health care is crucial.[4] Thus, these social determinants play a key role in the formation of the preventive strategy for a community.

6. The role of private healthcare sector in India

In India, more than 80% of health care is provided by the private sector[18] and dispenses nearly twice the amount of anti-Tuberculosis (TB) drugs as compared to the public sector.[11] More than 50% of patients seek care from the private sector that lacks homogeneity in providing treatment and using diagnostic methods.[19] Special training can be administered for the pharmacist dispensing medications so that the prevalence of MDR-TB and XDR-TB can be reduced. Furthermore, they have incomplete notification systems and require direct payments from the patients.[19] Diagnosis in the private sector is identified by inaccurate testing by using blood tests and lack reliable quality-assured diagnostics tools.[18] Only 35% of patients receive standard compliant care for TB with the lack of adherence without any backup or follow up protocols and over-extended use of antibiotics.[11] Thus, this gap in the uniformity in the private sectors needs an immediate sermon through the implementation of effective policies required to improve the private healthcare sector for the management of TB.

7. Availability of information and role of social media

India has launched a TB website called Central Tuberculosis Division which launches the NIKSHAY dashboard providing information TB notification systems, treatment services, drugs, comorbidities, PIP and expenditure, and direct benefit transfer.[16] This interactive webpage has data on where India is currently on the statistics for TB and provides data for each year starting from 2017 which is even further divided as data reported by the public and private sector statewide. Furthermore, NIKSHAY also provides data for state and district TB officers and the location of the medical facility from where people can get assistance.[16] Social media can play a major role in educating the population, many other social media campaigns like 'Swachh Bharat Abhiyan' and Polio vaccination have been successful.[27] The tool of social media can be used to educate the population about MDR-TB and XDR-TB through WhatsApp chat groups. This can be a huge development in educating the population at mass with minimal expenditure. The progress made by India through NIKSHAY is commendable in providing information not just for medical professionals, public health officials but also for the general public.

8. Cost-effective diagnostic techniques used in India

In 1895, after the discovery of X-rays by Rontgen, the chest X-ray was the main Tuberculosis (TB) diagnostic tool.[13] It is still an effective and cheap diagnostic tool used for detection of Ghon's foci to apical cavitation observed in TB.[13] Another cheaper alternative is the tuberculin skin test (or tuberculin purified protein derivative (PPD) test or Mantoux's test) which injects the PPD intradermally in the skin of the forearm.[13] The only inconvenience demonstrated by the test is that the patient needs to revisit the clinic after a period of 24–72 hours, and since the test is positive for patients with previous exposure to TB or patients that have taken the BCG vaccine, this test is not always accurate.[15] The third inexpensive technique is sputum culture which is accurate, fast and widely used in developing countries like India.[17] This technique may not be as accurate as the more advanced and expensive techniques but is cost-effective and provides enough data for diagnosis of TB.

9. Prevention strategies across the globe

TB infection control in Cambodia is managed through effective policy formation- National Infection Control Policy of Cambodia, 2009.[30] In accordance with this policy, Cambodia has published many key documents which provide guidelines for the annual operational plans at provincial and district levels for TB infection control activities; e.g., National Infection Control Strategic Plan (2011–2015), National Infection Control Guidelines (2010), National Guidelines on Healthcare Waste Management (2011) and TB Infection Control Standard Operating Procedures (2014).[29] Kenya in 2012 issued a new Social Protection Policy.[29] The Health Sector Strategy (2014–2018) addresses social protection, including movement in removing financial barriers to health services.[29] In addition, National TB and Leprosy Programme in 2015, included actions to reduce the financial burden of TB care and medical costs, such as transport, lost income and nutritional needs. The Republic of Moldova addressed the MDR-TB burden through evolution is the social support for TB affected individuals with an increase in the financial support.[29] In 2001, Brazil funded the TB network leading to the creation of REDE-TB which is an interdisciplinary group of researchers and students from Health Sciences, Engineering and Education, in collaborations with civil society partners and health service representatives from federal, state and municipal levels with an objective of promoting research and educational activities to contribute to TB and TB/HIV control. Ethiopia started a tuberculosis research advisory committee promoting TB prevention and research.[29] Different countries have used several different approaches to deal with the disease burden of TB.

10. Preventive strategies in India

The primary prevention includes administration of BCG (Bacille Calmette-Guerin) vaccine which is administered within 72 hours of birth[9] which was first started in the year 1951 and the National Tuberculosis Control Program was started in 1962.[12] Even though BCG is readily available only 31% of timely administrations have been reported.[23] Revised National Tuberculosis Control Program (RNTCP) works in favor of promoting public and private sector collaboration and improving the Directly Observed Treatment Strategy (DOTS) for control of TB.[1] They have established partnerships with 2569 NGO and collaborations with 13,150 private practitioners.[1] The beginning of TB programs and mandatory notification in 2012 has to lead to an increase in the number of cases.[29,1] Many policies have been formed by the different state governments like Gujarat, Maharashtra, Bihar and a few other states for the prevention and control of TB.[1] India is working on increasing collaboration between the public and private health care sectors with increasing awareness and improving the legislature. India launched the 'India TB Research Consortium (ITRC)' initiative in 2016 by the Indian Council of Medical Research (ICMR) which addresses work on research in collaboration of all major national and international stakeholders.[5] This initiative has already received national recognition and with the expertise already available, India has a lot of potential to end TB.

11. India's role in World Health Organization's "The End TB strategy"

The World Health Organization (WHO) in 2014 has devised a plan till 2035 to eliminate Tuberculosis (TB) with a goal of 95% reduction in deaths by TB, 90% reduction in incidence rate, and 0% financial burden on the TB affected families. TB health care facilities have been made available to everyone as a part of India's campaign in The End TB strategy.[28] India's priority

includes providing rapid diagnosis and free treatment for all forms of TB in public as well as private healthcare sectors and has started using a new web-based reporting system "Nikshay", a mobile application used for notifications, surveillance, prescription delivery, and even electronic cash transfer for patients.[30,1] This notification system also serves as a reminder system for the patient on when to get prescriptions filled, physician visits, educating about protecting family members from contracting the disease and India is making progress for control of TB using technology and resources at hand by actively participating in WHO's "The End TB strategy". India is also a key partner in the BRICS (Brazil, Russia, India, China, and South Africa) TB Research Network which was launched at the WHO Global Ministerial Conference in Moscow.[5]

12. Initiative for promoting affordable quality tuberculosis tests (IPAQT)

The World Health Organization (WHO) endorsed newer diagnostic techniques to be used for the diagnosis of Tuberculosis (TB) but most of them being expensive were not widely used in India.[18] In March 2013 through the launch of IPAQT initiative- an affiliation of private laboratories in India, funded by industry and non-profit groups.[18] IPAQT aims at providing WHO-endorsed tests to the TB patient at affordable prices and also spreading awareness among the private practitioners and laboratories while decreasing the costs for tests up to 50%, making this a great initiative to improve the quality of TB care in India.[18]

13. Conclusion

India has been working for more than 50 years in combating Tuberculosis (TB) but still experiences a heavy case burden of the disease, losing both manpower and financial resources. India faces many challenges like social prejudice, a lack of private sector comprehension and uniformity, deficient diagnostic tools, increased cases of Multi-drug resistant TB, and a lack of awareness among the population. India has also been contending through the enactment of various programs and policies for prevention and control of TB. India needs a more hands-on approach to the issue like educating the population and making diagnosis and treatment free and readily available. Another strategy that can be implemented is the use of social media like WhatsApp groups and introduction to telemedicine to educate the population, increase patient compliance, and improve the quality of life for TB patients. Moreover, India should focus further on primary prevention by decreasing the incidence of the disease. India needs public-private sector collaboration with more efficient policies and increased involvement of public health care workers so that they can reach their WHO End TB Strategy goal by 2035.

Conflicts of interest

The authors have none to declare.

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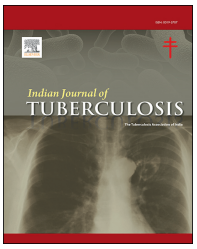

Review Article

BCG vaccination induced protection from COVID-19

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ABSTRACT

There are worldwide urgency, efforts, and uncertainties for the discovery of a vaccine against SARS CoV2. If successful, it will take its own time till useful for the humans. Till the specific vaccine is available, there are evidences for repurposing existing other vaccines. It is observed that countries having a routine BCG vaccination programme, have shown to have lower incidence of COVID-19, suggesting some protective mechanisms of BCG against COVID-19 in such countries. In countries like India despite vast population density and other adversities, and growing numbers of COVID19 infections, the mortality rate and severity of COVID has been low in comparison to some TB non-endemic countries (like Europe and USA). In addition, there are evidences that BCG vaccination offers partial protection and survival in low-income countries where tuberculosis is prevalent. The nonspecific effects (NSEs) of immune responses induced by BCG vaccination protect against other infections seem to be due to its immunological memory eliciting lymphocytes response and trained immunity. The protective effect on other viral infection in humans are believed to be mediated by heterologous lymphocyte activation and the initiation of innate immune memory may be applicable to SARS CoV2. The BCG vaccination at birth does not have a protective effect beyond childhood against COVID-19. In adults, there might be other factors dampening the virulence and pathogenicity of COVID-19. In the TB endemic countries like India, with high population density, similar to BCG vaccination, the environmental Mycobacteria might be imparting some immune-protection from severity and deaths of COVID-19.

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1. Introduction

The COVID-19 pandemic continues to ravage India and the world with its high transmissibility and varying degree of virulence. As the causative agent SARS CoV2 is a novel coronavirus, prior infection with other endemic coronaviruses does not confer any protection. Due to the immune naivety of the population and ease of international travel, the world faces the greatest ever global pandemic of the century. While uncertainty of an effective vaccine against SARS CoV2 persists, protective attributes of century old Bacillus Calmette-Guérin (BCG) vaccine is currently the hot topic of attention.

At the beginning of the pandemic, it was predicted that the developing countries will face the maximum case fatalities because of poor health infrastructure, lack of preparedness and poor health regulations. However, till now, the number of deaths have been higher in developed nations like USA and Europe. Surprisingly less number of cases have been reported from Africa, the majority of cases recovered with mild diseases. Even if the number is increasing in India the severity and mortality is less compared to some countries. In India, over 80% of the patients have mild symptoms are asymptomatic. Hence, the inter-regional variation in the clinical severity and mortality of COVID-19 is speculated to be through immune response impact. It is also claimed that BCG vaccination offers partial protection and survival in low-income countries where tuberculosis is prevalent.[1]

There is much variation of severity of inflammatory process of COVID-19 across geographical locations in world. The possible reasons could be individual's age and viral factors modified by population density, environment, ambient air temperature and humidity. High temperature and higher relative humidity have been demonstrated to have a negative effect on the spread of the virus.[2,3] The increase of temperature from spring to summer could facilitate the containment and the cold season may witness an upsurge in infections during 2020–2021 winter season.[3] In addition to geographic variation influencing COVID 19 spread and severity, there are other established factors like advanced age, inflammatory comorbidities, and immune compromised conditions for severe illness.[4]

Two basic steps by which the virus overcomes host immune response are recognition and evasion of SARS-CoV-2 to circumvent the cytosolic pathogen recognition receptors (PRR) and subsequent invasion of the host.[5] SARS-CoV-2 causes severe damage rapidly by excessive cytokine production (storm) or slowly through innate immune resistance manifesting as fever in order to provoke a delayed over inflammation.[6] More severe disease have inflammation-based sequelae due to uncontrolled systemic inflammatory response resulting from the release of large amounts proinflammatory cytokines that further affects the immune system, which contributes to severity of the disease. The excessive production and secretion of cytokines like tumour necrosis factor (TNF), IL-6, and IL-1β results in a critical state which is described as a cytokine storm. The cytokine storm leads to an increased vascular (hyper)permeability, multiorgan failure, and eventually death when the cytokine concentrations are unrestricted and high over time.[7] Therefore, controlling the immune evasion of SARS-CoV-2 is an important step in management.

2. Evidences of protection due to BCG vaccination against viral infections

BCG vaccine, a live attenuated strain derived from *Mycobacterium bovis*, has the ability to induce potent nonspecific immunity also known as so-called 'off-target' protection against bacterial and viral pathogens. BCG has shown to diminish the susceptibility to various respiratory tract infections. Such protection is mediated by the non-specific boosting of innate immunity. However the mechanisms of the beneficial effects of the BCG vaccine are now better understood. Protective effects of BCG vaccine against COVID 19 disease severity is partially explained by the different national policies respect to BCG vaccination.

The cellular and molecular mechanisms of the nonspecific protective effects of BCG vaccination against various DNA and RNA viruses, including herpes and influenza viruses have been studied in mice recently.[8] BCG vaccination is also shown to protect from herpes simplex virus type 2 (HSV2) infection in new-born mice.[9] Subcutaneous injection of component of the mycobacterial cell wall (muramyl dipeptide) protects against vaccinia virus and HSV2 infections in mice.[10] Such protection is facilitated by peritoneal macrophages.[10] The above effect suggests that there is substantial effects of BCG on the innate immune system. BCG administration acts through macrophages and have reduced viral titres of influenza A virus in the injected mice.[11]

Several studies underscored reduction in respiratory tract infections and risk of pneumonia upon BCG vaccination of elderly people.[12,13] However, limited period time of the acquired protection remains a caveat for trained immunity boosters.

A randomized study showed that BCG vaccination prior to influenza vaccination in healthy individuals resulted in a significantly higher antibody response against influenza A (H1N1) compared to placebo.[14]

The effectiveness of BCG in the promotion of long-lasting T cell immunity to human respiratory syncytial virus (hRSV) antigens was experimentally demonstrated without any observable adverse effects.[15]

In severe combined immunodeficiency (SCID) mice, with functionally depleted T- and B-cells, BCG vaccination had protected against a secondary non-Mycobacterial challenge, which highlights the importance of innate immune cells in protecting from diseases.[16]

Several studies have shown protective action of BCG against unrelated respiratory infections both in children and adults. A comparable protection effect of BCG on respiratory infections was shown among elderly population in Indonesia.[12] Prospective clinical trial performed in Japan has shown BCG vaccine to protect from pneumonia in tuberculin negative elderly populations.[13] Randomised controlled trials have demonstrated that the BCG vaccine have immunomodulatory effects to protect partially against respiratory infections. In South Africa, BCG-Danish reduced respiratory tract infections by 73% (95% CI 39–88) in adolescents.[17] In a

Mechanisms of BCG-induced protection against viral infections[23,24]

Heterologous lymphocyte responses	Innate immune memory
• Enhanced immune responses to secondary unrelated infectious agents induced as result of heterologous lymphocyte responses. • Initiate the activation of CD4 and CD8 memory cells, that are not for targeted antigens, modulate Th1 and Th17 responses to the infections other than mycobacteria in vaccinated individuals	• The functional effects of innate immune cells are altered upon some responses if cells come across a secondary stimulus. • BCG induce non-specific (off-target) effects by the stimulation of immunological memory in innate immune cells, particularly natural killer (NK) cells, monocytes and macrophages instead of T and B-cell-based adaptive immune mechanisms

Fig. 1 – Vaccines excite the initiation of the adaptive immune response and the development of immunological memory.[25,26] The immunological memory consists of the developments of antigen-specific T and B cells which protects against subsequent insult by the pathogen. This is thought to be due to secondary innate immune response induced by BCG vaccination, coined as nonspecific effects (NSEs). The efficacy to protect against other infections can be linked to its immunological memory eliciting lymphocytes response (Fig. 1) and trained immunity (Figs. 2 and 3).

randomized placebo controlled trial, BCG vaccination showed to induce significant reduction in viremia in an experimental infection with live attenuated yellow fever virus vaccine strain. The level of lowering of viremia was correlated with heterologous IL1-β production which was attributed for protection induced by BCG.[18]

3. Evidences of protection due to BCG vaccination against SARS Cov-2 infections

Miller et al[19] (Correlation between universal BCG vaccination policy) compared number of countries with BCG vaccination policies with the morbidity and mortality for COVID-19. They found that countries without universal policies of BCG vaccination (like Italy, USA) have been more severely affected compared to countries with universal BCG policies. They proposed that BCG vaccination attributed for reduced morbidity and mortality in countries with universal BCG policies.[19,20] Countries with high BCG vaccination coverage have shown lower incidence of COVID-19, suggesting some protective mechanisms in TB-endemic areas.[21] Ozdemir et al have shown proportionately less cases, milder illness and a lower death rate in BCG vaccinated population as compared to BCG non-vaccinated across countries and hemispheres.[22] BCG vaccination might alter a secondary innate immune response upon viral infection over month apart resulting in improved antiviral responses and lowering viremia.[18] This is so far proven that the countries more prone to be severely affected SARS-CoV-2 didn't adopt universal policies of BCG vaccination like Italy and Spain. The BCG vaccine likely reduces cytokine storm after SARS-COV-2 exposure, resulting mild COVID-19 and early recovery.

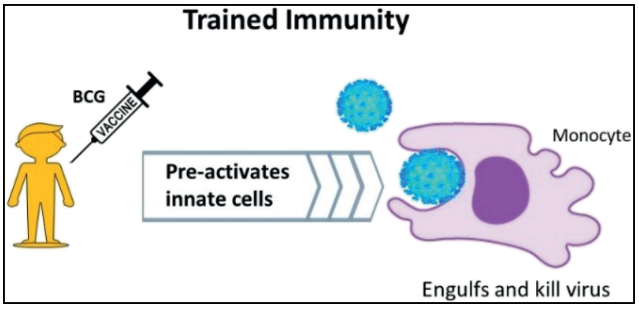

Fig. 2 – The NSE is a consequence of the type of non-specific immune memory induced after vaccination as part of protective "trained immunity".[27] This type of immunological memory (of past insults) is developed by innate immune cells, like monocytes, macrophages, and natural killer cells, and can be efficiently induced by BCG.[16,28]

4. Mechanisms of BCG-induced protection against viral infections[23,24]

The protective effect on viral infection in humans are believed to be mediated by heterologous lymphocyte activation and the initiation of innate immune memory.

5. COVID-19: children are protected?

The children might have some immune characteristic to incite the triggering active innate immune response to stop cytokine storm and progression to pneumonia/illness.[30] The immune dysfunction and extent of cytokine overproduction are minimal in children compared to adults. Lymphopenia in the

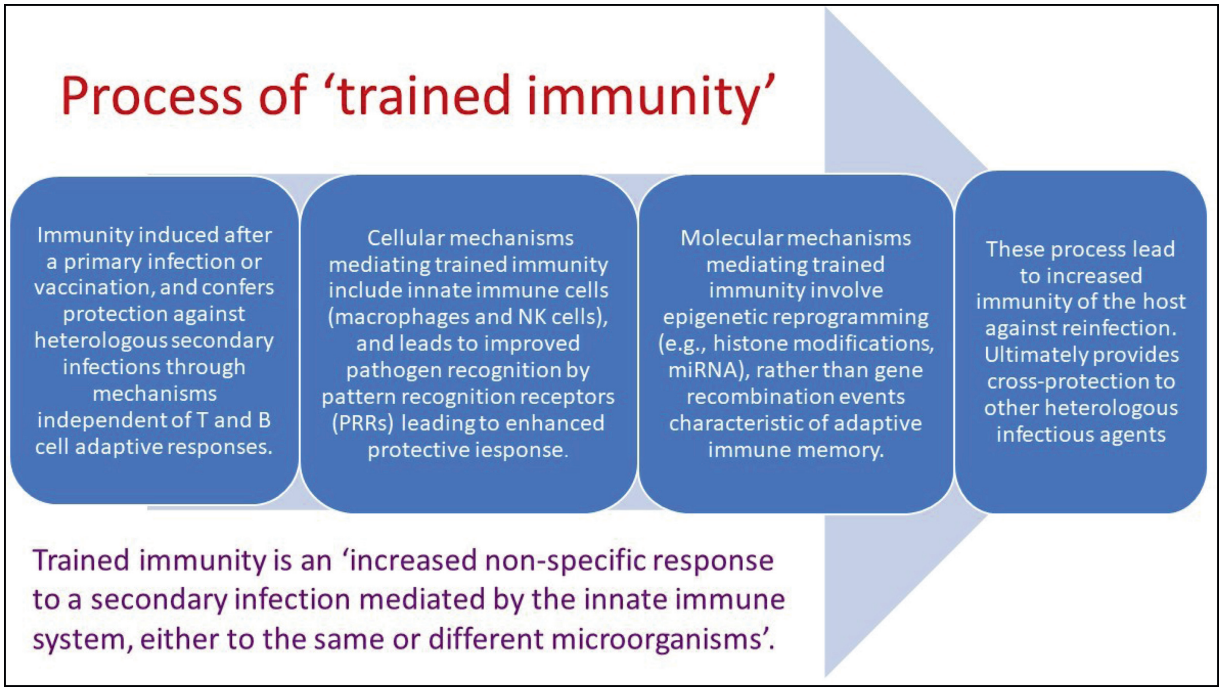

Fig. 3 – Severity of the COVID-19 depends on the level of cytokine storm and T cell lymphopenia and both are associated with pulmonary damage, respiratory distress and higher mortality. BCG induces epigenetic and functional reprogramming in human monocytes and increases immunity for un-related viral infections and Interleukin (IL)-1β plays as mediator of trained immunity responses.[8] Hence, durable epigenetic alterations to increase antiviral function of innate immune cells is observed after live vaccines, facilitating a faster and better responsiveness if exposed to re-infections.[16,29]

majority of paediatric COVID-19 patients is uncommon in contrast to adults.[31] It is possible that the innate immunity plays a protective role in the pathogenesis of COVID-19 in the paediatric age group as the adaptive immunity is not well-developed in early ages. There could be a cross-protective immunity developed in response to regionally prevalent viral infections and repeated mild upper respiratory tract infections. Some protection due to an immune system activation as a result of frequent viral infections decreases the susceptibility to severe illness.

A reasonable explanation is that children of the country where routine childhood BCG vaccination is a policy and BCG vaccinated children have some degree of protection from infection with SARS- CoV-2, and less severe diseases among those who infected. Ultimately there is less transmissibility of the virus. The children also seem to be better protected from COVID-19 than adults.

In late adulthood, there is an involution of the thymus, and the decrease in regulatory T cells can be a contributory mechanism underlying severe COVID-19 illness. In older ages, generalized inability to fine-control inflammation favours propensity toward sustaining the cytokine release syndrome (CRS).

6. Should BCG vaccination be given to all?

Considering the above evidences of BCG regarding its non-specific beneficial effect on non-tubercular infections including respiratory and other viral infections, reduction in mortality due to pneumonia and sepsis, a thought is worth given for indiscriminate BCG vaccination (in non BCG vaccinated countries) to reduce severity of Covid-19. Two separate multi-centre placebo-controlled parallel group randomized trials are currently underway in the Netherlands and Australia to assess whether BCG-Danish reduces health care workers absenteeism and to reduce hospital admission among the elderly during the COVID-19 pandemic through BCG vaccination.[32] These trials are 'BCG Vaccination to Protect Healthcare Workers against COVID-19 (BRACE) and, reducing health care workers absenteeism in COVID-19 pandemic through BCG vaccine (BCG-CORONA).[32]

In the present scenario WHO does not recommend BCG vaccination for the prevention of COVID-19. Curtis et al have explained the reasons why it is important to comply with the WHO's recommendation regarding the use of BCG vaccination only for COVID-19 trials till the results are complete,[1] i) there is no robust evidence regarding effectiveness of BCG against COVID19. According to WHO, the studies showing correlation between BCG vaccination and COVID-19 protection are grossly confounded by national demographics data, testing rate, disease burden and stage of pandemic. ii) The BCG vaccine is of limited supply, and unselective use could affect the supply of routine vaccination for children in high risk countries. Iii) It is unlikely that a BCG vaccine given during childhood will be effective to protect COVID-19 in adult age. Iv) If BCG vaccination is done for COVID-19, it could create a false sense of immunity, and v) The possibility of up-regulation of immunity to

exacerbate the severity of COVID-19 infection by BCG, though remote cannot be ruled out.[1]

7. Possible role of Environmental Mycobacteria

On the flipside of the flimsy evidence, the BCG vaccination in childhood may not have protective effect against COVID-19 in adulthood as the effect of BCG vaccination is moderate and lasts for nearly 20 years.[33]

So there might be some other factors modifying the virulence and pathogenicity of COVID-19. Is it the endemic infections like dengue, chikungunya, malaria and other tropical infections, have an inverse correlation with severity of COVID-19? It is to hypothesize that endemic infections in the community may protect through various interferons which retard subsequent disease progression through viral interference.[34,35]

We hypothesise on the possible mechanism behind the exact "environment-antiviral immunity" interplay on the pathogenesis of COVID-19.[36] In the TB endemic countries like India, with high population density, the environmental Mycobacteria play great role as over half of the population are positive for tuberculin skin test (TST). A study from southern India has shown that immune responses of non-vaccinated tuberculin reactors to have significantly higher than the vaccinated tuberculin non-reactors,[36] In addition there was no significant difference in the responses among the BCG-vaccinated tuberculin reactors when compared with the non-vaccinated tuberculin reactors.[36,37] Trials have described the protective effects of nontuberculous Mycobacterium species (like, *Mycobacterium vaccae*) in up-regulation of IFN-gamma secretion.[38] Again BCG vaccination used give a moderate protection against tuberculosis and only for up to 20 years, not lifelong. So the protection of BCG against COVID-19 if any looks to be applicable only to certain portion of population. On the other hand, the environmental mycobacteria are ubiquitous and are sustained in environment since long. The development of nonspecific partial immunity is likely from environmental mycobacteria as people from TB endemic countries like India get infected from time to time. For the same reason most of the people are TST positive.[36] Factually these conditions impact some degree of general immunity for new infections. TB endemicity or environmental mycobacteria seems to be correlated with reduced disease burden and severity of COVID-19.[39]

Like BCG, it is hypothesized that environmental Mycobacteria induce prolonged alteration in the immune system that results in increased level of innate and adaptive immunity.[39] The environmental Mycobacteria might have induced similar immunological memory eliciting lymphocytes response (Fig. 1) and trained immunity (Fig. 2) making epigenetic alterations in the similar mechanism to BCG at the promotor sites of various genes encoding inflammatory cytokines such as interleukin (IL)-1, IL-6, and tumour necrosis factor (TNF), resulting less cytokine storms compared to naïve population.[40]

It is possible that people from TB endemic countries like India despite vast population and growing numbers of COVID19 infection, have acquired some protections from severity and deaths from COVID-19 in comparison to TB non-endemic countries (like Europe and USA). Although it appears the immunity may not able to stop COVID 19 infections, but is likely to diminish its impact on severity and mortality.

If the BCG vaccine as an inducer of trained immunity induces non-specific protection to bridge the gap before a real specific vaccine is developed, this would be an important tool in the response to COVID-19 and future pandemics. Better understandings of the molecular mechanisms are still evolving. By identifying the factors that impact the non-specific effects of BCG, can be an important step towards novel therapeutic options and vaccination strategies, which might lead to a reduction in severe morbidity and mortality associated with viral infections.

Conflicts of interest

The authors have none to declare.

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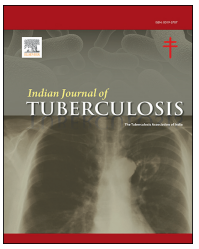

Viewpoint

75th National Conference of tuberculosis and chest diseases
DR KS Sachdeva Speech

Kuldeep Singh Sachdeva

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Respected dignitaries, senior colleagues, and my dear friends, a very good evening to all of you. As the President of the NATCON 2020, it is my privilege and honour to welcome you all to the platinum jubilee celebrations of the 75th National Conference of TB and Chest Diseases.

This year's event is unprecedented in more ways than one. Firstly, we are holding this entire event virtually and online.

Secondly, the event is being held during a ravaging global COVID-19 pandemic. The pandemic has laid unprecedented challenges before us both as citizens and as well as public health professionals and policy makers.

In fact, we are at the cusp of reinventing and re-writing the playbook on how pandemics are going to be managed in near future. This to my mind is both an exhilarating opportunity as well as a daunting task. I believe it is also an enormous privilege as public health professionals to witness and contribute in our own ways to the understanding of this global health crisis situation and manage it for effective outcomes.

I am sure this event is going to be an enormously enriching experience with distillation of knowledge and wisdom from scientific community, public health professionals and policy makers who have congregated here and attending the3-dayonline event. Indeed, the leanings will be both enlightening and the deliberations will be equally engaging for all of us. Hope you all are looking forward to it all as much as I do.

Significantly, COVID-19 pandemic has taught us valuable lessons and as the saying goes "every crisis brings with it a unique opportunity". This crisis has amply proved that. If we all could join force and come together to overcome COVID then what stops us from hoping to achieve victory over TB in the next few years.

As is evident, a massive social reengineering is taking place globally. The public discourse on health has now taken the centre stage. The COVID pandemic has put strenuously to test the health infrastructure and systems, be it in developed or developing countries. COVID-19, therefore, is a watershed moment for public health in the country on two counts.

Firstly, there is a heightened public health awareness among the common man today than ever before on Communicable diseases. COVID-19 and its highly contagious nature have created a huge health-related risk perception among the public.

However, other diseases have been silently claiming more lives annually in our country. Yet, the awareness and sensitisation regarding them are underwhelming. For instance, TB suffers from complete invisibilisation.

If we can stop COVID in its tracks in such a short time –undoubtedly, we can stop TB too with the same set of resolute determination and concerted efforts.

Due to COVID-19 pandemic the public is highly receptive now more than ever before to receive risk communications and health messages. There is a fundamental shift in the perception of one's vulnerability among the masses both

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individually and collectively cutting across the rich and poor divide. The pandemic has jolted the public into seeking steps for health and wellness.

I would like to add here that while focus predominantly remains on Communicable diseases - Non-communicable diseases should not be neglected and put on the backburner. We need to advocate about these as public health professionals and the health programmes in the country have to actively evolve this and strengthen them further.

Secondly, COVID-19 pandemic has given an entry point to structurally reimagine our core public health delivery systems. More so in the context of respiratory infections and importantly when you have an ambitious goal of ending TB in the country by the year 2025.

The National TB Elimination Programme (NTEP), under the Ministry of Health and Family Welfare, has taken several steps in that direction and that have the potential to become the "new normal".

Innovations such as doorstep delivery of drugs to TB patients, teleconsultation, active screening for TB through outreach activities, etc in response to the pandemic, have proved to be a boon for many patients, during the lockdown who struggled to access public/private health care.

The programme in collaboration with the states is ensuring minimal visits to health facilities by the patients who are on treatment by providing sufficient drugs required for more than a month as well as using digital innovations to monitor treatment adherence. All this to ensure there is no inconvenience and interruption in their treatment.

This is a paradigm-shifting opportunity in the health delivery system in the country and can become more of a norm than an exception. The overall public health system is getting an uplift to ensure they are compliant with air-borne infection control measures and the frontline healthcare workers getting used to newer protocols.

Extending the service delivery further, the programme is going to the doorsteps of the patient to collect the samples to aid in early detection, diagnosis, and initiation of the treatment. It exemplifies the programmes resolve for last-mile access and quality care delivery.

Extensive contact tracing, isolation facilities and sanitoria are again coming back in vogue thanks to their efficacy and practicality in containing a community level spread and pandemic situations.

We are also observing that from a mere patient-centric care approach the systems will need strengthening around community-centric health approaches. The social and environmental determinants need to be addressed in the process. Disease surveillance and enforcing public health regulations will become rigorous and not remain a matter of individual's choice.

Despite the challenges posed by COVID-19, TB programme has bounced back. There is unprecedented focus and momentum to end TB. India is making rapid strides to achieve this goal by 2025, five years ahead of the global schedule.

We have introduced several mitigative measures including bi-directional screening for TB-COVID and convergence in case finding efforts for TB-COVID in the country.

I would like to highlight the several policy reforms made in the last three years. TB has been made a notifiable disease in the country. This has improved the identification of TB cases and helped reduce the gap in identifying the missing cases in the country. One million missing cases were reported in 2017, it has been reduced to 2.4 lakh in 2019. Financial support is being provided to all TB patients under Nikshaya Poshan Yojana, a significant step to reduce out of pocket expenses for the patients and increase treatment adherence. Since April 2018, a total of 940 Crores rupees has been disbursed to TB patients till date. In addition, free drugs and diagnostics are being provided to the TB patients availing treatment in the private sector. The community plays a vital role, and their participation is crucial for any public health programme success. In view of that we have created TB Forums covering all the districts in the country with an aim to provide a platform for all stakeholders, including patient groups to voice their concerns and offer suggestion that can be integrated into the programme.

TB diagnostic and treatment capacities in the country has been ramped up. We have undertaken massive expansion of the diagnostic capacity and currently more than 21,000 microscopic centers are operational across the country. In the last two years we have increased Rapid Molecular Testing devices (CBNAAT and Truenat) to more than 3000 devices with at least one in every district of the country. NTEP has incorporated latest evidence based and injection-free regimen for drug resistant as well as drug sensitive TB. We have also introduced newer drugs with more than 15,000 patients having received Bedaquiline and Delamanid containing regimen treatment from more than 700 DRTB centers spread across various parts of the country. Moreover, the programme is heavily investing in the capacity building of frontline workers to deliver quality care and for effective programme outcomes.

There is an 18 per cent and 12 per cent increase in TB case finding under National Tuberculosis Elimination Programme (NTEP) in 2018 and 2019 respectively. The government has heavily invested in TB research. The Indian Council of Medical Research and India Tuberculosis Research Consortium are jointly conducting next-generation research on diagnostics, therapeutics, vaccines, and other such critical areas. World's largest National TB Prevalence Survey with a massive sample size of 5,00,000 is underway in the country. It is a significant push towards TB elimination goals in the country.

From increased funding for TB, the discovery of newer drugs and diagnostics, increased access to health facilities, greater investment in research and expanded reach of public health education, seasoned with TB activism and media's proactive role, private sector participation to political advocacy and community engagement, coupled with vaccine trials has renewed the hope of finding the elusive and miraculous breakthrough to END TB and it seems the goal is within the realms of the possibility. The goal to end TB by the year 2025 may look daunting-however, the recent paradigm shift in the policy and the drive of several states & UTs to move towards TB free status through rigorous population-based vulnerability mapping and screening coupled with active case finding will substantially yield results and act as the driving force and will add to the momentum towards Ending TB in the country.

In the end, I would like to congratulate the entire organising team behind the event and for creating this

platform. Also, as you all are probably aware this year, we are celebrating the Platinum Jubilee of NATCON and it has become a key annual calendar event in the country for bringing various medical professionals and experts in the field of Tuberculosis, Chest Diseases under one umbrella for scientific deliberations and share knowledge and advancements with the goal towards Eliminating TB from India by 2025. I extend my warm wishes and congratulation to the Tuberculosis Association of India, Mahatma Gandhi Memorial Medical College, Indore, and MP-TB Association for putting this event together and bringing a galaxy of voices to enrich and enlighten the discourse surrounding TB and Chest Disease and provide leadership to the country.

Conflicts of interest

The author has none to declare.

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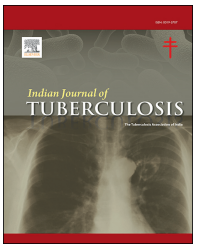

Viewpoint

TB control in India in the COVID era

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ABSTRACT

COVID-19 pandemic has disturbed the delivery of health care in almost all countries of the world. This has affected mostly the public health control programs. Because of lock downs, restrictions in movement, psychological fear of contacting the disease in health care facilities, diversion of health care workers for containment and management of COVID-19, utilization of diagnostic facilities like CBNAAT machines for COVID work, conversion of hospitals for care of these patients, financial diversion etc has created issues in the NTEP to focuss on TB control in India. Case notification and other areas of the program to achieve End TB by 2025 have suffered. Various ways of overcoming these difficulties have been discussed.

The COVID-19 pandemic caused by the novel corona virus, severe acute respiratory syndrome corona virus 2 (SARS-CoV-2), has upset the major public health care system throughout the world. Globally, by 3rd July 2020, there have been 10,719,946 confirmed cases of COVID-19, including 517,337 deaths, reported to WHO. In India, from Jan 30th to 3rd July 2020, there have been 625,544 confirmed cases of COVID-19 with 18,213 deaths.[1] The COVID 19 pandemic has placed unprecedented demands and pressure on the health system. Health facilities and workforce are diverted and assigned a wide variety of activities related to controlling the outbreak. In doing so, other essential health services would be severely compromised. It is likely that seeking health care may be deferred because of social/physical distancing requirements or community reluctance owing to perceptions that health facilities may be infected. Continuing to provide essential services, while focusing on COVID 19 related activities, is important not only to maintain people's trust in the health care delivery system,[2] but also to minimize an increase in morbidity and mortality from other health conditions. During the Ebola outbreak in 2014–15, increased number of deaths was caused by measles, malaria, HIV/AIDS and tuberculosis (TB) because of failure in the health system and that exceeded deaths from Ebola itself.[3,4] Prevention and treatment services for non-communicable diseases (NCDs) are affected severely since the pandemic began. A WHO survey completed by 155 countries during a 3-week period in May 2020, confirmed that the impact is global, but low-income countries are the most affected.[5] More than half (53%) of the countries surveyed have partially or completely disrupted services for hypertension treatment; 49% for treatment for diabetes and diabetes-related complications; 42% for cancer treatment, and 31% for cardiovascular emergencies. Rehabilitation services have been disrupted in almost two-thirds (63%) of the countries,

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even though rehabilitation is key to a healthy recovery following severe illness from COVID-19. In almost all (94%) health staff working in the area of NCDs are reassigned and diverted to support COVID-19. The postponement of public screening programmes (cancer) was also widespread, in more than 50% of countries. Most common reasons for discontinuing or reducing services were cancellations of planned treatments, a decrease in public transport available and a lack of staff because health workers had been reassigned to support COVID-19 services. One of the main reasons for discontinuing services was a shortage of medicines, diagnostics and other technologies in about 20% of countries. Many countries had devised alternative strategies for continuing care which may or may not be the ideal.[6] Many countries implemented lockdowns and quarantines to curtail the spread of the virus, and a large number of global populations are still under these restrictions. These restrictive measures, like physical distancing, gatherings, travel, etc has led to many adverse impact on societies, economies, and health care delivery systems. All countries of the world are struggling to maintain their health care systems to cope under such extraordinary conditions. In addition to affecting medical care of various diseases, whether therapeutic or preventive, COVID-19 has bad prognosis if associated with certain disease conditions like cardiovascular disease, chronic respiratory diseases (COPD and bronchial asthma), diabetes mellitus, hypertension, chronic kidney diseases, and cancer etc.

However, the medical and social consequences of association of TB and COVID-19 are not clearly understood and experience on COVID-19 in TB patients and vice versa are limited. There are certain similarities and differences between the two diseases. Limited and preliminary observations suggest that TB infection is likely to increases susceptibility to SARS-CoV-2 with increased COVID-19 severity.[7] If it is so it will have a major impact in India as one third of its population is infected with TB. There are striking similarities between the two. Both cause major infection-related morbidity and mortality. While COVID-19 had caused over 0.5 million deaths so far over a period of 6 months, TB was the leading cause of mortality from an infectious disease worldwide in 2018, causing 1·2 million deaths out of the nearly 10 million new cases reported that year.[8] COVID-19 cases have already crossed that figure within 6 months of its origin. In India COVID-19 mortality is above 18,000 over a period of 3 months out of the over 5 lakh infections during this time. On the other hand, in India in 2019, 2.41 million new TB cases were reported and there was a mortality of nearly 79,000 in that year.[9] The global Case Fatality Rate (CFR) for TB is about 3.5% among patients who were HIV− and 18.8% for HIV+ of all ages.[10] However, a recent review has found the an overall case fatality ratio among Indian patients with TB during treatment of 5.16% (95% CI 4.20%–6.34%).[11] On the otherhand, the CFR for COVID-19 for the world is 4.8% and for India it is 2.92% only.[12] While the Basic reproduction number (R_0) is 2.2 for COVID-19; the same for TB is (R_0) higher like it was 4.3 in China (2012); and 3.55 in Southern India (2004–2006).[13]

Both COVID-19 and TB present with respiratory symptoms with small differences. During the COVID-19 pandemic, diagnosis and treatment of TB, or TB and COVID-19 co-infection, are likely to be compromised. Elderly and associated co-morbidities are increased risk factors for severe disease and cause adverse outcomes in both conditions. Considerable social impact like stigma, discrimination, and isolation are associated with both diseases in addition to the economic impact because of loss of productivity and catastrophic costs to individuals and households. There are some important differences between the two also. TB has been labelled as a pandemic many times over the past three centuries, whereas this is the first COVID-19 pandemic. Children are often less severely affected by COVID-19, whereas 1·1 million children had TB disease in 2018, of whom 200,000 died and in India about 3,42,000 incident cases of paediatric TB are estimated to occur every year accounting for 31% of the global burden and 13% of the overall TB burden in the country as per the 2019 India TB Report. The association between poverty and COVID-19 is unclear. TB will be associated with the poverty, in which poorer people have a higher likelihood of infection, disease, and adverse outcomes. Moreover, unemployed populations including contract workers will experience increases risk of TB. While most of the cases and deaths from TB occur in low- and middle-income countries, COVID-19 occurred more in the developed countries following China and most deaths occurred in USA.[1] COVID-19 has mobilised more global and human resources in a few months than TB has in decades. However, the number of COVID-19 cases and mortality might increase in future as now India is the fourth highest number.

The exact relationship is still unclear despite many similarities and dissimilarities. The clinical and epidemiological interactions of COVID-19 with TB (with or without HIV) seem to be highly complex. Transmission of TB might rise because of increased respiratory symptoms associated with COVID-19, or it may even decline due to COVID-19-related self-isolation, use of masks and quarantine and no social gatherings and mass travel. Millions of people treated for TB that have residual, long-term lung damage are likely to be at a higher risk of severe disease and death from COVID-19. Because of extreme pressures on health systems, exacerbated by COVID-19, people with TB are likely to face decreased access to diagnostic and treatment services, which might also result in adverse outcomes.[14]

Both TB and COVID-19 spread by close contact between people, although the exact mode of transmission differs, explaining some differences in infection control measures to mitigate the two conditions. Hospital procedures that generate aerosols predispose to infection of both conditions and should only be conducted within recommended safeguards.

Although clinical course and outcome of COVID-19 is well reported from different parts of the world, including commentaries, perspectives and reviews, information is scanty about the clinical course of co-infections with TB. Global and national experience with concomitant TB and COVID-19 is extremely limited. In an analysis of 1217 consecutive respiratory specimens collected from COVID-19 patients, TB bacillus was not detected.[15] Because of its immunological effects, COVID-19 pandemic is likely to affect TB in many ways in many countries. A Global Tuberculosis Network (GTN) study of 49 cases of TB and COVID-19 from 8 countries and 3 continents[16] revealed that most patients had prior TB with one-third having first COVID-19; 18.3% had both diseases

diagnosed within the same week. Most patients had active TB and 7 (14.3%) had post-TB sequel. The impact on the healthcare system (e.g., days of admission, intensive care unit beds, etc.) was relevant in this study. The information on BCG (Bacillus Calmette-Guérin) vaccination was modest. Another study data from 69 consecutive cases in 8 countries and 20 hospitalised patients with TB and COVID-19 showed that 8 out of 69 (11.6%) patients died. Most of them were young migrants. It was noted that mortality was more in elderly patients with co-morbidities; TB was not a major determinant of mortality and migrants had lower mortality due to younger age and lower number of co-morbidities. However, the authors postulated that in settings where advanced forms of TB frequently occur and are caused by drug-resistant strains higher mortality rates can be expected even in young individuals.[17] In another small series of 20 TB patients[18] diagnosed with COVID-19 co-infection from North Italy, most were males and the median age was 39 with a range of 27–47 years. 50% of patients had a BMI < 18.5 Kg m^{-2} at admission and eight had co-morbidities but none had HIV co-infection. Three patients reported having been vaccinated with Bacillus Calmette-Guérin (BCG).

Even if there is scarcity of data about the interaction and coexistence of both the diseases, one can draw conclusions or may expect similar outcomes from experience gained from other viral diseases occurring in the pat and their impact on TB. Crisan-Dabija et al[19] examined the issue of the effect of the three human coronaviruses known to cause fatal respiratory diseases: the SARSCoV-1 that led to a global epidemic in 2002; the Middle-East respiratory syndrome coronavirus discovered in 2012 and still affects people from 27 countries; and most recently, the novel coronavirus (SARS-CoV-2)and the influenza pandemic of 1918–19. The authors noted that these epidemics have a negative impact on TB patients; transmission prevention was crucial for containing the epidemics and in order to decrease the opportunity of SARS-CoV-2 spreading amongst TB cases, hospital treatment for TB patients should be limited to severe cases. Immunopathogenesis of these viral illnesses also will affect course of TB[19] and diagnostic confusions. Similar observations are also made by a consensus by the World Association for Infectious Diseases and Immunological Disorders (WAidid), GTN and members of ESCMID Study Group for Mycobacterial Infections (ESGMYC).[20] Similarly, Ebola virus disease (EVD) in 2013–15 in Liberia, West Africa had major negative effects in the form of significant decreases in diagnoses of smear-positive pulmonary TB, the declines in HIV testing and antiretroviral therapy uptake and poor treatment success.[21] The devastating EVD outbreak of 2014–2015 in West Africa impacted significantly on all sectors of the healthcare systems in these countries, including the TB prevention and control programmes. The outbreak had an adverse impact on the healthcare workforce and healthcare service delivery. At the height of the EVD outbreak, numerous staff members in these countries contracted EBV at the Ebola treatment units and died. Many healthcare workers were also infected in healthcare facilities that were not Ebola treatment units but were national hospitals and peripheral health units that were unprepared for receiving patients with EVD. In all these countries, the disruption to TB services due to the EVD epidemic would have increased *Mycobacterium tuberculosis* transmission, TB morbidity and mortality, and decreased patient adherence to TB treatment, and the likely impact will not be known for several years to come. Many other aspects of the dual disease have been described by different authors.[22–29]

The COVID-19 pandemic will impact existing and well-performing public health programs including the TB control programs.[30] There is likely to be grave consequences for the existing and yet to be diagnosed TB patients, more so in low and middle income countries where TB is endemic and health services are not well equipped. TB control programmes will be under severe strain due to diversion of resources, loss of focus with increased attention of COVID-19 care, constraints due to overutilization of laboratories meant for TB work, issues related to availability of TB care workers, restriction of movements of patients and contacts etc with DR-TB centres being diverted for COVID related work because of change in the priorities of health care delivery. This is going to lead to a reduction in quality of TB care and poor outcomes. The Government of India has already made these arrangements of diverting the man power and use of CBNAAT machines for COVID work. This is an enormous challenge for the Governments and societies for ensuring that the pandemic has the least possible impact on key health programs that will need continued close monitoring. There is a significant decline in the claims made under the Ayush Bharat- Pradhan Mantri Jan Arogya Yojana during the lockdown period in India. There was a steep decline of 64% (as compared to two weeks earlier) in the claims made under the health scheme in the first week since the lockdown was announced. The report confirms the concerns about reduced access to healthcare due to the sudden imposition of the nationwide lockdown to contain the COVID-19 pandemic.[31]

Under the Revised National Tuberculosis Control Program (RNTCP), India has an ambitious goal of Ending TB by 2025, 5 years ahead of the Global target. The strategy aimed to end the TB epidemic, with targets to reduce TB deaths by 95% and to cut new cases by 90% compared to that was in 2015; and to ensure that no family is burdened with catastrophic expenses due to TB. To achieve these goals, the RNTCP, India developed the National Strategic Plan (NSP) 2017–2025. Due to various challenges and issues for achieving these goals, and to put thrust on the strategies, in January 2020 the RNTCP, was renamed as the National Tuberculosis Elimination Program (NTEP). A revised draft NSP 2020–2025 is under preparation to enhance these strategies. The COVID-19 pandemic will disturb the balance jeopardizing various TB control activities working in full swing and despite political commitments at the highest level – the Prime Minister.

TB case notification through Nikshay, an online case notification system through the e-platform, is a key to the NTEP. Case detection, treatment and compliance are the key factors in the End TB strategy. COVID-19 pandemic in India has adversely affected the TB case notification. Table 1 depicts the decline in case detection and notification.

Thus, there is a lare gap in the case detection although the case notification was steadily increasing. This happened as a result of repeated lockdowns. Between March, 20th and 3rd July of every year the number was increasing, but for this year of COVID-19, the case notification has drastically reduced to less than a half.

Table 1 – Nikshay Dash-board showing TB notification.

Year	Public Sector	Private Sector	Total reported	Between 20th March till 3rd July	Target (Both sectors)	Percentage reported
2017	14,10,579 (99%)	3,24,386 (36%)	17,35,262	5,62,161	23,25,312	75%
2018	15,98,105 (110%)	5,02,823 (35%)	21,00,928	6,79,222	21,00,928	73%
2019	17,26,656 (92%)	6,82,068 (69%)	24,08,724	7,53,087	28,71,755	84%
2020 (3rd July)	6,55,633 (34%)	2,37, 520 (22%)	8,93, 153	3,62,604	29,99,030	30%

Weekly reports were diminished by 75% in the three weeks following 22 March (average 11,367 weekly cases), compared to an average of 45,875 weekly cases during the previous weeks of 2020, when a strict nation –wide lockdown was imposed. This drop was attributable to a combination of factors including delays in entering the data onto the real-time national online TB surveillance system Nikshay, reduced attendance to health services, reassignment of health personal and a reduction in TB testing and detection. Similar reduction by 20% was noticed for February 2020 in comparison with the number of cases detected in February 2019. According to estimates the global TB case detection were decreased by an average of 25% over a period of 3 months (as compared to the level of detection before the pandemic). This will lead to a predicted additional 190,000 (56,000–406,000) TB deaths (a 13% increase), bringing the total to 1.66 (1.3–2.1) million TB deaths in 2020, near the global level of TB mortality of the year 2015.[32]

Modelling analysis by Collaboration between Stop TB Partnership and Imperial College, Avenir Health, Johns Hopkins University and USAID project to examine the potential impact of the Covid-19 response on tuberculosis in High-burden countries that included India, Kenya and Ukraine predicted that if there is a 2-month lockdown with 2 months recovery, then for India, an excess of 5,14,370 cases will be detected between 2020 and 25 (3.55% increase and an excess of TB related deaths of 1,51,120 during this period of 5 years which is an excess of 5.70%. With a three-month lockdown and a protracted 10-month restoration of services, an additional 6.3 million cases of TB will develop between 2020 and 2025 with an additional 1.4 million TB deaths during the same period. India will have an additional burden of 1,788,100 new cases (increase of 12.32%) and 511,930 excess deaths (19.31%) during this period. The modeling also found that the global response to the COVID-19 pandemic is having unintended yet drastic consequences on TB services, with lockdowns and limitations on diagnosis, treatment and prevention services expected to increase the annual number of TB cases and deaths over the next five years leading to loss of gains obtained during the past years.[33]

Operational research on tuberculosis is an important focus of the End TB strategy. Because of the above mentioned factors and difficulty in getting TB patients, close down of facilities has slowed down the operational research areas. TB Research Consortium of the Indian Council of Medical research had undertaken many priority areas like vaccine trial, newer therapeutics, active case finding in vulnerable groups and prevalence survey in the country are either stopped for the time being or recruitment had slowed down drastically.

Urgent measures need to be taken to minimize the impact of the COVID-19 pandemic on TB, and to save lives of TB patients and to get the country back on track in achieving the targets. Steps should be taken to ensure continuity of TB diagnostic services, notification, treatment and prevention services during the lockdown period and to undertake a massive catch-up effort to actively diagnose, trace, treat and prevent. Stop TB Partnership and partners has called upon the leadership of all countries—particularly those with high TB burdens—to ensure the continuity of the TB response in the time of COVID-19, to take proactive measures that include those who are most vulnerable and to provide protection against economic hardship, isolation, stigma and discrimination. Further, the NTEP need to secure the human and financial resources needed for seamless continuation of TB services amid the COVID-19 response. Recognizing that this is an unprecedented situation, the Stop TB Partnership and the WHO are continuing support for national TB Programmes and partners through their multiple technical, innovative and people-centered platforms. The Union also is providing technical help in form of guidance during this time.

Infection control practices for vulnerable populations and lessons to care for the sick should be the goal. This will benefit both the diseases. Protection of health care workers is an important issue and by all means they should be protected to continue providing TB care as front-line warriors. One important positive effects of COVID-19 is about the awareness of infection control practices, including use of face masks, cough etiquettes, and social distancing which are to be and practised after the COVID-19 pandemic that will help TB control also. TB treatment should not be stopped. TB preventive treatment, treatment for drug-susceptible or drug-resistant TB and TB-HIV need special attention. Support for uninterrupted TB preventive treatment and treatment of TB disease should be ensured alongside the COVID-19 response. TB services are not to be disrupted during the COVID19 response. The Stop TB Strategy, the Union and WHO, as well as our NTEP has published guidelines for the programs how to work during the COVID-19 pandemic.[34] People with TB should make far fewer visits to TB clinics and healthcare facilities, and should be provided with enough medication so that they can complete their treatment at home. Staff at healthcare facilities must receive urgent training on the importance of universal safety precautions, appropriate use of personal protective equipment (PPE) and criteria for self-isolation to reduce the spread of COVID-19 in TB clinics. All people with TB should receive and wear a surgical mask while attending a TB

clinic and be screened for COVID-19 through an appropriate triage system. Telephonic conversations/consultations will be the order of the day and TB patients be provided with the number to contact whenever necessary. All-oral regimens for drug-resistant TB (DR-TB) need to be administered. People with TB - HIV and who are not on antiretroviral therapy (ART) should be started on ART on the same day as TB treatment, with ART and TB prescriptions aligned. The program needs to ensure TB patients to receive necessary psycho-social, nutritional, and economic support. TB care providers are to be well briefed and must use essential personal protection equipment. The program should ensure systems that are in place for remotely monitoring side effects and minimizing hospital visits. It is of vital importance to **m**aintain uninterrupted TB drugs supply by planning early procurement and careful planning of local distribution and transportation in lock down situations. The National and sub-national governments should support special vulnerable population group because these populations are at greater risk of TB, because of living conditions, work**in**g environment or because of other socio-economic factors that result in barriers to accessing health services. Despite the emergency nature of the COVID-19 pandemic, health approaches, as well as social policies, should consider rights and gender equity. Social, legal and economic protections are to be ensured to maintain good mental health and to act against stigma and discrimination.

Although India aims to End TB by 2025, the present COVID-19 crisis and its consequential direct and indirect effects on TB have derailed the efforts and therefore, there may be a need in a shift in priority. However, if the programs continue to focus on remedial measures to reverse this trend the situation could be saved and if the NTEP does not take remedial measures, the country may have to revise its End TB target of 2025.

Declaration of competing interest

The author has none to declare.

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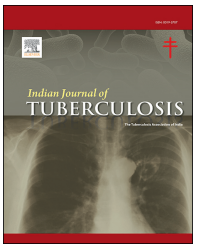

Correspondence - Post Graduate Corner

White paper on challenges and opportunities for TB elimination with focus on COVID & Post-COVID era developed through scientific roundtable resolutions at NATCON 2020

Keywords:
TB
Elimination
Challenges
Opportunities
Post-Covid
Covid

ABSTRACT

A group of TB experts with vast clinical and epidemiological experience were drawn from a pool of doctors, epidemiologists and scientists participating in NATCON 2020 Conference in a closed-door session to discuss, highlight, and prioritize key resolutions that are most pertinent at present to eliminate TB from India and other developing countries in the Covid and post-COVID era. These Scientific experts were non-industry persons who met on 17th December, 2020 and used the prevailing scientific literature along with 2019 Joint Monitoring Mission document as a starting point of the discussion on this specific topic to build an agreement upon the resolutions. After the meeting on the virtual platform, all the attending doctors gave a set of recommendations on rebuilding TB Elimination programme in the Covid and Post-Covid era. Focused scientific roundtable discussion on rebuilding TB Elimination Post-Covid. Develop actionable recommendations for the scientific community and the government leadership to consider in moving forward. To prioritize the recommendations in the categories of ***Build-Prevent-Detect-Treat***.

1. Introduction

The 2019 novel corona virus or recently renamed as severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) by the World Health Organization (WHO) was first notified from Wuhan City of Hubei Province of China in December 2019 in the form of unexplained pneumonia.[1] Disease associated with SARS-CoV-2 also termed as corona virus disease 2019 or COVID-19 has now become a potential threat to global health within a short span of time by spreading across 210 countries.[1,2]

Tuberculosis (TB) is existing as an unprecedented pandemic worldwide for the last three decades and it was declared a global health emergency by the WHO in 1993.[3] The causative agent of COVID-19 is the novel virus SARS-CoV-2, whereas for TB, it is bacteria *Mycobacterium* tuberculosis. Both can manifest with similar respiratory symptoms such as fever, cough, breathlessness, and weakness with varying severity and are dealt by the same set of doctors (pulmonologists). It is the chronicity of symptoms in TB as compared to acute or rapid progression in case of COVID 19 that helps in differentiating the patients of these respective diseases. The estimated global burden of TB is 10 million, with nearly half of them having drug resistance in 2018.[4] Of 10 million cases, 3 million (30%) remain undiagnosed. Approximately 3 of 10 TB patients (27%) in the world belong to India. Around 1400 people die and 7500 people fall ill every day due to TB even in India.

Both the diseases are associated with huge social stigma and have created an unprecedented economic impact worldwide, hence it is imperative to have India specific recommendations to rebuild or re-strategize TB Elimination programme in the Covid and Post-Covid era. The objective of the round table was precisely that and participants believe that the set of recommendations which have been finalized will help in re-energizing the NTEP with an eye on elimination by 2025.

2. Recommendations

The recommendations are dealt under four sub-headings or categories: ***Build-Prevent-Detect-Treat.***

The participants were very optimistic about the positives derived from the pandemic and the host of opportunities and possibilities which have emerged from it. "Nothing seems Impossible" was the chorus as this was reflected by overnight scaling up of well equipped modern molecular diagnostic laboratories with bio safety cabinets and overwhelming response from the administration, industry and public at large. The change that was seen in the society with respect to their health seeking behaviour using masks, social distancing and hand sanitisation which became the new normal. Media came out with plenty of information on a daily basis and kept the tempo up and the stigma (associated with COVID) down along with administration introducing "*COVID warnings symptoms*" on the ***caller tunes*** of the teeming millions. The biggest game changer was the launch of "***Aarogya Setu App***" (***ASA***); which was downloaded by 50 million users within days and now boasts of 100 million users. Such unprecedented measures ensured that India remained at the bottom of the COVID CFR list, which was the lowest in the world at 1.5%.

The TB experts were of the opinion that if the same gusto is put in early diagnosis, aggressive treatment and contact tracing of TB patients, then we can achieve the elimination plan by 2025.

3. Build

Both diseases require contact tracing and infection control measures that include hand washing, cough etiquette, social distancing, regular cleaning of surfaces, isolation, prolonged quarantine, and respiratory protection by using barriers like masks and gloves. There is no doubt that these measures have been prioritized to prevent COVID-19 but still remain underutilized for TB. Both are transmitted mainly through close contacts. Hence the first recommendation was centred at the active education, surveillance of active TB cases and their contacts. The experts believed that this participatory approach between the care givers and recipients is a win–win strategy and the gains achieved in the war on COVID shouldn't be diluted. On the contrary these efforts should be converted into TB Elimination by 2025.

> **1st*Recommendation*:** Resources and notification system used in COVID like ***"Aarogya Setu App"; Caller tunes*** & ***Advertorials in print/broadcasting media*** can be used for active education and surveillance of current cases of TB on treatment & their contacts.
>
> "***Aarogya Setu App***" can be used for *active Surveillance* of *all chest symptomatic* in NTEP in the *family or work place* at the time of "*Sputum testing*" of the patient in NTEP (***To assess their dual status of COVID and TB***).
>
> *Digital paperless reporting tool* for TB and COVID along with ***NIKSHAY***.

Some participants were of the opinion that a similar APP for TB can be developed or some modifications in the NIKSHAY may be enough to achieve the above goal of surveillance of active TB cases and their household contacts. When the user types cough, he/she should be directed to the nearest testing centre. Another suggestion was that instead of piggybacking on **ASA**, we could incorporate the features of ***Aarogya Setu APP*** into ***NIKSHAY*** for the sake of patient confidentiality and to avoid the stigma associated with neighbourhood surveillance and patient policing. Self surveillance by the patient may be more appropriate in TB. .

As COVID is still not over in India and is likely to impact the healthcare system for at least next one and a half years, we must be prepared to diagnose and treat both the diseases together in this COVID and Post COVID era by the same set of doctors. TB programme was pushed back due to COVID and the "lost cases" can be retrieved through the gains in the form of new infrastructure and increased funding in COVID care. We must take help from the Ministry of Health, State departments; STOs, Medical Institutions and other stake holders for there could be state to state variations and challenges in implementing these recommendations.

4. Prevent

Success of a Covid-19 vaccine reignites hopes that a New TB vaccine is imminent if sufficient financial resources are deployed by governments, industry, and academic institutions. ICMR is involved in the development of new more effective TB vaccines for our country, which may fructify before 2022. This fact was also highlighted by some experts. These vaccines may be a potential game changer in our fight against TB.

> ***2nd Recommendation***: The Governments and private foundations must *fast tract and prioritize the development of a TB vaccine by 2022* as an end game for TB disease. National and international scientists need to pivot from COVID to TB as their first priority for disease elimination with the same set of financing, rigor, and support.

Diagnosis and treatment for LTBI are important for TB, especially in high-risk populations especially in high prevalent country like India. TB can exist in active or latent form depending on the immune status, whereas the latent period is not defined for COVID-19.

The Indian TB National Strategic Plan (NSP) 2017–2025 is the plan produced by the government of India (GoI) which sets out what the government believes is needed to eliminate TB in India. One of the four main "thrust" or priority areas is preventing the development of active TB in people with latent TB for people in "high risk" groups. The high risk groups are the one containing immunocompromised population. Currently, India carries a huge TB burden, and therefore the burden of LTBI is proportionately large, estimated at 33–40% of the population. A huge proportion of the Indian population is amenable to progression to active TB disease from LTBI.

Japan has made the notification of LTBI mandatory since 2006. Patients detected with LTBI are offered treatment based on risk factors for progression of disease.[5] The risk factors chosen were HIV/AIDS; organ transplant; Silicosis; recent infection; poorly controlled DM and use of corticosteroids.

This approach followed by Japan has resulted in the decrease in TB burden over the years, with total number of TB cases detected falling drastically. Japanese targets for 85% treatment of all LTBI patients with requisite risk factors have been met and this has resulted in ameliorating the TB scenario in the country.

This means that without the elimination of latent TB, India's efforts to eliminate TB by 2025 will not bear fruit. Therefore pragmatism dictates that India must actively treat LTBI patients who are at risk of progression to active TB.

3rd Recommendation: An unequivocal policy of diagnosis, treatment and screening of LTBI in "high risk" groups to be developed for the country (India). ***India can make the notification of LTBI in the contacts mandatory put in the NIKSHAY at the time of DBT*** to the patient in RNTCP.

Clinical trials can be undertaken to study the efficacy of BCG in protection of adolescents and elderly population against *M.* Tuberculosis reactivation. A study from China is the first to assess the potential impact of new tuberculosis vaccines targeting older adults and to provide a comparison with adolescent vaccination, which has been a strategic focus over the past 5–10 years.[6] They match results of a study by Huynh and colleagues, which showed the importance of controlling reactivation disease in people aged 65 years or older.[7,8]

4th Recommendation: Consider ***clinical trials of re-vaccination of Mantoux negative adult population in two age targets*** between the ***Age of 15-19 years and 60–64 years*** in the Country in the post-COVID era to provide dual CD4 protection against TB & other respiratory viral infections. Such an exercise may help in the goal of TB elimination by 2025.

In developing countries like India; *BCG revaccination practices*, particularly in the *elderly* age group, may provide *additional protection against severe COVID-19*. BCG is the only vaccine available for TB that prevents dissemination, whereas for COVID-19, vaccines are still under development. *Data from few epidemiological studies reported reduced morbidity and mortality (CFR) for COVID-19 in Asian and African counties where BCG vaccination policy is adopted universally in contrast to Europe and the USA with low vaccination coverage*.[9] WHO does not recommend BCG vaccination for the prevention of COVID-19. WHO continues to recommend reserving BCG for neonatal vaccination in settings with a high risk of tuberculosis.

5th Recommendation: N-95 masks can be made mandatory for all healthcare workers who are actively involved in RNTCP henceforth by notification from the health ministry.

Many experts pointed out that masking is an important exercise in especially the highly infectious sputum positive pulmonary TB patients as the source of infection needs to be capped. The masks will have a great impact in breaking the chain of transmission especially in aerosol generating procedures undertaken by HCWs. *But this exercise may have some challenges in its implementation on a Pan India basis*. Some experts pointed out that current guidelines include this practise and only reinforcement needs to be done with *more emphasis on surveillance, infection control and biomedical waste management*. May be a subset of serious immunocompromised TB patients with drug resistant TB who are under institutional care can be provided with these masks. They may not be mandatory for drug sensitive TB patients. But as *masks have become more acceptable in society among HCWs and patients*, it is ***practise which can be encouraged voluntarily*** as seen in some more developed countries.

5. Detect

Estimation of TB and COVID-19 coinfection is not possible at this moment but could not be underestimated in India. Malnutrition, social diversity, poverty, and overcrowding in unauthorized colonies, especially slums, are also rampant in our densely populated country (1.34 million) and this can create a significant hindrance to containment plan. All these factors will be responsible for delay in diagnosis and treatment of both TB and COVID-19, which *may lead to a spike in both diseases and increased transmission of infection in community*. The impact of lockdown can be perceived as only 34 566 TB patients were notified nationwide during the past 3 weeks in comparison to 1, 14, 460 patients in early March 2020 (pre-lockdown phase).[10] ***Between 2020 and 2025 an additional 1.4 million TB deaths could be registered as a direct consequence of the COVID-19 pandemic***.

COVID-19 pandemic *led to a global reduction of 25% in expected TB detection for* 3 months – a realistic possibility given the levels of disruption in TB services being observed in multiple countries – then *we could expect a 13% increase in TB deaths*, bringing us back to the levels of TB mortality that we had 5 years ago. India will need to manage 232 665 excess TB cases for every month of lockdown and 71 290 excess TB deaths.

What we have built recently for COVID-19 pandemic like effective notification (Aarogya Setu App), promotion of active surveillance, contact tracing (active local administration), and effective infection control measures (masks, disinfectants) may provide an opportunity in future to end TB.

Community volunteers may be appointed for awareness raising, prevention, and early notification for Active TB, Latent TB and COVID-19. Molecular testing is the currently recommended method for the identification of infectious COVID-19 and just as for TB. Amongst these is the Xpert Xpress SARS-CoV-2 cartridge for use on GeneXpert machines, which are machines used in TB diagnosis. WHO is currently evaluating this cartridge as well as other tests for dual testing.

6th Recommendation: Developing a *test kit to simultaneously test the same patient for both* tuberculosis (TB) and COVID-19. Research in next-generation sequencing and pooling for large scale testing needs to be implemented.

Integrated TB & COVID laboratories based on molecular testing will pave the way for tackling TB and *any other future pandemics with point of care common testing platforms*. Need to take care of transmission risks to the patients in such set ups with good airborne infection control measures. *COPD clinics at the periphery* can be *clubbed well with screening both TB & COVID along with tobacco cessation*. ***We need to protect the TB staff so that they are not all reassigned to COVID-19***.

6. Treat

Unlike Covid-19, TB has good treatment options for both DSTB and DRTB are available.

7th Recommendation: Digital platforms such as ***Tele-consulation OPD or video-observed therapy, smart pill boxes, and other mobile phone-supported adherence strategies*** in the form of teleconsult like **99DOTS** must be ***enhanced and strengthened***.

99DOTS is a pharmaco-economic approach for monitoring and improving adherence to TB medication. 99DOTS introduces anti-TB blister pack wrapped in a custom envelope, which includes hidden phone numbers that are visible only when doses are dispensed. After taking daily medication, patients make a free call to the popped up phone number which is hidden till then, yielding high confidence that the dose was "in-hand" and has been taken. As a very high success rate (of about 99%) is expected by this remote in-built techno-supervision, it is termed as 99DOTS. Mobile phones can cover all these areas and be a boon in bringing compliance and thus TB cure for patients. Andrew et al in his study on Using Mobile Phones to Monitor Adherence to Tuberculosis Medications found that Over 90% of all doses were reported correctly using 99DOTS.[11]

During lockdown these technologies proved a boon in many places in India along with smart pill boxes and *e-pharmacies*. Many participants highlighted the *successful models of door step delivery of drugs and sample collection* along with *Video assisted DOTS* and *tele-consultations* during these months of the pandemic. ***E-Sanjivini*** *in Tamil Nadu* and ***e-pharmacy model*** *in Madhya Pradesh* with door step delivery of TB drugs were live examples given by the panellists. *The need of the hour is to scale up this model along with virtual clinics with telemedicine and VOT for DS and DR TB patients*.

The ***integrated dashboard in NIKSHAY*** will ensure a *digital paperless platform for uniform implementation with seamless integration* in the future.

8th Recommendation: Drug Resistance TB treatment should be prioritized so as to prevent DRTB from becoming an endemic disease. A ***universal regime*** needs to be ***formulated for both DS and DR TB*** patients ***preferably without an injectable drug*** to simplify the therapy.

Regimens that could treat both rifampin-resistant (RR) and rifampin-susceptible tuberculosis (TB) while shortening the treatment duration have reached late-stage clinical trials. A Markov state-transition model of 100 000 representative South African adults with TB was used to simulate implementation of the regimen **BPaMZ** (***bedaquiline, pretomanid, moxifloxacin, and pyrazinamide***), either for *RR-TB only or universally for all patients*. Using BPaMZ exclusively for RR-TB increased the proportion of all RR-TB that was cured by initial treatment from 60 ± 1% to 67 ± 1%. Expanding use of BPaMZ to all patients increased cure of RR-TB to 89 ± 1% and cure of all TB from 87.3 ± 0.1% to 89.5 ± 0.1%, while shortening treatment by 1.9 months/person.

Novel regimens such as BPaMZ could improve RR-TB outcomes and shorten treatment for all patients, particularly with universal use and may be the need of the hour in India to eliminate TB by 2025.

Acknowledgement

The scientific round table was ***moderated*** by ***Dr. Manoj Jain, Dr. Salil Bhargava, Dr. KK Chopra*** and ***Dr. VK Arora***. The representatives were drawn from various academic TB Institutions, NTEP-CTD, NTEP-State, WHO and partner organizations along with other key stake holders. Their contribution has been duly recognised in the acknowledgement. The ***rapporteur of the round table*** was ***Dr Sanjay Rajpal***.

The participants represented: *NTEP–CTD, NTEP-State, WHO, In-Country Partners, International Partners, TB Association of India, NATCON, Indian & International TB academic Institutions, FIND, UNION, USAID, Stop TB Partnership, PATH, REACH, NIRT, NITRD, Gates Foundation and Clinton Foundation*. Some of the active participants were Dr. Rohit Sarin, Dr. Raghuram Rao, Dr. Nishant Kumar, Dr. Kiran Rade, Dr. Malik Parmar, Dr. Ranjani, Dr. Surya Kant, Dr. Roopak Singla, Dr. Padma Priya, Dr. Ravi Dewan, Dr. Jyoti Jajoo, Dr. Shibu, Dr. Sara, Dr. Reuben Swamickan, Dr. Xavier Padanilam, Dr. Sahu, Dr. Ramya, Dr. Sameer Kumta, Dr. Ashwani Khanna, Dr. Radha Munje, Dr. Simon Tiberi, Dr. Nidhish and Dr. Sanjay Rajpal (*rapporteur*).

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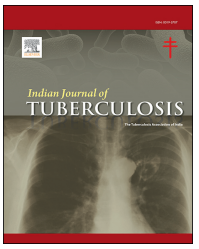

Correspondence - Post Graduate Corner

Highlights of pre conference workshop on paediatric tuberculosis

Keywords:
Paediatric TB
Multidrug resistant TB (MDRTB)
Drug Resistant TB (DRTB)

Pre conference workshop on Paediatric Tuberculosis was conducted under the banner of NATCON-2020, on the occasion of 75th National Conference of Tuberculosis and Chest Diseases on 18th December 2020 by Dr. Sangeeta Sharma. The workshop was truly an international sessional workshop covering all important aspects of paediatric tuberculosis with international faculty from all the continents of the world including World Health Organization (WHO) Geneva, USA, Australia, United Kingdom, South Africa and National pediatrics TB experts from whole of India.

The workshop enlightened the delegates on the latest recommendations in the Global and National TB Elimination Programme (NTEP) of India, including the present implementation status of the management protocols as regards specifically to children and with what is in store for this vulnerable population in the future. The detailed deliberations were very useful for the delegate doctors in their day to day clinical practice. The main highlights of the workshop were the following discussion points, namely:

The latest "WHO update on United Nations General Assembly High Level Meet (UN GA HLM) on TB targets and WHO New policy Recommendations for Pediatric TB" global performance status of the milestones and targets set in the End TB Strategy, Sustainable Development goals and pillars of UN GA HLM as regards to children showed that except Europe and the United States which were in line with achieving the targets, closely followed by South Africa, rest majority of other countries were lagging behind. Performance status in India was discussed in detail. About 3.42 lakh children get TB every year in India, which is approximately 31% of the total global case load of 12 lakh (1.2 million) and 230,000 global deaths, making India as the single largest contributing country.[1] While only 6% of the total National TB Elimination Programme (NTEP) Notification enrolment occurs in children ≤15 years which is significantly lesser than the expected projected case load as there is a significant overall paediatric case detection gap of almost 56%, which is more than 70% in infants. It was suggested that though India was making considerable progress but implementation gaps do exist and need to be plugged on all fronts. Inclusion of children as an executional priority in the National TB Elimination Programme with scaling up of newer better diagnostics including point-of-care (POC) tests, notification of all diagnosed cases in children, start of proper timely treatment with adherence monitoring, involvement of private sector and other stake holders. Further, Active Case Finding and contact tracing covering especially this vulnerable section of population, that is, children alongwith management of LTBI needs to be implemented throughout country in an endeavor to End TB in India.

Management of Paediatric TB and Drug Resistant TB as per National Tuberculosis Elimination Program (NTEP) Paediatric Guidelines of 2020 is in line with the latest WHO Consolidated Guidelines 2020 (modules 1–4) and adult National TB Elimination Program. It is a valuable guide to the attending doctors about the diagnosis and treatment of Paediatric TB (both Drug Sensitive and Drug Resistant TB strains) as per the NTEP. It addresses specifically the peculiar needs of children, in the form of their dependence on parents for drug delivery, missing of school, psychosocial and emotional disturbances especially social stigma faced by the adolescent girls was discussed in detail.

"WHO policy recommendations on TB diagnostics and future prospects", including their role in different patient subpopulations and case scenarios in children was presented. It was stressed that in the past, relying on conventional tools

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like chronic symptoms, chest radiology, tuberculin skin test would result in most paediatric cases to be clinically diagnosed as definitive diagnosis was not even attempted due to poor sensitivity and long laboratory turn around times (weeks-months). Most new cases would be presumed as having drug sensitive TB and no workup attempted for achieving microbiological confirmation and drug sensitivity testing (DST). At best, drug sensitivity testing was done only for those cases at high risk of resistance leading to delay in diagnosis and probably further amplification of resistance on the standard therapy.

Role of newer and better WHO recommended rapid diagnostic tests (WRDTs) including POC tests, aiming at achieving universal drug sensitivity in children, has been highlighted in the recent WHO Diagnostic Consolidated recommendation (Module 3).[2] Analytical presentation and evidence on performance of Xpert Ultra, with its limit of detection (LOD) of 16 cfu/ml as compared to 131 cfu/ml for Xpert MTB/Rif™ and TrueNat™, has led to the recommendation for its use in the following situations such as smear negative PTB, extra pulmonary TB and extrapolation to its use in paucibacillary disease like paediatric population and PLHIV. As disease is usually paucibacillary in children and sputum sample collection is difficult in small children, but children of all ages do have bacilli in their biological specimens and attempt should always be made to demonstrate AFB and confirm DST with WRDTs taking help of alternate specimens like induced sputum, gastric aspirate/lavage, bronchoscopy assisted lavage (IS,GA/GL, BAL) and specialized investigations like bronchoscopy, EBUS, EUS, USG, CECT, MRI etc.

Use of stool Xpert in small children, diagnostic utility of urinary lipoarabinomannan (LAM) assay in HIV positives and loop-mediated isothermal amplification (TB-LAMP) test as a replacement to smear examination because of its limited infrastructure requirements and relative ease of use to emerge a rapid point of care diagnostic test for resource limited settings was also discussed in detail. In the 11 studies conducted on stool Xpert MTB/Rif™, the sensitivity was 61% among nonHIV children and 69% among CLHIV respectively. It was highlighted that there is a requirement of sample preparation and additional apparatus such as "squeeze bottles" for stool collection and processing. This has not yet been implemented in India as sample collection is yet to be standardized and as it is highly cumbersome, this could pose a limitation in its immediate implementation though it has a definite role in small children who are unable to cough up and hence swallow their sputum making sample collection difficult. As scaling up is already underway in the national programme for easy accessibility of alternate specimens like induced sputum, gastric aspirate/lavage by training of staff in SOPs of their collection at the periphery, stool Xpert MTB/Rif™ could be a diagnostic to be implemented by programme in the future. Xpert MTB/XDR, with its ability to detect 6 drug resistance to not only rifampicin (R) but to isoniazid(H), fluoroquinolones (FQ), second line injectables (SLI) and ethionamide(Eth) is also being validated in children.

"Emerging newer drugs and regimens: present and future" is a hunt for shorter, safer and equally or more effective regimens which have been tested and tried in adults for both drug sensitive (HR sensitive) and drug resistant TB strains. Children often tend to be left out in the clinical drug trials involving newer agents. This results in a lag period in children without access to the drug innovation. Thus, data remains limited in children. Results of a phase III drug sensitive trial namely, Shorter Treatment for Minimal TB in Children (SHINE) trial in children has shown that four month of daily treatment with rifampicin, isoniazid, pyrazinamide with or without ethambutol (2HRZE/2HRE) in smear negative and non-severe TB was non-inferior to the standard six (6) month (2HRZE/4HRE) of treatment in drug sensitive TB. Further, there was no statistically significant difference in the unfavourable outcomes (treatment failure, TB recurrence, death from any cause and lost to follow up).[3] Also, results of another multicentric phase III trial on use of shorter four month regimen with daily high-dose rifapentine (P) with moxifloxacin (Mfx) (2HPZMfx/2HPMfx) has shown to be as effective as the presently used six (6) month of treatment.

While every year 25,000–30,000 children develop rifampicin resistant TB (RR TB), only 5% are started on appropriate treatment even after diagnosis and active case finding. Most conventional regimens use injectables. This can lead to permanent sensory neural deafness in about a quarter of children given these injection based regimens, resulting in a strong recommendation by the WHO to use injectable free, all-oral regimens with repurposed and newer drugs, bedaquiline(Bdq) and delamanid (Dlm). Special age related restrictions exist for these drugs in the children. WHO has recommended Bdq and Dlm for children $\geq$ 6years and $\geq$ 3years respectively based on the results of phase III clinical trials.[4] These drugs have however been given to children of all ages in situations where only limited treatment options are available, with no reported serious adverse effects.[5] Recently, 95th Subject Expert Committee (Antimicrobial and Antiviral) Meeting of Central Drugs Control Organization (CDSCO) held on 18.11.2020 has granted approval to BDQ 20mg tablet alongwith recommendation to use Bdq in children $\geq$ 5–18yrs weighing $\geq$15 kg under conditional access through NTEP. Presently, Dlm is recommended for children $\geq$ 6years in India pending approval for $\geq$ 3years from Drug Controller General of India (DCGI). Administration of crushed Bdq and Dlm tablets shows bioequivalence and 15% loss of potency respectively. Thus, there is a shift towards these novel all-oral regimens for multidrug/rifampicin resistant (RR) TB with or without resistance to other drugs. All-oral regimens with potential label expansion for new TB medicines – for example, concomitant bedaquiline and delamanid use, extended bedaquiline use for more than 6 months and age relaxations for Bdq and Dlm, if treatment options are limited.

Latent TB Infection (LTBI) prophylaxis needs to be implemented for household contacts and children of all age groups, including HIV seropaositives irrespective of CD4 count, or ART status after ruling out active disease in symptomatics. For Latent TB Infection prophylaxis, 3HP and 1HP are preferred to 6H as they are non-inferior and improve adherence. Weekly 3HP or daily 1HP can only be given in children more than 2 and 12 years respectively. Contacts of drug resistant MDR TB are given 6 months of levofloxacin. Pyridoxine supplementation is

given to all children put on anti-tubercular treatment or prophylaxis.

Conclusion

India contributes almost 31% of the global TB case load of 1.2 million children. A significant overall case detection and management gap exists. Children have been accorded executional priority in the NTEP with scaling up efforts on all fronts, with the use of newer better rapid diagnostics including POC tests, notification of all cases, proper timely treatment, active case finding, contact tracing and management of LTBI. Though disease in children is usually paucibacillary and sample collection is difficult but all efforts must be made to achieve microbiological diagnosis with universal drug sensitivity testing using rapid diagnostic tests. Paediatric and adult treatment guidelines are in concordance incorporating the appropriate age related modifications. Newer drugs and injection free all oral regimens are being tried for both drug sensitive and drug resistant TB. WHO has recommended Bedaquiline and Delamanid for children $\geq$ 6years and $\geq$ 3years respectively. Latent TB Infection prophylaxis needs to be scaled up to include children of all ages after ruling out active disease.

Conflicts of interest

The author has none to declare.

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