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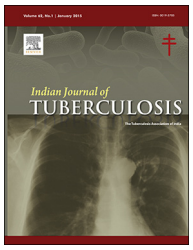

Editorial

Time to think about pathways to TB care from a different perspective

Under the Sustainable Development Goals world leaders have agreed to end TB as an epidemic. The World Health Assembly in 2014 endorsed a new strategy to end TB.[1] Recognizing that progress so far has been grossly inadequate to end TB by 2030, the Stop TB Partnership's Global Plan to End TB 2016–2020 calls for a paradigm shift in the fight against the disease.[2] Diagnosis and treatment of all TB, including drug-resistant TB and TB infection is needed. Yet appropriate treatments for TB are often not available to people for many reasons. To understand these reasons and take corrective action an important approach is to focus on the pathways people take to receive diagnosis, care and cure. This approach looks at the issues from the perspective of a person with TB and is different from the usual approach that takes a provider perspective.

In the TB community, our focus often is on providing the best diagnostic test, or screening algorithm as the beginning of the process. This focus often neglects the fact that before this interaction can take place there is a person and a family behind a series of actions, decisions and costs to arrive at a place where a diagnostic algorithm can begin. The concept of a 'TB journey' is one that the Stop TB Partnership is introducing to help better serve the millions of people who get TB each year.[3] This journey does not begin with a diagnosis nor does it end when a box is checked and the last drug is administered. Understanding and supporting people along their individual journeys will help accelerate the gains we are making in the fight against TB, in India and beyond. Research on TB journeys in India is probably more advanced than any other country, with detailed investigations about the convoluted and long paths that people must take to get a proper diagnosis and treatment, and the tests and costs that people who have symptoms can endure.[4–6] This journey as a care-seeker in India involves multiple consultations with family members, informal care providers, pharmacy outlets, private sector clinics, public sector health facilities, and often quite complex movements between these care seeking points before finally embarking on treatment.

It is estimated that 2–3 billion people, are infected with mycobacterium tuberculosis.[7] Most of them do not know that they are infected and therefore they do not start on the pathway to seek care. Some of these people will require treatment to prevent the development of active TB disease. While in many higher income countries such people often know their infection status and can seek treatment, in most other countries people cannot access diagnosis and treatment for TB infection. WHO currently recommends that in higher TB burden countries people living with HIV and childhood contacts of people with TB should receive treatment for TB infection,[8] yet people do not always have access to this therapy and coverage levels are extremely low.[7] Additionally, treatment regimens are long and onerous, and can cause side effects. Forcing a seemingly healthy small child to take medicine for 6 months is difficult – until active disease develops.

Every year an estimated 9.6 million people develop active TB disease; all of them need to be diagnosed and treated. However, currently less than two-thirds of people with active disease are diagnosed, notified and treated successfully.[7] India alone accounts for 2.2 million people with active TB disease each year and a large proportion of them are not able to access quality TB care. Many people with active TB disease initially may not appreciate that their symptoms are serious and may postpone care seeking. Prevalence surveys have consistently shown that as many as 30–40% of people with culture confirmed TB do not report symptoms.[9] However, after a worsening of symptoms, often to the point of not being able to perform daily functions, most people with active TB disease will ultimately seek care. Unfortunately, by that time they often have already transmitted the infection to others. These delays are part of the journey that people with TB endure, even before the providers are thinking of tests and diagnoses. Delays may come from needing to work to support a family, not having enough money to make a long journey to a facility where proper care is available, social norms, or other competing priorities amongst people who are the most socially and economically disadvantaged. Delayed treatment seeking also means more transmission and advanced disease which is more difficult to treat.[10] Then, the first point of care may be a pharmacy, chemical seller, traditional healer, quack, informal provider,[4] or less frequently a private sector or public sector provider all who may initially miss the root cause and leading to a longer journey for the sick individual. Care givers may or

may not identify symptoms as suggestive of TB and accordingly may or may not ask for a test for TB.[11,12] Tests are often poorly sensitive like smear microscopy, or of no diagnostic use like blood tests.[13,14] Multiple visits may be required and more will pass. Few tests are actually offered at no cost, either because of payments for consultations, or other adjunct costs.[15] Diagnostic testing may be available at the point of seeking care or the person may have to travel to another health facility or laboratory incurring additional costs and spending more time. Some care seekers may not take the test or may drop out of the diagnostic process. Others may have a form of disease that may not be diagnosed by the test being used. Most people in India and other countries where the TB burden is high are unlikely to get the best molecular test upfront at point of care,[16] and therefore some may have to go through a series of tests and repeat consultations before they are diagnosed. During the diagnostic process some people often seek alternative care providers incurring additional expenses and further increasing the time to start treatment. Once diagnosed, people must buy medicines for treatment or get it free from the national TB programme; both have several barriers. Once on treatment people with TB need to continue treatment even after symptoms have subsided for a minimum of 6 months. Education about the treatment, side effects, and what to expect can be poor and may impact treatment outcomes.[17,18]

Pathways for people with drug resistant TB are even more complex and difficult. Upfront drug sensitivity testing (DST) among new patients was limited to less than 4% in Southeast Asia in 2014.[7] In its absence, people with drug resistant TB receive inadequate first line treatment, often multiple times, before a DST is done and resistance is detected, and even then there can be long delays for treatment initiation.[19] After a diagnosis of drug resistant TB, people face significant barriers in starting treatment, including drug availability, travel and often hospital admissions, etc.[20] Once treatment has started, hospital stays, consultation visits, follow up cultures and other tests are required. All these complications take tolls on people and their families.[21]

To improve the journeys people who have TB take for quality TB care, it is essential to understand behaviour and actions taken by care-seekers, constraints and barriers, and the sociology-economic setting within which they live. Qualitative studies, such as focus-group discussions, are a useful means of studying these pathways, their determinants.[22] Population education is required for people to take early health seeking action and to demand standard-of-care services at the point of need. Pathways to care need to be fast-tracked and barriers removed for easy access to the best quality diagnosis and treatment for TB. People who have TB go through different pathways and each of them is a valuable experience that helps the national TB programme and partners learn and improve how TB care is provided to people. It is therefore important to publish experiences of people who have had TB and ensure their participation in policy making meetings as well as programme reviews.

All individual stories are different and the complexity and needs of people with TB cannot be explained nor addressed with a focus on an algorithm or drug regimen. Whether it is a person in Mumbai spending his savings on a useless blood test, the child who has extra pulmonary or drug resistant disease, a man in prison without access to basic services, or the HIV positive mother who is shunned from her family, all 9.6 million people have an individual story to tell and should be able to make the journey for illness to cure with support and compassion. Looking through the perspectives of the people with TB rather than providers is an important mindset change that must happen to ensure universal access to quality TB care.

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Review Article

Scaling up of HIV-TB collaborative activities: Achievements and challenges in India

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ABSTRACT

India has been implementing HIV/TB collaborative activities since 2001 with rapid scale-up of infrastructure across the country during past decade in National AIDS Control Programme and Revised National TB Control Programme. India has shown over 50% reduction in new infections and around 35% reduction in AIDS-related deaths, thereby being one of the success stories globally. Substantial progress in the implementation of collaborative TB/HIV activities has occurred in India and it is marching towards target set out in the Global Plan to Stop TB and endorsed by the UN General Assembly to halve HIV associated TB deaths by 2015. While the successful approaches have led to impressive gains in HIV/TB control in India, there are emerging challenges including newer pockets with rising HIV trends in North India, increasing drug resistance, high mortality among co-infected patients, low HIV testing rates among TB patients in northern and eastern states in India, treatment delays and drop-outs, stigma and discrimination, etc. In spite of these difficulties, established HIV/TB coordination mechanisms at different levels, rapid scale-up of facilities with decentralisation of treatment services, regular joint supervision and monitoring, newer initiatives like use of rapid diagnostics for early diagnosis of TB among people living with HIV, TB notification, etc. have led to success in combating the threat of HIV/TB in India. This article highlights the steps taken by India, one of the largest HIV/TB programmes in world, in scaling up of the joint HIV-TB collaborative activities, the achievements so far and discusses the emerging challenges which could provide important lessons for other countries in scaling up their programmes.

1. Introduction

Starting in the 1980s, the HIV epidemic led to a major upsurge in TB cases and TB mortality in many countries. WHO, UNAIDS and the Stop TB Partnership have set a target of halving TB mortality rates among people who are HIV-positive by 2015 compared with 2004.[1] HIV prevalence among incident TB patients in India is estimated to be 5.95%. 130,000 HIV-associated TB patients are emerging annually. India accounts

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for about 10% of the global burden of HIV-associated TB.[2] The last decade has seen some inspiring progress in the response to HIV-related TB with an estimated 1.3 million lives saved between 2005 and 2011 due to scale-up of collaborative TB/HIV activities. WHO Global TB Strategy with its ambitious targets aimed to end the global TB epidemic and reinforces a focus within the strategy on collaborative TB/HIV activities.[3]

2. India's response to HIV/TB dual infection

India's National AIDS Control Programme (NACP) has progressed a long way over the last two decades. Evidence on HIV trends and estimates has shown that India has achieved an overall reduction of HIV prevalence, new infections and AIDS-related deaths in the country. While globally there has been 33% reduction in new infections and 30% reduction in AIDS-related deaths, India has shown over 50% reduction in new infections and around 35% reduction in AIDS-related deaths, thereby being one of the successful models in the world. The adult HIV prevalence has also decreased to an estimated 0.27% in 2011 that translates into 21 lakh persons living with HIV in India.[4] Substantial progress in the implementation of collaborative TB/HIV activities has occurred globally since WHO policy guidelines on collaborative TB/HIV activities were first issued in 2004 and later on in 2012. India has been implementing HIV/TB collaborative activities since 2001 for increasing the universal access to prevention, early diagnosis and treatment services in combating the threat of HIV/TB. Department of AIDS Control and Central TB Division jointly developed a "National Framework for HIV/TB collaborative activities" in 2008, 2009 and latest in November 2013 to address the intersecting epidemics.[5] As per the National Framework, Co-ordination Committees and Technical Working Groups mechanisms are established at National, State and District level across India to strengthen coordination between NACP and Revised National TB Control Programme (RNTCP) at different levels. Intensified TB case finding at all HIV care settings, HIV testing of TB patients and presumptive TB cases, decentralised provision of co-trimoxazole preventive therapy (CPT) and linkage of HIV infected TB patients to anti-retroviral treatment (ART), isoniazid preventive treatment and infection control are core activities as per the National Framework. A systematic monitoring and evaluation mechanism exists for these joint activities, which helps to ensure good quality programme implementation and close co-ordination.

3. Rapid scale-up of facilities in NACP and RNTCP

There was significant scale-up of infrastructure across the country during past decade in RNTCP and NACP. The voluntary counselling and testing services were launched in 1997 with establishment of one facility per district for HIV testing that were scaled up as Integrated Counselling and Testing Centres (ICTC) initially stand-alone for HIV services and supported by manpower and logistics by NACP. To enhance reach of the HIV testing services, NACP adopted a strategy to establish Facility Integrated Counselling and Testing Centres (F-ICTC), i.e. HIV testing facility through the existing health facilities. This model entails provision of training to existing health staff, i.e. a nurse for providing counselling and laboratory technician for HIV testing. During NACP phase III (2007–2011), the F-ICTC model was expanded across the country. Similar to F-ICTC at Primary Health Centres, the Public Private Partnership (PPP)-ICTCs were established in private facilities (for profit/not-for-profit hospitals, laboratories, Non-Governmental Organizations, etc.), and have been supported by NACO/SACS in supply of rapid HIV testing kits, training of existing staff, quality assurance, supply of protective kits and prophylactic drugs for post-exposure prophylaxis for staff, supply of information, education and communication materials, etc. required for ICTC. Community-based HIV screening is also conducted by frontline health workers (auxiliary nurse midwives) at the sub-centre level using the Whole Blood Finger Prick Test.

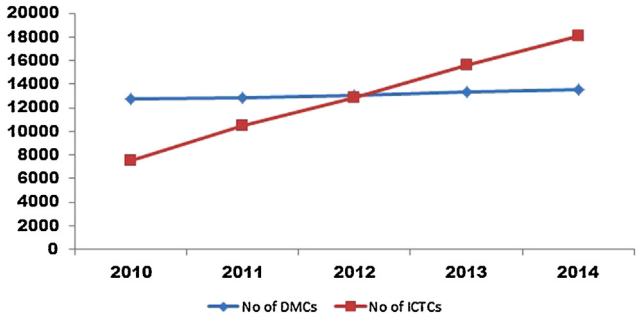

Fig. 1 – Scale-up of HIV testing facilities (ICTCs) and Designated Microscopic Centres (DMCs) for TB diagnosis in India, 2010–2014.

RNTCP has also established a nationwide laboratory network of over 13,000 Designated Microscopic Centres (DMCs), which are supervised by the Intermediate Reference Labs at the state level and the National Reference Labs and Central TB Division at the national level. Fig. 1 shows rapid scale-up of RNTCP and HIV testing facilities in India. The programme has also achieved dramatic scale-up of care, support and treatment services in India, since the roll out of ART in 2004 (Table 1). This has averted an estimated 1.5 lakh deaths due to AIDS-related causes, and it is projected that further scale-up will save around 5 lakh lives by 2017.

4. Achievements in HIV/TB collaborative activities

NACP and RNTCP have been successful in increasing access and uptake of HIV testing and counselling for all TB patients (Fig. 2). In the year 2014, about 1,034,712 out of 1,443,942 (72%) registered TB patients had their HIV status assessed. 38,721 (94%) of HIV-infected TB patients registered in 2013 cohort were put on CPT. The coverage of ART among TB patients who were known to be HIV-positive increased from 49% in 2008 to 91% in patients registered in 2013. Intensified TB case finding is implemented at all HIV care settings as per the National Policy. In 2014, total 691,013 presumptive TB cases were referred from ICTCs/F-ICTC to RNTCP Microscopic Centres and 42,971 (6%) TB

Table 1 – Scale-up of infrastructure under care, support and treatment services in India.

Facilities	2012	2014
ART Centres	355	425
Link ART Centres	685	870
Centres of Excellence	10	10
Paediatric Centres of Excellence	7	7
ART Plus Centres	24	37
Care and Support Centres[a]	0	224

[a] In 2013–2014, the scheme of CCC was revised to CSC.

cases were diagnosed among the clients attending ICTC/F-ICTCs in India. Routine screening of presumptive TB cases for HIV is being implemented in phase-wise manner throughout the country. Rapid molecular test (CBNAAT) is used for early diagnosis of TB/RIF resistance among people living with HIV (PLHIV) at more than 80 sites in India. Airborne infection control at ART Centres and associated HIV care settings has been prioritised by NACP and RNTCP.

5. Challenges in HIV/TB collaborative activities

While the successful approaches have led to remarkable achievements in HIV/TB control in India, there are emerging challenges. Some of the low prevalence states including Gujarat, Jharkhand, Odisha, Punjab, etc. have been showing rising trends in HIV, although at low prevalence levels. Ten low prevalence states of North India now contribute to 57% of new HIV infections in the country. The programme needs to strategically address these regional variations. If ICTCs and DMCs are not co-located (within the same facility), there are delays and dropouts leading to low HIV testing of TB patients or TB screening of PLHIVs. Although HIV and TB facilities are scaled up, only 67% of DMC in the country have a co-located HIV testing facility and they are mostly concentrated in six high prevalence states in the country. Co-location of DMCs and ICTCs is challenging in bigger states in North and Central India.

With increasing coverage of treatment and decreasing AIDS-related mortality, a significant number of people are likely to require first and second line ART treatment in the coming years. Major challenge for the programme will be to ensure that the treatment requirements are fully met without

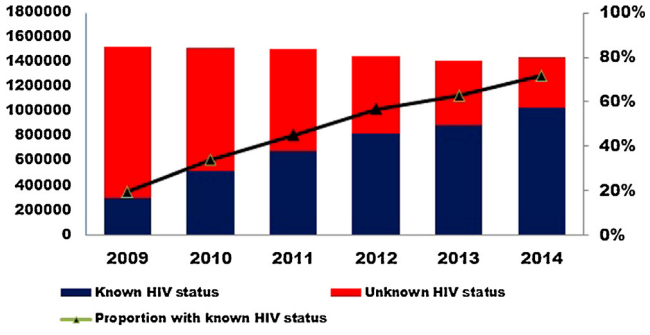

Fig. 2 – Trend of proportion of TB patients with known HIV status, India 2009–2014.

sacrificing the needs of prevention. Improving adherence on ART and avoiding drug resistance remain key challenges. India also faces a large burden of drug resistance TB which is estimated to be 2–3% of newly detected TB cases and about 12–17% among the previously treated TB cases.[6] Although linkage of TB/HIV cases to ART is improving due to revised ART guidelines in India, it is noted that mortality rates among HIV/TB co-infected patients are consistently high (13%) compared to HIV-negative TB cases. The programmes also need to realize that vertical HIV/TB interventions are not adequate to address all the requirements of the PLHIV and TB patients. There is a strong need for multi-sectorial response. Private sector involvement, especially in TB/HIV, remains a challenge. Both HIV and TB disease are associated with negative influences like social discrimination and neglect. Stigma and discrimination is an important barrier for effective treatment for TB patients and PLHIV.[7,8]

6. Conclusion

India has made substantial progress in reducing new infection and scaling up infrastructure to address the HIV/TB problem. Many challenges are emerging before the programme which needs to be addressed. Key interventions needed to achieve the desired targets include increasing the access to testing services by increasing co-location of ICTCs and DMC facilities, reducing the mortality by early diagnosis of TB among PLHIV by improving the referrals and use of newer rapid diagnostics like Cartridge Based Nucleic Acid Amplification Test (CBNAAT), decentralisation of ART services and improving adherence, ensuring the Infection control practices and implementation of INH preventive therapy, providing on-going staff training to improve the quality of their service, enhancing multi-sector coordination. As per the Standards of TB Care in India, PLHIV infection who are diagnosed with TB should receive daily regimen as HIV-negative TB patients, which needs to be scaled up in entire country.

Sustaining prevention focus and intensity in the areas where significant declines have been achieved is highly critical to consolidate the gains, while effectively addressing the emerging epidemics. To achieve the global targets of 'zero new infections, zero AIDS-related deaths and zero discrimination', more focus is needed for early diagnosis of TB among PLHIVs, improve treatment success rate, reduce stigma and discrimination and develop linkages with private sector though PPPs.

Authors' contribution

All authors (DR, AS, SKS, SAN, GRS, KSD) contributed to the conceptualisation of this viewpoint and writing manuscript. All authors (DR, AS, SKS, SAN, GRS, KSD) revised the paper for important intellectual content, reviewed the final draft and agreed on the decision to publish.

Conflicts of interest

The authors have none to declare.

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Review Article

Accelerating TB notification from the private health sector in Delhi, India

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ABSTRACT

Introduction: In India, almost half of all patients with tuberculosis (TB) seek care in the private sector as the first point of care. The national programme is unable to support such TB patients and facilitate effective treatment, as there is no information on TB and Multi or Extensively Drug Resistant TB (M/XDR-TB) diagnosis and treatment in private sector.
Objective: To improve this situation, Government of India declared TB a notifiable disease for establishing TB surveillance system, to extend supportive mechanism for TB treatment adherence and standardised practices in the private sector. But TB notification from the private sector is a challenge and still a lot needs to be done to accelerate TB notification.
Methods: Delhi State TB Control Programme had taken initiatives for improving notification of TB cases from the private sector in 2014. Key steps taken were to constitute a state level TB notification committee to oversee the progress of TB notification efforts in the state and direct 'one to one' sensitisation of private practitioners (PPs) (in single PP's clinic, corporate hospitals and laboratories) by the state notification teams with the help of available tools for sensitising the PP on TB notification – TB Notification Government Order, Guidance Tool for TB Notification and Standards of TB Care in India.
Results: As a result of focussed state level interventions, without much external support, there was an accelerated notification of TB cases from the private sector. TB notification cases from the private sector rose from 341 (in 2013) to 4049 (by the end of March 2015).
Conclusion: Active state level initiatives have led to increase in TB case notification.

1. Introduction

India accounts for the highest tuberculosis (TB) burden in the world. An estimated 2.2 million TB cases (incidence, includes HIV-TB) were reported in 2014.[1] It is estimated that private health sector in India manages 40% of TB cases and nearly half of self-reported TB patients were missed by TB notification system.[2] Notification is one of the earliest measures taken in health practice, especially done for communicable and other acute diseases where an individual case may be the indication that a disease outbreak is occurring.[3]

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Non-standardised practises in the private sector and lack of supervision for ensuring treatment adherence have increased treatment interruptions and subsequent drug resistance among TB symptomatic in the country. In India, 71,000 multidrug-resistant TB (MDR-TB) cases are estimated to emerge annually among notified pulmonary TB cases,[1] while a similar volume of cases are expected to be managed by the private sector but remain un-notified. In order to curb all non-standardised practices, Government of India declared TB as a notifiable disease on 7th May 2012.[4] Notification gives an opportunity to support private sector for better practices with reference to Standards TB Care in India (STCI) which include helping the patients to get right diagnosis, treatment, follow-up, contact tracing chemoprophylaxis and facilitates social support systems.[5] The Revised National Tuberculosis Control Programme (RNTCP) has introduced a web-based case-based online reporting platform called 'Nikshay' which enables notification of TB cases from either public or private sector using ICT applications – (a) 'Nikshay' (Case-Based Web Online application) itself, (b) convenient web-login or (c) mobile apps for the purpose of direct notification of TB cases in 'Nikshay' TB notification portal (http://nikshay.gov.in/HFUSER/HFLogin.aspx).

However, weak notification of TB cases from the private practitioners (PPs) in 'Nikshay' web-portal due to inadequate measures for effective private health sector engagement is a key challenge. Until December 2013, in Delhi state, only 583 health facilities were registered in 'Nikshay', of which 564 were registered from five out of 25 chest clinics only. These health facilities in Delhi notified only 320 patients. In Delhi, number of TB cases notified by private sector per 100,000 population is 9.5, which is very less in comparison to private TB notification from other states like Maharashtra (17.4) and Gujarat (24.7).[6]

Previous studies have looked into the causes of delay and programmatic challenges related to knowledge assessment and gaps of private health care providers on notification.[7–9] But there is limited information on the utility of existing TB notification mechanisms through ICT-based applications for improving TB notification.

Therefore, to accelerate TB notification from the private health sector, we did an intensified TB notification drive in the year 2014 with objectives to improve private health facility establishment (HFE) registration in 'Nikshay', to sensitise health care providers in the private sector about TB being a notifiable disease and to establish mechanisms for notification of TB cases. This study describes initial experience in accelerating TB notification from the private providers using various ICT-based applications in Delhi, India.

2. Methodology

2.1. *Study design and period*

Descriptive study from 1st January 2014 to 31st March 2015.

2.2. *Study setting*

In Delhi, a predominantly urban state, RNTCP is currently being implemented in a flexible mode through the State TB Control Department, headed by a State TB Officer, 11 Revenue Districts and 25 Chest Clinics covering an estimated projected population of 176 Lakhs. The TB infrastructure in the state has been aligned with National Health Mission (NHM) since April 2013. In this alignment, at administrative unit level, there is appropriate representation of key stakeholders like the Delhi Government, Municipal Corporation of Delhi, New Delhi Municipal Council and autonomous NGOs under the Integrated District Health Society (IDHS) umbrella of NHM. At the implementation level, there is decentralised service delivery with equal participation of all stakeholders, thus making everyone responsible for development. The private sector in Delhi is diversified and complex in nature, having large number of single clinics, secondary and tertiary hospitals, corporate hospitals and private laboratories.

In 2014 year, Delhi State TB Control Programme took special initiatives for accelerating notification of TB cases. A state level TB notification committee was constituted to oversee and plan the notification process with the Director, State Training and Demonstration Centre (STDC) as the chairperson of the committee, under the overall supervision of the State TB Officer of Delhi. The State TB Notification Committee constituted of medical officers from the state TB control office, selected district TB officers, representatives from the STDC and a RNTCP Medical Consultant. Two-pronged strategy for improving private and public sector TB notification was adopted.

In the private sector, key PPs were identified randomly from the line lists of private health establishments in the districts based on the general outpatient department (OPD) load. The identified PPs were directly 'one to one' sensitised by state level TB notification teams for providing options on TB notification modalities using ICT based applications – 'Nikshay' (Case-Based Web Online application) and convenient web-login or mobile apps for the purpose of direct notification of TB cases in 'Nikshay' TB notification portal. PPs were sensitised with the help of available tools for sensitising the PP on TB notification – TB Notification Government Order, Guidance Tool for TB Notification and Standards of TB Care in India. Those PPs who could not directly notify TB cases using web-login were actively supported by the field staff (TB health visitors or TBHVs and field staff of IPAQT laboratory network) for collection of data on TB notification in the standard TB notification format and getting it entered in 'Nikshay' by the district data entry operators (DEOs). State TB Notification Committee convened total 10 focussed meetings with all stakeholders for strengthening TB notification in the state. A live online demonstration on direct TB notification using web-login, by generating username and password through establishing linkages with the district nodal officer for TB notification, was given by the RNTCP Medical Consultant to PPs, wherever it was possible. All queries by the private providers on TB notification modalities were addressed by the State TB Notification Committee during the sensitisation visit itself. Besides, active collaboration with the interface agencies like Delhi Medical Association (DMA) for placing TB notification advertisements periodically in their news bulletin and Initiative for Promoting Affordable Quality TB Tests (IPAQT) to facilitate notification from the IPAQT partner laboratories were established.

For improving notification from the public sector besides registration of RNTCP TB cases in 'Nikshay', a state level policy

decision to notify all TB cases in 'Nikshay' TB notification portal whose feedback on treatment initiation could not be obtained after a month of referring out such cases outside the district was taken.

2.3. *Study participants*

Registered private providers in 'Nikshay' in the identified Chest Clinics from January 2014 to March 2015 and TB case notification by them.

2.4. *Data collection and variables*

Data on HFE registration of private health care facilities and number of TB patients notified by the private providers were pushed from the 'Nikshay' database and was imported electronically into the excel sheet. Number of registered PPs visited for direct 'one to one' sensitisation on TB being a notifiable disease and given 'Nikshay' web-login access for direct TB notification was entered in a structured performa.

2.5. *Data analysis and validation*

Data analysis was done through use of Microsoft Excel. Data were tabulated and the following was calculated – proportion of PPs started to notify post-sensitisation using various ICT based applications. Pulled data on health establishment registration details from 'Nikshay' database were cross-checked for correcting any errors with the line list of the health establishment visited, captured in the structured performa, manually.

3. Ethical considerations

Necessary consent was taken from the State TB Notification Committee to perform the study experiments. Since this study was a review of reports pulled from the 'Nikshay' database and did not involve patient interaction, individual patient consent was deemed unnecessary.

4. Results

A total of 102 PPs were sensitised on TB notification modalities, of which 40 PPs were also given live on-line demonstration using web-login (Table 1). Eight private laboratories were sensitised in Nikshay and direct web-login process (see Table 1). 83% (85/102) of PPs post-sensitisation started to notify TB cases in Nikshay and total of 2837 TB cases were notified by the private sector (see Table 1). 38% (15/40) of PPs directly notified 110 TB cases using web-login access and 100% (70/70) PPs notified 2727 TB cases in Nikshay using active support from the field staff, including of IPAQT (see Table 1). 1212 TB cases with no referral feedback were notified from the public health facilities in 2014, including that of medical colleges, in Nikshay TB notification portal (see Table 2). Total of 1932 HFE was registered in 'Nikshay' by 31st March 2015 (see Table 3).

Table 1 – Notification by private practitioners (PPs) based on notification modalities using ICT-based applications – Nikshay, direct web-login or mobile apps from 1st January to 31st March 2015.

Type of health facilities	No. sensitised – 'One to One' using Nikshay and Guidance Tool on TB notification	No. sensitised – 'One to One' using web-login and Nikshay Guidance Tool on TB notification	Total PPs sensitised	No. of PPs started to notify using active support from the field staff (TBHV's and District DEO)	No. of PPs started to directly notify using web-login	Total PPs started to notify	TB notification using web-login directly by PP	TB notification from active support from the programme using web-login	Total TB notification
Private practitioner – clinic (single)	24	14	38	24	4	28	12	532	544
Private practitioner – hospital (multi)	38	18	56	38	11	49	98	897	995
Private practitioner – laboratory	8	8	8	8	0	8		1298	1298
Total	70	40	102	70	15	85	110	2727	2837
Proportion of PPs started to notify post-sensitisation				100%	38%	83%			

Table 2 – TB notification by type of health facilities until 31st March 2015.

Type of health facilities	Total TB notification
Private practitioner clinic (single)	544
Hospital (multi)	995
Laboratory	1298
Public hospitals	1212
Total	4049

Table 3 – Proportion of health facility establishments (HFE) notifying TB cases from 2Q13 to 2Q15.

Quarter	Health establishment (HE) registration	% of HFE notifying TB cases
2Q13	341	
3Q13	583	
4Q13	612	(31) 5%
1Q14	1240	(42) 4%
2Q14	1433	(63) 4%
3Q14	1556	(79) 5%
4Q14	1565	(88) 6%
1Q15	1932	(102) 5%
2Q15	2103	(109) 6%

5. Discussion

This is the first study which demonstrates that direct 'one to one' sensitisation of the PPs can accelerate TB notification, especially, with the help of active support from the field staff in entering the notified TB cases using ICT-based applications. The possible implications on accelerated TB notification drive on policy and practice are discussed next.

Firstly, as a result of such focussed activities in 2014, vis-à-vis, constitution of a state level TB notification committee to oversee the progress of TB notification efforts closely in the state and direct 'one to one' sensitisation of PPs (in single PPs clinic, hospitals and laboratories) by the state notification teams, there was an upsurge in TB notification from the private sector in Delhi from the private sector in 2Q15 in comparison to 2Q13 (Fig. 1).

Secondly, 70/70 (100%) PPs started to notify using active support from the field staff (TBHVs and District Data Entry Officers), clearly suggesting that close collaboration with the district programme staff for extending supportive service to PPs is of paramount significance for ensuring TB notification from them. Also, there was an initiation by 15/40 (38%) PPs to directly notify TB cases using web-login services in 'Nikshay', as a convenient and easy method on TB notification, without depending or burdening the district programme staff to collect and enter the notified TB cases in 'Nikshay'. This initiative required online demonstration of direct notification of TB cases using web-login and this could be done only to small number of PPs for their sensitisation using laptop. The programme could scale up this initiative by constituting small district level teams with a medical officer for interacting with the PPs on routine basis. 'Nikshay' also needs to be popularised as a notification tool that helps in understanding the burden of TB and serves as a surveillance system to monitor the TB case management in the country. Coincidently, none of the PPs used mobile application as a tool to notify TB cases.

Thirdly, it is observed that notification of TB cases from the private sector rose significantly in 2014. But this is only 102/1932 (5%) of registered private HFEs in 'Nikshay' notified TB cases by end of March 2015 (see Table 3). More than 90% of private health facilities in Delhi are still not notifying the public health authorities. Therefore, though active state level initiatives have led to increase in TB case notification, not much improvement is seen in number of PPs notifying the cases. Lack of regulatory measures at policy level and lack of awareness among private health care providers are major challenges in TB notification implementation.[9] Public health efforts thus need to be aligned through a framework of complementary measures, both regulatory and enabling, that promote an adequate level of vigilance.[10]

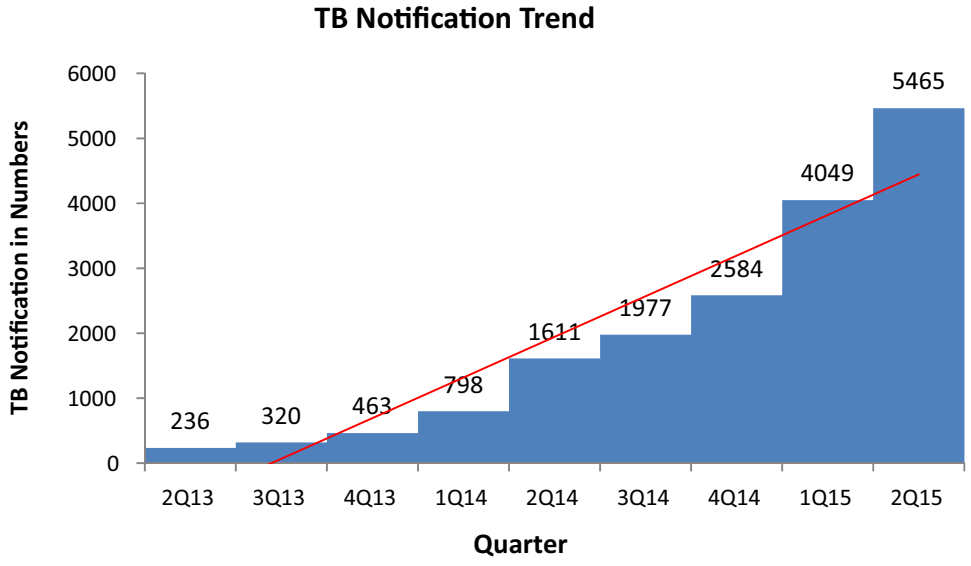

Fig. 1 – TB notification trend in Delhi from 2Q13 to 2Q15.

Fourthly, programme could capture 1212/4049 (29%) of public sector notification in Nikshay (see Table 2), which otherwise could have missed to be notified in the programme. It is therefore pertinent to notify such TB cases, which are without any referral-feedback information, in Nikshay as a strategy to improve TB notification from the public sector, especially medical colleges.

This study has limitations. We could not look into the aspect of active surveillance measures to improve TB notification from the private sector and follow-up the notified TB cases, from the PPs for supporting TB treatment as per the STCI. Information on notified TB and MDR TB patients (diagnosed in the private laboratories) needs to be followed up for understanding adherence to TB treatment, linkages to social supports to TB patients and can be a topic for further research.

Direct 'one to one' sensitisation of the PPs can accelerate TB notification, especially with the help of active support from the field staff in entering the notified TB cases using ICT-based applications. State level initiatives and collaborations with interface agencies can improve awareness on TB notification. Notification of TB should be made compulsory at all levels.

Conflicts of interest

The authors have none to declare.

Authors' contribution

Conceived and designed the study by DK/KK/AK.
Conducted the study: DK/KK.
Analysed the data: DK/KK/NB/TP.
Contributed reagents/materials/analysis tools: NB/TP.
Wrote the paper: DK/KK.
Contributed to discussion: DK/KK/AK/NB/TP.

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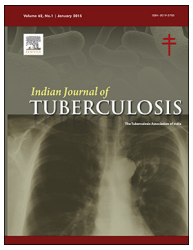

Review Article

Vaccines against tuberculosis: A review

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ABSTRACT

Tuberculosis (TB) has taken toll of many lives, therefore a need of effective TB vaccine, which can provide sufficient immunity to prevent developing of disease has been felt for a longer time.

BCG, the only available vaccine, though prevents against severe form of primary tuberculosis in paediatric population, failed to have its efficacy in pulmonary patients. Few candidates are in the pipeline undergoing clinical trial. An extensive research is needed to ensure their safety and efficacy before their acceptance as a TB vaccine to be incorporated in national immunization programmes.

1. Introduction

Tuberculosis (TB) is one of the oldest diseases known to mankind having its description in Vedas. The causative organism, a rod-shaped, non-spore forming aerobic bacilli engulfs about two million lives worldwide annually. Despite highly effective available pharmacotherapy, the control programmes are being blocked by accelerating effect of HIV co-infection and development of MDR strain. *Mycobacterium bovis* based BCG vaccine, available for last 90 years, has shown some protective efficacy in combating serious paediatric TB like tubercular meningitis and disseminated tuberculosis. But it proved to have poor outcome in terms of protecting pulmonary disease and especially the non-paediatric population.[1] Therefore, improved TB control strategy is of utmost importance and a more effective TB vaccine is a major public health priority.[2]

2. Problem and magnitude of tuberculosis

As per WHO global TB report 2014, almost 9 million people developed the disease worldwide with 1.5 million mortality, of whom 3,60,000 were tested positive for HIV. About one-third of world population is infected asymptomatically with tubercular bacilli,[3] and at the risk of reactivation. India accounted for one-fourth of total global incidence of TB cases annually which equals 2.3 million out of 8.6 million total cases in 2012. National Tuberculosis control programme was launched almost 50 years ago and revised in 1993 with country-specific goals and objectives. In the history of TB control in India, there are three important setbacks: first, BCG was found to be ineffective in TB control in 1979; second, the rapid spread of HIV, with TB as its commonest opportunistic infection since 1984 and third, the emergence of MDR and its prevalence since 1992. TB drains national economy worth US $ 23 billion

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annually. Therefore, it warrants a structural renovation to cover loop holes and incorporation of de novo ideas in control programmes for a better TB control.[4]

3. Presently used vaccine-BCG

Mycobacterium bovis bacillus Calmette–Guerin (BCG), the only licensed TB vaccine, is a live attenuated strain of *M. bovis* which was passaged by Calmette and Guerin almost hundred years ago. *M. bovis* was isolated by Nocardia in 1902. Two French Scientists – Calmette, a Physician and Guerin, a Veterinarian – sub-cultured the organism for 230 generations using culture media containing glycerol, potato and beef bile. BCG was thus developed after a long series of passage of virulent *M. bovis* strain from year 1908 to 1921 and it took almost 13 years to obtain a safe TB Vaccine. It was then first administered orally in 1921 in Paris and injected intradermally in 1927. In India, first intradermal BCG vaccine was administered in Madanapalle, Andhra Pradesh in 1948. Since 1921, many clinical trials in different parts of the world have evaluated the efficacy of BCG in preventing TB disease. These trials demonstrated that BCG confers consistent protection against severe forms of childhood TB like meningitis and disseminated TB, and leprosy, in endemic zones.[5–9] However, it provides highly variable protection against pulmonary disease, which alone accounts for the major burden of global TB, and is an important cause of morbidity and mortality.[10] Furthermore, revaccinating with BCG during adolescence in a population already vaccinated at birth, does not improve the protective efficacy as shown in a large, randomized controlled trial (RCT) in Brazil.[9] BCG is currently being administered to neonates of high-risk populations as part of the World Health Organization (WHO) Expanded Programme on Immunization (EPI).[11]

BCG is indicated for the infants living in high endemic TB areas or to the infants and children at risk of TB exposure in otherwise low endemic areas. BCG efficacy varies from 0% to 80%. It protects neonate and children against serious forms of primary disease such as meningeal and disseminated TB and saves 40,000–70,000 children a year. BCG vaccination also prevents massive lympho-haematogenous dissemination of the disease.

4. Limitations of BCG

Despite its record of being the most widely used vaccine in the world, BCG has no apparent impact on the growing global TB epidemic and the latter still remains the second leading cause of infectious disease deaths. It is not well in protecting TB in adults or the cases of latent TB (due to which nearly two million people die each year). BCG is not reliable against pulmonary TB, which accounts for most of the TB disease worldwide. It is also not recommended for use in infants infected with HIV for the fear of increased risk of severe BCG-related complications. Apart from these, it has got some negative recommendations or contraindications too. BCG vaccine should not be given to persons with impaired immunity, symptomatic HIV infection, known or suspected congenital immunodeficiency, leukaemia, lymphoma, or generalized malignant disease. It is also contraindicated in patients taking immunosuppressive treatment (e.g. corticosteroids, alkylating agents, antimetabolites and radiatiotherapy) and should be avoided in pregnancy.[11] Revaccination with BCG in adolescents does not improve protective efficacy.[5]

5. Future vaccines

Vaccines are known to be an incredibly efficient health tool, and TB vaccines that prevent adolescents and adults from developing infectious TB would be the single greatest advancement in the global fight against the disease.[2]

5.1. *Expectations from TB vaccine*

Future vaccine should be safe and effective in preventing TB in children, adolescents and adults, including people living with HIV. It should provide protection against all forms of TB – including LTBI MDR and XDR TB.[2] It should reduce the cost and burden of TB on patients, health care systems and national economies. Safety and efficacy in at-risk infants, children and adults (including people living with HIV) should be assured.[5] Timing of vaccination should not interfere with other childhood immunizations. It should be feasibly manufactured on a mass scale and should be stored and administered under low-technology conditions.[5]

5.2. *Science behind future vaccine*

To achieve the effective protection against *M.tb* by vaccination, there is a need to induce the relevant arm of the immune system. *M.tb* is an intracellular bacillus and primarily remain inside the macrophages. Therefore, humoral immunity is unlikely to play a major role in protection against *M.tb* and intact cellular immunity response is essential,[11] especially the Class II restricted CD4+ T cells.[2] The increased susceptibility to TB disease in HIV infected patients signifies the importance of Class II restricted CD4+ T cells in protective immunity to *M.tb* Class I restricted CD8+ T cells also play an important role probably in maintaining the latent state, although the precise mechanism by which they work is yet not clearly elucidated. Interferon gamma (IFN-g) secreted by both CD4+ and CD8+ T cells may have a role by inducing the activation of the infected macrophages and by increasing expression of MHC Class I and II proteins on antigen presenting cells. Defect in IFN-g gene in mice has shown to markedly increase the susceptibility to *M. tb*[2] and treatment with exogenous recombinant IFN-g delayed the infection in these mice. In humans, mutation in IFN-g receptor 1 gene, makes individual more susceptible to severe atypical mycobacterial infections[11] and perhaps also to TB. Therefore, as far as currently available information is concerned, an ideal vaccine against TB should seek to induce both CD4+ and CD8+ protective T cells.[5]

5.3. *T cell inducing vaccines*

In general, induced antibody level has been used as a potency marker in new vaccine development. However, in the last

10–15 years, there have been developments of new vaccines which can induce T cells with or even without antibodies, e.g. protein/adjuvant combinations, DNA vaccines and recombinant viral vectors. However, there are several limitations in inducing both strong CD4+ and CD8+ T cell responses. Protein/adjuvant combinations are able to induce good CD4+ T cells and antibodies level, but currently there are no adjuvants effective in inducing substantial CD8+ T cell responses. In mice, DNA vaccines have been very potent, but in humans and other primates, they have only weak responses. On the other hand, recombinant viral vectors are very good at inducing CD4 + and CD8+ T cells as well as antibodies. However, none of the two delivery systems have been found to induce very high levels of antigen specific T cells when used alone. Hence, use of several of these subunit vaccines in combination has led to the development of heterologous prime boost immunization strategies to induce higher levels of cell-mediated immunity.[5]

5.4. *Heterologous prime-boost immunization strategies*

In heterologous prime-boost immunization strategies, two different vaccines are used. Each of them expresses the same antigen and is administered several weeks apart. The incorporation of recombinant modified vaccinia virus Ankara (MVA) to boost DNA vaccine in the murine model of *Plasmodium berghei* infection led to induce higher levels of antigen-specific class I-restricted CD8+ T cells. This heterologous prime-boost immunization offers greater levels of protection against challenge than homologous boosting with either vaccine alone.[5]

5.5. *Vaccine candidates in pipeline*

In TB vaccine development, two main strategies are being pursued. The first is to replace current BCG vaccine with an improved whole organism mycobacterial priming vaccine, which can be either an attenuated strain of *M.tb* or a recombinant BCG. The second is to develop a subunit boosting vaccine, which will be enhancing the protective efficacy of BCG when administered after it.[11,12]

5.5.1. *Replacements for bacille Calmette–Guerin*

5.5.1.1. *Mycobacterium vaccae*. Initially, an inactivated whole cell *Mycobacterium vaccae* (*M. vaccae*) was developed as a therapeutic TB vaccine candidate.[13] Variable results were obtained in different geographical areas. In South Africa, there was no difference between treatment and placebo groups in a double blind RCT.[14] *Mycobacterium vaccae* has since been evaluated as a prophylactic vaccine. In Tanzania, one RCT of five doses of *M. vaccae* in BCG-vaccinated, HIV-infected patients demonstrated significant protection against the secondary endpoint of definite TB, although not against the primary endpoint of disseminated bacteraemic disease[15] or the other secondary endpoint, Probable TB.

5.5.1.2. *Attenuated strains of Mycobacterium tuberculosis*. A second approach in improving BCG as a mycobacterial priming vaccine is to develop an attenuated strain of *M.tb*. Currently, there are two groups, evaluating the safety and protective efficacy of attenuated strains of *M.tb* in preclinical models.[15] One of these vaccine candidates can confer level of efficacy comparable with or superior to BCG in guinea pigs and non-human primates.[16] There are some safety concerns with the evaluation of attenuated strains of *M.tb* in clinical trials and two recent WHO workshops have addressed how this might best be achieved.[17,18] With detailed preclinical safety studies, it is likely that at least one of these candidates will advance to early stage clinical testing in the next few years.[15]

5.5.1.3. *Recombinant bacille Calmette–Guerin strains*. There are two recombinant strains of BCG that have been evaluated in clinical trials. The first one was developed at the University of California, Los Angeles.[19] This vaccine candidate, engineered to over-express the 30 kDa major secreted antigen from *M.tb*, was more protective than the wild-type strain in the guinea pig model. This candidate was safe and immunogenic in humans in phase I clinical trial.[20] A second approach is to generate a BCG strain that targets the specific immune-processing pathways. A recombinant BCG strain, constructed to secrete listeriolysin, has been shown to be more protective than the wild-type strain in the murine model.[21] Listeriolysin increases acidification of the phagosome, leading to antigenic escape to the cytoplasm and enhanced cross-priming of an HLA class I-restricted CD8+ T cell response. This vaccine has now been evaluated in a phase I clinical trial in Germany and is currently being evaluated in a phase IIa trial in South Africa. A combination of the two approaches described above is being pursued by the TB vaccine foundation Aeras, who have developed a recombinant strain of BCG expressing several antigens from *M.tb* together with perfringolysin. This recombinant BCG is soon to enter into a phase I clinical trial in the US.[15]

5.5.2. *Bacille Calmette–Guerin booster*

5.5.2.1. *Vaccines*. In this alternative strategy, it is to leave the BCG in its current form, to be administered in early infancy, and to develop a booster vaccine, which can be administered at a later point in time. Such vaccines may either be administered as booster vaccine in infancy, soon after the BCG vaccination, or might be administered in adolescence, when the effects of BCG are starting to wane. Development of a subunit booster vaccine requires two things: first, the selection of antigen(s) for inclusion in the vaccine and the other one a suitable antigen delivery system. Two main approaches in the development of a booster vaccine are currently being pursued in this field. First is to use a protein vaccine, where an adjuvant needs to be co-administered in order to induce a higher level of cellular immunity. The alternative approach is to develop a recombinant viral vector, as some viruses themselves are an effective method of inducing strong cellular immunity.[15]

5.5.2.1.1. *Protein-adjuvant vaccines. (i) M72/MTB72F*

This is being developed by Glaxo-SmithKline Biologicals (GSK). The recombinant protein used is MTB72F (now remade as M72), a 72 kDa polyprotein of the M. tb32 and M. tb39 antigens, M72 is to be delivered with the GSK adjuvants, which are a mixture of either a liposomal formulation (AS01) or a proprietary oil-in-water emulsion (AS02) with the immunostimulants monophosphoryl lipid A and Quillaja saponaria fraction 21. Preclinical efficacy studies with this protein–adjuvant combination have demonstrated efficacy

comparable with BCG in mice and guinea pigs.[22] A phase I study with MTB72F and AS02A, administered as a three dose regimen in purified protein derivative (PPD)-negative healthy volunteers demonstrated a moderately reactogenic profile, with nine of 12 subjects (75%) experiencing a Grade 3 adverse event.[23] This trial demonstrated the induction of antigen-specific CD4+ T cells measured both by short-term enzyme-linked immunosorbent spot (ELISPOT) assay where peripheral blood mononuclear cells (PBMC) are restimulated in vitro for one day prior to transferring to an ELISPOT plate and flow cytometry. The median peak response measured on short-term ELISPOT assay, at day 56 (day of second vaccination), was approximately 100 spot-forming cells per million PBMC. IgG antibody responses was also demonstrated which peaked at day 56. A further phase I study with this vaccine candidate demonstrated a similar safety profile and comparable CD4+ T cell responses, with no detectable CD8+ T cell responses.[24] This vaccine is currently being evaluated in phase IIa studies in South Africa.[15]

(ii) Hybrid I/HyVAC IV

Here, the protein used is a fusion protein made up of two secreted antigens, the early secreted antigenic target 6 (ESAT 6) and antigen 85B, developed by Statens Serum Institut, Copenhagen and when administered with the mucosal adjuvant LTK63, it led to improvement in BCG-induced protection in mice but not guinea pigs.[25,26] In phase I clinical trial, this fusion protein was given with an adjuvant, composed of an anti-microbial peptide and an immunostimulatory oligodeoxynucleotide, IC31 (Intercell, Vienna). There was induction of antigen-specific CD4+ T cells, as measured by short-term ELISPOT assay (approximately 600 spot-forming cells per million PBMC) and enzyme-linked immunosorbent assay (ELISA).[27] However, ESAT6 inclusion has a potential risk to confound the tests routinely used for the diagnosis of latent *M.tb* infection.[28] In the above said phase I trial with Hybrid I, 2 of the 12 subjects (17%) in the high dose group developed a positive Quantiferon gold response and one of them remained positive at 131 weeks post-vaccination.[27] This problem got rectified in next generation vaccine HyVAC IV, where ESAT6 was replaced by another *M.tb* antigen, TB10.4.[29] Phase I trial with Hybrid I is on the way in Ethiopia and that with HyVAC IV in Sweden and South Africa.[30]

5.5.2.1.2. *Recombinant viral vectors. (i) Aeras 402/Ad35-85B-TB10.4*

Here, recombinant replication deficient adenovirus, serotype 35 (Aeras 402), is exploited as vector in carrying the vaccine candidate, a fusion protein made up of antigens Ag85A, Ag85B and TB10.4 from *M.tb*. One limitation of this approach is pre-existing immunity induced by natural adenoviral exposure, e.g. with AdHu5 strain,[31] though of lower intensity[32] Preclinical studies have shown this vaccine as immunogenic and protective in mice and non-human primates.[33,34] A phase I clinical trial in South African with BCG-vaccinated adults demonstrated high levels of particularly monofunctional CD8+ T cells, with acceptable safety profile.[35] A phase II safety and efficacy clinical study is underway in HIV-infected adults and BCG-vaccinated infants in South Africa.[30]

(ii) Modified vaccinia virus Ankara 85A

MVA85A is a novel TB vaccine candidate originally developed by the University of Oxford with funding from the Wellcome Trust. This vaccine is a recombinant strain of modified vaccinia virus Ankara (MVA) expressing antigen 85A from *M.tb*. MVA is an attenuated strain of vaccinia virus and has an excellent safety profile and does not replicate in human tissue. It was used at the end of the smallpox eradication campaign in Southern Germany.[36] Antigen 85A is part of the immunodominant antigen 85 complex, a component of which is part of many of the subunit vaccines in development. MVA85A can improve BCG-induced protection in mice, guinea pigs, non-human primates and cattle in preclinical studies.[26,37–39] Phase I/IIa clinical trials with MVA85A in Gambia and South Africa demonstrated good safety profile, and acceptable immunogenicity.

The results from Phase IIb trial, involving 2797 HIV-negative infants previously vaccinated with BCG showed that MVA85A met the primary objective of safety. However, the differences between the rates of TB development in infants vaccinated with MVA85A and in the placebo group were not statistically significant, indicating that MVA85A was not effective in preventing TB in BCG-vaccinated infants. MVA85A was well tolerated and induced modest cell-mediated immune responses. Reasons for the absence of MVA85A efficacy against tuberculosis or *M. tuberculosis* infection in infants need exploration. Researchers are further exploring the results from the Phase IIb infant study and will carefully evaluate data for any trends that may be helpful for the development of MVA85A and future vaccine candidates. The partners will consider whether the MVA85A immune response can be improved or whether MVA85A combined with other vaccines is worth evaluating. While MVA85A was not effective at preventing TB or latent TB infection in HIV-negative, BCG-vaccinated infants, the candidate may still be proven effective in other populations, such as adults. No matter what direction is taken by the MVA85A programme, the candidate's Phase IIb trial marks another step forward in the effort to develop new, effective TB vaccines. The entire portfolio of candidate will benefit from the knowledge and data gained from this study.[40].

5.6. *Ideal vaccine strategy*

Ideal vaccine strategy should be based on the natural history of TB, which is complex. Healthy uninfected individual when exposed to a source case can result in primary infection with *M. tuberculosis*.[41] This primary infection can develop either into primary TB disease or into a persistent, asymptomatic infection. Individual often remains clinically silent throughout a person's life.[41] However, in about 10% of people, this latent infection may ''reactivate'' and cause symptomatic TB disease.[41] Thus, according to natural history of TB, there may be at least three possible vaccination strategies: first is to prevent primary infection and disease following exposure; second to prevent reactivation in those already infected and third, an immunotherapeutic adjunct to standard TB treatment, which would be given along with anti-tubercular treatment to enhance recovery of TB patient.[41] Each of these strategies has their own advantages and disadvantages.[41]

6. Conclusion

BCG is the only Tuberculosis Vaccine available since its development about 90 years ago, and it is the most widely administered vaccine in the world, but it has failed to stop the global TB epidemic. However, it does reduce the risk of severe paediatric TB disease and protect the neonates and children against serious forms of primary disease such as meningeal and disseminated TB. BCG vaccination also prevents massive lympho-haematogenous dissemination. Considering all these, it should be continued to be used until a better TB vaccine is available. After a long time, great efforts to develop a new vaccine are started and are going on. There is urgent need to enhance these efforts and to provide economic support to the group.

Summary

TB, one of the oldest diseases known to mankind, is still not under control. The disease remains one of the leading infectious causes of death throughout the world. The only licensed vaccine bacille Calmette Guerin (BCG) derived from *Mycobacterium bovis* confers highly variable protection against pulmonary disease. The most efficient way to control the TB epidemic would be an effective vaccination regimen. Cellular immunity plays an important role in protection against TB. Thus, all the new vaccines in development are focused to induce a strong and life time cellular immunity. In vaccine development against TB, there are two main strategies being pursued. The first is to replace current BCG with an improved one, which can either be a recombinant BCG or an attenuated strain of *M.tb*. The second strategy is to develop a subunit booster vaccine, which is to be administered after BCG vaccination to enhance the protective efficacy of BCG.

Conflicts of interest

The authors have none to declare.

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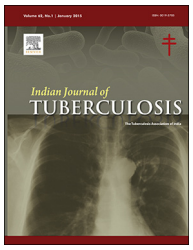

Original Article

Cost analysis of different diagnostic algorithms for pulmonary tuberculosis varying in placement of Xpert MTB/RIF

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ABSTRACT

Background: We undertook cost analysis for diagnosis of pulmonary tuberculosis (PTB) using present algorithm under Revised National Tuberculosis Control programme and using Xpert MTB/RIF (Xpert) as frontline test or in conjunction with smear microscopy and/or chest radiography.

Methods: Costs were estimated for different strategies: (A) present algorithm involving sputum smear examination followed by antibiotic trial in smear negative patients, repeat smear examination (RE) if symptoms continue and chest radiography if RE negative; (B) direct Xpert; (C) smear microscopy followed by Xpert in smear negative patients; (D) radiography followed by Xpert in those having abnormal pulmonary shadows; and (E) smear examination followed by radiography among smear negative patients and Xpert in presence of abnormal pulmonary shadow.

Results: Cost to program was estimated lowest with Strategy A and highest with Strategy B. Compared to the latter, program cost reduces by 7%, 4.5%, and 17.4% by strategies C, D, and E, respectively.

Cost to the group of individuals with presumptive PTB and their attendants is significantly higher for Strategy A compared to other four strategies. Among the latter, the patients' cost was minimum with Strategy B and maximum with Strategy C.

Program cost per case diagnosed was lowest by Strategy A and highest by Strategy B. Patient cost per case diagnosed was highest by Strategy A and lowest by Strategy B. Using Xpert, Strategy E had the lowest program as well as overall cost per case diagnosed.

Conclusion: Strategy E may be chosen for diagnosis of PTB. When resources would no longer be a constraint, direct Xpert would reduce costs incurred by the patients.

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1. Introduction

Revised National Tuberculosis Control Programme (RNTCP) in India has hitherto recommended an algorithmic approach for diagnosis of pulmonary tuberculosis (PTB) (Fig. 1).[1] Individuals with presumptive PTB disease presenting at Health Centers implementing RNTCP with persistent cough for ≥2 weeks are subjected to smear microscopy of two sputum specimens (one spot, one early morning) at designated microscopy centers (DMCs). Smear microscopy is usually performed using Ziehl–Neelsen (Z-N) stain based microscopy by conventional microscope. However, in high workload centers, smear examination is undertaken using the Light Emitting Diode based Fluorescent Microscopy. If either specimen is positive for acid fast bacilli (AFB), diagnosis of smear positive PTB is made. If both specimens are negative on initial sputum smear examination (ISE), a trial with broad spectrum antibiotics for 10–14 days is recommended. If symptoms persist, repeat smear examination (RE) by sputum smear microscopy is recommended. In the event of RE being negative for AFB, chest radiography using X-ray is advised and patient is diagnosed to be suffering from smear negative PTB in the presence of a suggestive shadow on radiograph. For this purpose, there is one DMC per 100,000 populations on an average and one laboratory technician (LT) is posted at each of the DMCs. A senior tuberculosis laboratory technician (STLS) based at the tuberculosis unit (TU) covering 500,000 populations undertakes supervision of DMCs under its jurisdiction. LTs are trained at the district and STLSs at Intermediate Reference Lab (IRL) at the State level. External quality assurance (EQA) mechanism involves onsite visits by STLS and random blinded rechecking of a proportion of slides at the district level.[2] In addition, the district level LTs and STLSs are assessed through a set of standard slides prepared at the IRL. The State level laboratory team consists of a Microbiologist and Senior LTs who undertake supervisory visits to the districts periodically. For radiography, facilities available with the general health system are utilized.

However, the sensitivity of sputum smear examination is known to be low.[3] Also, recent studies have shown poor implementation of algorithm after smear negative result at ISE.[4,5] With the approval of a new rapid molecular test by World Health Organization, the Xpert MTB/RIF (Cepheid USA) an automated Cartridge Based Nucleic Acid Amplification Test (CBNAAT) having a sensitivity of 88% and specificity of 98% for PTB, the future prospects of increased diagnostic efficiency and early case finding look brighter than ever before.[6,7] Under RNTCP, testing by Xpert MTB/RIF is presently restricted to presumptive multi-drug resistance tuberculosis patients and for diagnosis of PTB in children and HIV sero-positive patients.[8] Scaling up Xpert MTB/RIF as a frontline test for diagnosis of PTB would require significant investment of funds. Therefore, we undertook a cost analysis for PTB diagnosis if Xpert MTB/RIF is

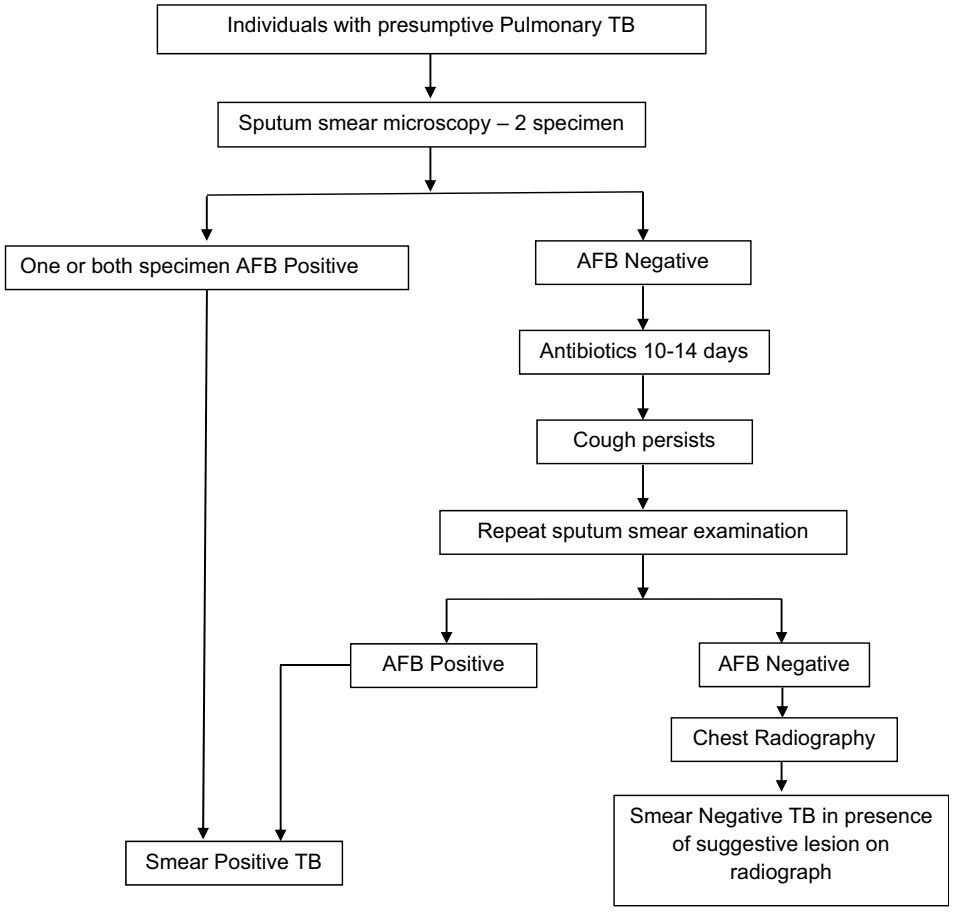

Fig. 1 – Strategy A – Present algorithm for diagnosis pulmonary TB.

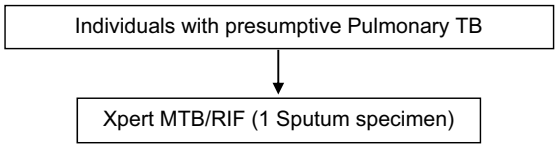

Fig. 2 – Strategy B – Testing by Xpert MTB/RIF as a frontline diagnostic test for pulmonary TB.

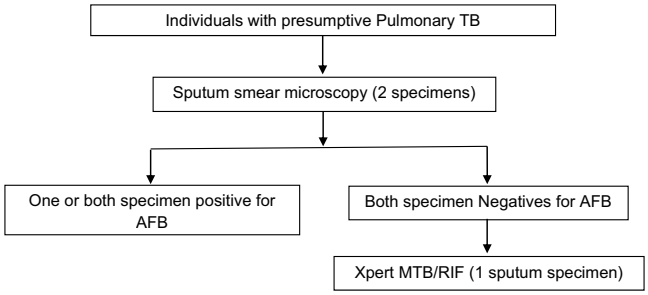

Fig. 3 – Strategy C – Smear microscopy followed by Xpert MTB/RIF in smear negative patients for diagnosis of pulmonary TB.

used as a singular frontline test or in conjunction with smear microscopy and/or chest radiography with variation in its placement in the diagnostic algorithm. We also undertook cost analysis for the present algorithm if implemented efficiently. The strategies thus considered for cost analysis are presented as flow chart in Figs. 1–5.

2. Material and methods

The cost analysis was undertaken for the number of presumptive PTB patients enrolled under RNTCP in 2012 in

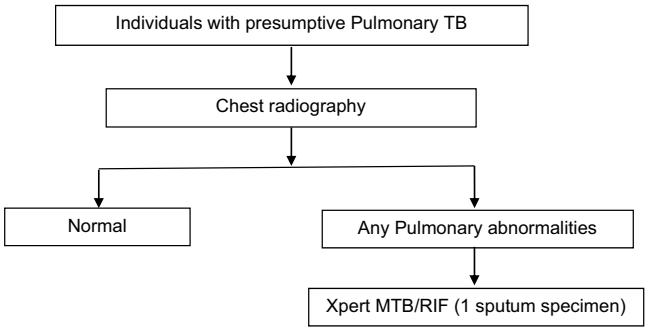

Fig. 4 – Strategy D – Radiography followed by Xpert MTB/RIF in those having abnormal pulmonary shadows for diagnosis of pulmonary TB.

Karnataka state having a population of 62.8 million residing in 31 districts.[9]

The potential case yield and the numbers of tests – sputum microscopy, Xpert MTB/RIF, chest radiography, and number of antibiotic trials – required for the number of individuals with presumptive PTB presenting at health centers providing RNTCP services since the year 2012 per 100,000 population, by each strategy were first estimated. Follow-up sputum smear examinations considering the potential case yield by each strategy were included for costing. Further steps involved estimating the annual cost of DMCs where Xpert MTB/RIF machines would also be placed, cost of radiography, antibiotic trial, costs of district and state level laboratory, and costs incurred by patients and their attendants.

Cost analysis was undertaken using the existing data sources: RNTCP routine surveillance system, published studies on accuracy of chest radiograph, Xpert MTB/RIF and its field evaluation, implementation of present algorithm, RNTCP

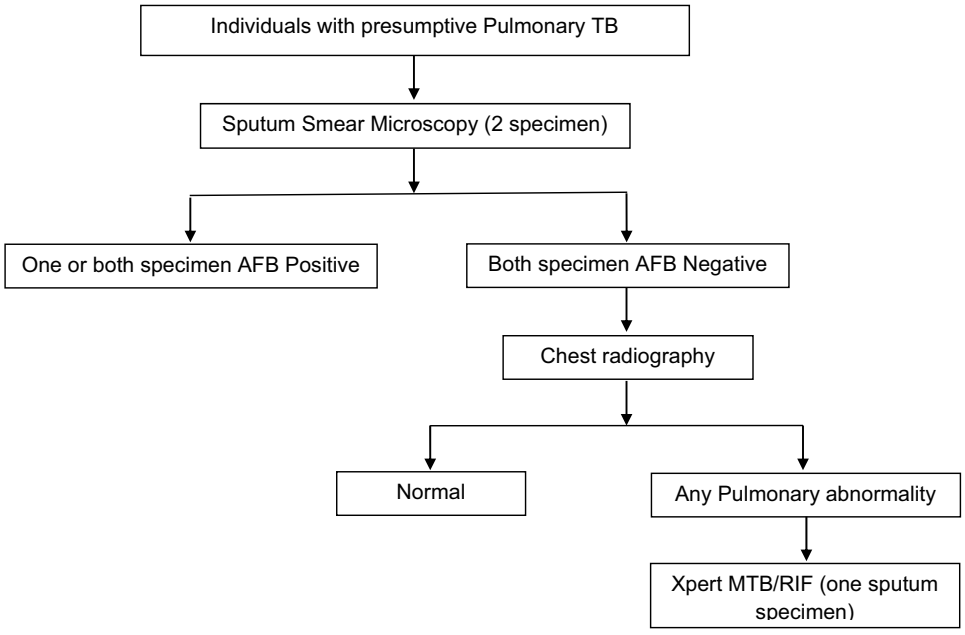

Fig. 5 – Strategy E – Smear examination followed by radiography among smear negative patients and Xpert MTB/RIF in presence of abnormal pulmonary shadow, for diagnosis of pulmonary TB.

Table 1 – Potential case yield of true PTB cases per 100,000 population, by diagnostic strategy.

Strategy	No of cases	Basis of deriving potential yield
A (present)	112	Cases found smear positive on ISE (a) = 90 Of the remaining 44, cases diagnosed by RE or radiograph (b) = 22 *[22 (50%) of 44 cases given antibiotics experience transient remission of symptoms and would be missed* [12]] Total potential case yield = a + b
B (GX)	118	Sensitivity of Xpert MTB/RIF for all PTB cases = 88%[7,13]
C (SM–GX)	119	Cases found smear positive on ISE (a) = 90 Of the remaining 44, cases detected by Xpert MTB/RIF (b) = 29 *[Sensitivity of Xpert MTB/RIF for smear negative pulmonary TB cases = 68% cases*[7,13]] Total potential case yield = a + b
D (CX–GX)	117	Cases picked up by radiography = 131 *[sensitivity of radiograph = 98%*[7,13]] Of them, cases detected by Xpert MTB/RIF (a) = 124 [*Sensitivity of Xpert MTB/RIF for all PTB cases = 88%*[7]] Total potential case yield = a
E (SM–CX–GX)	118	Cases found smear positive on ISE (a) = 90 Of the remaining, cases picked up by radiography = 43 Of them, cases diagnosed by Xpert MTB/RIF (b) = 38 [*Sensitivity of Xpert MTB/RIF for all PTB cases = 88%*] Total potential case yield = a + b

Table 2 – Number of tests required, including follow-up smear examination, per 100,000 population, by diagnostic strategy.

		Strategy				
		A[b] (present algorithm)	B (GX)	C[c] (SM–GX)	D[d] (CX –GX)	E[e] (SM–CX–GX)
No. of smears to be examined, at	ISE	1636	–	1636	–	1636
	RE	436	–	–	–	–
	Follow-up[a]	224	236	238	248	236
Antibiotic trial		728	–	–	–	–
Radiography		205	–	–	818	728
Xpert MTB/RIF[f]		–	818	728	410	320

ISE: initial sputum smear examination; RE: repeat sputum smear examination.
[a] One specimen each at the end of Intensive Phase and end of treatment for the no. of cases to be diagnosed by strategy as per the potential case yield given in Table 1.
[b] 818 presumptive PTB patients undergo smear positive on ISE; 90 of them being smear positive, 728 require antibiotic trial. Of them, 510 (70%) assumed to become asymptomatic and 218 (30%) require RE of 2 sputum specimens. Expecting 6% to be positive at RE[14], remaining 205 require radiography.
[c] 818 undergo smear examination at ISE, after 90 being smear positive, 728 undergo testing by Xpert MTB/RIF.
[d] 818 undergo radiography; of them, 410 (90 smear positive and 44% of remaining 728 based on findings of a recent study[15]) expected to have abnormal pulmonary shadow undergo testing by Xpert MTB/RIF.
[e] 818 undergo smear examination at ISE; 90 of them being smear positive, 728 being smear negative undergo radiography. Of them, 320 (44%) expected to have abnormal pulmonary shadow undergo Xpert MTB/RIF.
[f] One sputum specimen to be tested by Xpert MTB/RIF.[6]

guidelines for manpower, salaries, consumables, maintenance of building and equipment, and current procurement costs and fee for radiography under public health services. Therefore, the present cost analysis study did not involve direct experiments with humans and thus approval of the Institutional Ethics Committee and any patient consent was not required.

2.1. *Potential case yield*

In Karnataka state, of 818 individuals with presumptive TB disease examined under RNTCP for every 100,000 populations in the year 2012, 90 (11.0%) were found to be smear positive.[9] All of these were presumably diagnosed on ISE since RE is practically not being implemented, as observed during our recent studies.[4,5] In Xpert MTB/RIF evaluation studies, the additional yield of cases positive by Xpert MTB/RIF among presumptive PTB patients smear negative on ISE was about 33%.[10,11] With sensitivity of one sputum specimen test with Xpert MTB/RIF at 68% for smear negative PTB,[7] there would be 44 additional cases making it a total of 134 in the cohort of 818 individuals with presumptive PTB.

The potential case yield by each strategy per 100,000 populations and the basis of calculation is given in Table 1. The potential case yield by using the present diagnostic strategy would be lower at 112 per 100,000 populations when compared to the other four strategies in which the estimated potential case yield varied between 117 and 119 (Table 2).

2.2. *Numbers of tests required*

Numbers of different types of tests required for each strategy and the basis of calculations are given in Table 3.

2.3. *Annual cost of each DMC*

Cost calculations included the capital cost of civil works required for up-gradation of a given room to DMC and of

Table 3 – List of items included for costing for each laboratory (DMC and/or Xpert MTB/RIF) per lakh population – Karnataka State.

Item		No. of units by strategy				
		A (present algorithm)	B (GX)	C (SM–GX)	D (CX–GX)	E (SM–CX–GX)
Civil works for laboratory and its maintenance	Civil works	Unit = RNTCP capital cost allocation for civil works per DMC[16] converted to annual cost considering life span of fixtures at 25 years (includes overhead tank, electrical fittings, wash basin, furniture)				
	Maintenance of laboratory building	Unit = RNTCP allocation for civil works per DMC per year[16] (includes running expenses and electricity bill)				
Manpower	Laboratory technicians	LT – 1 for each strategy[16]				
Equipment[a]	Binocular microscope[b]	1 for each strategy				
	Xpert MTB/RIF[c]	–		1 for each strategy		
	Autoclave[b]	–		1 for each strategy		
	AC[b]	–		1 for each strategy		
AMC of equipment[16]		1 Binocular Microscope		1 Microscope, 1 Autoclave, 1 AC, calibration of Xpert MTB/RIF		
Consumables[16] (sputum cups[d], slides[d], cartridges and other consumables[e])		Quantity of each consumable estimated as per the no. of tests (smear examination, Xpert MTB/RIF) required by strategy, as given in Table 2.				
Transport of sputum specimen		Assuming 20% of sputum specimens required to be transported from PHC to DMC[17]				

EQA: external quality assurance; AC: air conditioner.
[a] Capital cost of all equipment converted to annual cost considering life span of 10 years.
[b] As per market price in 2012.
[c] As per GOI negotiated price with Foundation for Innovative New Diagnostics (FIND) for four module machine.
[d] Considering 20% wastage.
[e] As required for Ziehl–Neelsen microscopy.
Follow-up examination is undertaken by sputum microscopy – one specimen each at the end of Intensive Phase (IP) and end of treatment.

Table 4 – District level annual cost for EQA and training per district – existing algorithm, Karnataka State.

Item		No. of units by strategy				
		A (present algorithm)	B (GX)	C (SM–GX)	D (CX–GX)	E (SM–CX–GX)
Civil works for Laboratory and its maintenance	Civil works	Unit = RNTCP cost allocation for civil works per DTC[16] converted to annual cost considering life span of fixtures at 25 years (includes overhead tank, electrical fittings, wash basin, furniture, slotted angle racks for storing reagents)				
	Maintenance of Laboratory Building	Unit = RNTCP allocation for civil works per DTC per year[16] (includes running expenses and electricity bill)				
Manpower	Senior TB Laboratory Supervisor	5 for each strategy[a]				
	Laboratory Attendant	1 for each strategy[16]				
Equipment[b]	Binocular Microscope[c]	Capital cost of 5 microscopes converted to annual cost considering life span of 10 years				
	Xpert MTB/RIF[d]	–		1 for each strategy		
	Autoclave[e]	–		1 for each strategy		
	AC[e]	–		1 for each strategy		
AMC of equipment[16]				5 Microscopes, 1 Autoclave, 1 AC, calibration of Xpert MTB/RIF		
Consumables[16] (sputum cups[e], slides[e], cartridges and other consumables[f])				Includes cartridges for EQA, training, POL for local travel by STLS		
Training of LTs[16]		For training in two batches of 5 LTs each, includes course materials and refreshments				

DTC: District TB Center.
[a] Average of 5 TUs per district.
[b] Capital cost of all equipment converted to annual cost considering life span of 10 years.
[c] As per market price in 2012.
[d] As per GOI negotiated price with Foundation for Innovative New Diagnostics (FIND) for four module machine.
[e] Considering 20% wastage.
[f] As required for Ziehl–Neelsen microscopy.

Table 5 – Annual Cost of EQA and training at State level, Karnataka State.

Item		No. of units by strategy				
		A (present algorithm)	B (GX)	C (SM–GX)	D (CX–GX)	E (SM–CX–GX)
Manpower	Microbiologist for EQA	1 for each strategy				
	Sr. LTs for EQA	2 for each strategy				
Equipment[a]	Binocular Microscope[b]	5 for each strategy				
	Xpert MTB/RIF[c]	–	1 for each strategy			
	Autoclave[b]	–	1 for each strategy			
	AC[b]	–	1 for each strategy			
AMC of equipment[16]			5 Microscopes, 1 Autoclave, 1 AC, calibration of Xpert MTB/RIF			
Consumables[16] (sputum cups[d], slides[d], cartridges and other consumables[e])			Including cartridges for EQA,			
Training of STLs[16]		For training of 8 STLS in a single batch, includes course materials and refreshments				
Travel for EQA supervision		1 Microbiologist and 1 LT for 10 visits of 5 days each				

[a] Capital cost of all equipment converted to annual cost considering life span of 10 years.
[b] As per market price in 2012.
[c] As per GOI negotiated price with Foundation for Innovative New Diagnostics (FIND) for four module machine.
[d] Considering 20% wastage.
[e] As required for Ziehl–Neelsen microscopy.

equipment converted to annual costs and their maintenance, salaries, and consumables (Table 3).

2.4. Cost of antibiotics

For Strategy A, cost of antibiotics at current rates was calculated for amoxicillin capsules thrice a day for average of 12 days for each individual with presumptive PTB smear negative on ISE.

2.5. Cost of radiography

Cost of radiography was calculated at a consolidated rate of Rs. 150 per radiograph (this amount is required to be paid for radiography by patients other than individuals with presumptive PTB to the public health service in Karnataka; it is free for the latter). The cost for infrastructure, service, and salaries were not included as the radiography facilities are also used for other purposes.

All the above costs calculated per 100,000 populations were scaled to the entire population of state.

2.6. Annual district level laboratory cost (Table 4)

For district level laboratory cost, annual cost of one DMC to be maintained for EQA of sputum examination in the district under each strategy, besides procurement and maintenance of five microscopes for EQA and training were included. For strategies B–E, cost of one Xpert MTB/RIF machine (for training) and consumables and maintenance thereof were included. Additional cost for salary of one lab attendant and 5 *STLSs* and annual cost of training of two batches of LTs in each district were added, as per RNTCP norms.[16]

Each district level cost was multiplied for 31 districts.

2.7. Annual state level laboratory cost (Table 5)

For state level laboratory cost, annual cost of one DMC to be maintained for training and EQA besides procurement and maintenance of five microscopes was included. Additional cost for salary of one microbiologist and two senior LTs and annual cost of one training course for 8 STLSs including organizing expenses, course material, travel, and food were added. Expenses for supervision included travel for 10 visits per year by one microbiologist and one LT covering 3 districts on each visit over 5 days.[18] For strategies B–E, cost of one Xpert MTB/RIF machine (for training) and consumables and maintenance thereof were included.

All the above costs were summed up to obtain the program cost for the entire state.

2.8. Cost incurred by patients and attendants

For each strategy, the number of visits by 818 individuals with presumptive PTB *disease* to complete the required stages of the respective algorithm was calculated (Table 6). Cost of travel per visit was considered using public transport for the average distance to be traveled. Cost of loss of wages for each visit was calculated considering per capita income in 2012 as per World Bank estimates.[19]

The total costs to the program and to the patients and their attendants were added to obtain total costs.

2.9. Cost per case PTB diagnosed

The program cost by each strategy was divided by the potential yield of cases to obtain cost per case diagnosed. Similarly, cost incurred by all presumptive PTB patients and their attendants and the total costs per PTB case diagnosed were calculated.

3. Results

The overall cost to the program was estimated to be the lowest with the present strategy (Strategy A) and highest when Xpert MTB/RIF is used as a frontline diagnostic test (Strategy B). Compared to the latter, the program cost reduces by about 7% when Xpert MTB/RIF is used after smear microscopy (Strategy C), by 4.5% when used after screening by radiography

Table 6 – Cost incurred by individuals with the presumptive pulmonary TB and their attendants[f], Karnataka State.

Item	No. of visits by strategy				
	A (present algorithm)	B (GX)	C (SM–GX)	D (CX–GX)	E (SM–CX–GX)
Travel	7466[a]	2108[b]	5204[c]	2952[d]	5840[e]
Loss of wages	Includes loss of wages considering per-capita income for total number of visit-days as above for respective strategy				

[a] 1636 (2 visits each by 818 patients) at ISE, 436 (2 each by 218) for RE, 1456 (2 each by 728 patients) for antibiotics, 205 for radiography, 224 for follow-up microscopy – 1 specimen at each of 2 follow-ups, 1 for radiography.
[b] 1 visit each for 818 patients at diagnosis and 236 for follow-up microscopy.
[c] 1636 (2 visits each by 818 patients), 1 each by 728 for Xpert MTB/RIF 238 for follow-up microscopy.
[d] 1 visit each for radiography by 818 patients, 410 for Xpert MTB/RIF and 248 for follow-up.
[e] 1636 (2 visits each by 818 patients), 728 for radiography, 1 visit each by 320 for Xpert MTB/RIF, 236 for follow-up microscopy.
[f] Equal number of visits by attendants as above, for each strategy.

Table 7 – Consolidated costs by strategy (Indian rupees in millions), for Karnataka state, by diagnostic strategy.

Cost components	Strategy				
	A (present)	B (GX)	C (SM–GX)	D (CX–GX)	E (SM–CX–GX)
Annual DMC lab cost	103.43	445.04	413.09	346.28	293.17
Cost of antibiotics	31.08	–	–	–	–
Cost of chest radiograph	5.79	–	–	77.06	68.58
District level lab cost	29.70	33.62	33.56	33.56	33.56
State level lab cost	1.95	1.13	1.13	1.13	1.13
Sub-total: program cost	172.67	479.79	446.78	458.03	396.44
Patient cost	1031.50	287.27	605.35	348.74	300.54
Total cost	1204.17	767.06	1053.13	806.77	696.98

Lab: laboratory.

Table 8 – Cost per PTB case diagnosed, in Karnataka state, by diagnostic strategy.

		Strategy				
		A (present)	B (GX)	C (SM–GX)	D (CX–GX)	E (SM–CX–GX)
Program cost per case	INR	2454.9	6474.5	6078.9	6233.6	5304.7
	USD[a]	46.1	121.5	114.0	117.0	99.5
Patient cost per case	INR	14,665.4	3876.6	8238.7	4746.3	4021.6
	USD[a]	275.1	72.7	154.6	89.0	75.4
Total cost per case	INR	17,120.3	10,351.1	14,317.6	10,979.0	9326.4
	USD[a]	321.2	194.2	268.6	206.0	175.0

INR: Indian Rupees; USD: US Dollars.
[a] Average exchange rates in 2012.

(Strategy D), and by 17.4% when used after screening by radiography among smear negative patients (Strategy E).

The estimated cost to the overall group of symptomatic patients and attendants is highest for the present strategy by 1.4–1.7 times when compared to the other four strategies (Table 7). Among the latter, the patients' cost was estimated to be minimum with Strategy B and maximum with Strategy C.

The overall societal cost (including the costs to the program and to the patients and their attendance) was estimated at the highest with the Strategy A and the lowest with Strategy E (Table 7).

The program cost per case diagnosed was estimated to be the lowest by Strategy A when implemented with full efficiency and highest by Strategy B (Table 8). The patient cost per case diagnosed was highest by Strategy A and lowest by Strategy B. Among the algorithms using Xpert MTB/RIF, Strategy E had the lowest program cost as well as overall cost per case diagnosed.

4. Discussion

The estimated program cost was lower with the present algorithm, than all the strategies using Xpert MTB/RIF but the patient-cost was very high. Also, the estimated potential yield was lowest with this strategy. Moreover, present algorithm is unlikely to achieve the diagnostic potential due to poor implementation efficiency. In the recently conducted studies in Karnataka state, almost all the smear negative PTB cases registered for treatment were diagnosed without having gone through the algorithm.[5] An earlier study had demonstrated that as many as two-thirds of chest radiograph based diagnosed

cases could be false positive cases.[20] This not only would lead to loss of precious resources in wrongly treating with anti-TB drugs but also in the health system missing the actual diagnosis resulting in higher morbidity and mortality, and calls for introduction of Xpert MTB/RIF for PTB case finding under RNTCP. Among the four algorithms deploying Xpert MTB/RIF, cost to the program per case diagnosed was estimated to be lowest when ISE was followed by screening using chest radiography among those smear negative on ISE followed by testing by Xpert MTB/RIF in those with any pulmonary abnormality on radiograph (Strategy E). On deploying Xpert MTB/RIF as a frontline test (Strategy B), the cost to the program was highest but the cost to the patient was lowest. However, cost to patient by the strategy E was only marginally higher compared to Strategy B. The estimated potential case yield by different strategies deploying Xpert MTB/RIF was estimated to be similar. Therefore, it would be desirable to select Strategy E for case finding under RNTCP. When resources would not be a constraint, direct Xpert MTB/RIF for all individuals with presumptive TB disease would not only reduce the patient-cost but also help in early diagnosis of pulmonary TB as well as early detection of resistance to rifampicin.

High costs incurred by patients and their attendants also suggest that re-imbursement of transport costs and compensation for loss in wages to all presumptive PTB patients to complete the required stages of the respective algorithm would not only reduce the financial burden on them and their family but also facilitate completion of the algorithm.

This analysis is good for a comparison and provides inputs to policy makers in developing appropriate scale-up plans and helps decide on the placement of Xpert MTB/RIF in the diagnostic algorithm for PTB. It may, however, be noted that the cost estimations per case diagnosed by each strategy may not be applicable to other situations, as the values will differ depending upon proportion of actual PTB cases among presumptive PTB patients. Another uncertainty pertains to the assumption that with Strategy A, 30% of presumptive PTB patients need to undergo radiography after antibiotic trial. In a neighboring country, 64% of those prescribed antibiotics after smear negative result on ISE did not return to the health center.[14] Of those who returned, 60% were required to undergo radiography.[14] More reliable data on this aspect needs to be generated. Another minor limitation of our analysis pertained to the numbers of follow-up sputum examinations. The patients likely to be initial defaulters, loss to follow-up, and those who die during the course of treatment were not subtracted. This proportion being small and affecting only the cost of sputum cups and slides is not expected to affect our estimates significantly.

For further validation of the interpretations made in the present analysis, it would be useful to conduct comparative evaluation of the actual case yield by different algorithms employing Xpert MTB/RIF, under program conditions. Cost effectiveness studies in terms of cost per DALY saved or death prevented would also be useful.

5. Conclusion

Our cost analysis suggests that the program cost per pulmonary TB case diagnosed is lower by using the present algorithm, provided it is implemented with full efficiency compared to all the other plausible diagnostic strategies using Xpert MTB/RIF. However, studies have shown that the present algorithm is not being implemented efficiently after a smear negative result on ISE. Therefore, the full potential of the present algorithm is not being utilized. Moreover, the cost incurred by the overall group of individual with presumptive pulmonary TB disease is very high with the present algorithm. This calls for introduction of Xpert MTB/RIF for increasing the case finding efficiency. Our analysis suggests that the diagnostic strategy where initial sputum examination is followed by screening using chest radiography and testing by Xpert MTB/RIF would be most cost effective from program point of view. However, the costs to the patients and their family would be minimum if Xpert MTB/RIF is used as a singular frontline diagnostic test among individuals with presumptive pulmonary TB disease. When resources would no more be a constraint, direct Xpert would reduce costs incurred by the patients.

Conflicts of interest

The authors have none to declare.

Author contribution

Protocol development: VC. Cost analysis: VC, GS, NS. Paper writing: VC, GS, NS.

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Original Article

General and tuberculosis mortality in two states of India: A population-based survey

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ABSTRACT

Background: General and cause-specific mortality data for causes of death are not available for the states of Andhra Pradesh (AP) and Orissa in India.
Objectives: To estimate general mortality rate (GMR) and the tuberculosis mortality rate (TMR) among the general population in the two states.
Methods: All permanent residents in households of selected districts of AP and Orissa states were registered in the survey in 2005–2006. A sample size of 380,000 persons was selected from each state. Health workers carried out house-to-house enumeration. Demographic and occurrence of death data were collected. The cause of death was determined using the instrument of verbal autopsy.
Results: The GMR for AP and Orissa was 636 (95% CI: 610–662) and 616 (95% CI: 588–643) per 100,000 person years (p-ys) respectively. The TMR for AP and Orissa was 76 (95% CI: 67–85) and 41 (95% CI: 34–48) per 100,000 p-ys respectively. The difference in TMR between the states was statistically significant ($P < 0.0001$).
Conclusion: The GMRs are similar in AP and Orissa states. Tuberculosis accounted for 12% and 7% of deaths in AP and Orissa respectively. Focused strategies are needed to reduce mortality due to tuberculosis.

1. Introduction

Globally, the number of incident tuberculosis (TB) cases is estimated to be falling slowly since 2006. Despite all the interventions, death due to TB is still significant. The 2014 WHO Global TB Report estimated that 9.0 million incident cases of TB and 1.5 million people died from the disease in 2013. India alone accounted for 24% of the total TB cases and about one-third of TB deaths in that year.[1] Multidrug-resistant TB continues to present significant challenges to TB control.

Reliable TB mortality data are not available especially from countries of the South East Asian Region. Medical certification of cause of death is generally of poor quality, because of lack of proper training for the doctors and poor enforcement. WHO estimates of TB mortality for these countries are derived indirectly from incidence (which itself is indirectly estimated) and reported case fatality rates. Such estimates are also not accurate. Mortality surveys using the verbal autopsy (VA) tool are an accepted method for estimating mortality rates for various health conditions and diseases.

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Usually mortality surveys are conducted using prospective follow-up design. Such surveys require at least one-year follow-up period to collect mortality (deaths due to all causes) data. They require more personnel, financial resources, and time. On the other hand, retrospective study designs such as the one used in this survey, require less time, personnel, and money. The present study was conducted to estimate the general mortality and cause specific mortality rates in two states from India. Cause-specific mortality rates are essential to prioritize the health needs of a community and to assess the impact of control measures. For example, reduction of TB mortality rate by 50% from 1990 to 2015 is a global health target proposed in the Millennium Development Goals.[2] In India, crude death rate for the nation as a whole and for the states are periodically measured through Sample registration systems (SRS) and general census.[3] In fact, the proportion of deaths in 2001–2003 attributable to TB was 5.1% for South India in one report.[4] The Register General of India survey is a prospective survey which is time consuming and very expensive. The National Institute for Research in Tuberculosis in Chennai conducted mortality surveys in Andhra Pradesh (AP) and Orissa states in India using a retrospective study design to collect data on death due to all causes, and TB in particular.

Objectives: 1. To estimate general mortality rate (GMR) for the states of AP and Orissa. 2. To estimate the TB mortality rate (TMR) among the general population in these two states.

1.1. *Sampling and sample size*

Our study was designed to detect enough TB deaths which could be stratified by age and sex. The required sample size was estimated to be 380,000 for an annual incidence of deaths due to TB of 36 per 100,000 population, a precision of 20% at 95% confidence level, and 25% of calculated sample size was accounted for absentees. Twenty-five percent of districts (6 from AP and 8 from Orissa states) were selected by systematic sampling method. In total, 380 units (urban/rural) were distributed proportionately to size of the population of urban (includes wards) and rural areas of the selected districts of each state. The size of each unit was fixed at 1000 persons to represent more units and the required sampling units were chosen randomly in urban and rural areas from each district.

2. Methodology

The survey was carried out during 2005–2006. Trained health workers visited each house in the selected areas and registered into the survey all permanent residents (who were residing in that unit permanently and belonging to the household) as they existed on the day of previous ''Sankaranthi'' for AP and ''Holi'' for Orissa in 2005 (both prominent festival days). During registration, the household number, names of the members in the household, age in completed years, and gender of the individuals were recorded. In addition, information on occurrence of death in each household (between ''Sankaranthi'' for AP and ''Holi'' for Orissa and the date of registration) was recorded. Similar information was also recorded for those who had migrated out of the selected areas. All household registration forms reporting deaths were handed over to the supervisors (non-medical graduates specially trained in the VA instrument and proficient in the local language), for detailed VA to ascertain leading causes of death among the population.

VA was conducted by supervisors through an interview of the head of the family or any other adult household member of the deceased. Respondents were asked to describe the chain of events, circumstances, symptoms, and signs of the illness leading to death. The questionnaire used for VA consisted of the following three sections:

Section I: Dealt with general information of the deceased and the respondent.
Section II: Comprised of structured questions to probe the nature of symptoms and signs the deceased had immediately preceding the death and also past medical history.
Section III: Deals with the written narrative (a standardized symptom list was used as a filter to define additional probing questions related to a particular symptom).

The narrative was written in the local language as narrated by the respondent and included information gathered on the symptoms in the order of occurrence, the nature of medical help sought, findings of investigation reports and hospital diagnosis, and records whenever available. The average recall period was 342 days and 307 days for AP and Orissa states, respectively. 5% of randomly selected household registration forms and VA forms were cross-checked by coordinators/supervisors, through repeat visits to households and re-interview of the respondents of the diseased.

In both states, two medical officers specially trained in coding cause of deaths (ICD-10 version 2005) reviewed and coded all completed VA forms independently. The coded forms were reviewed by an adjudicator. The adjudicator's code was considered as the final code of the underlying cause of death, defined as the disease which initiated the train of events leading directly to death or the circumstances of the accident or violence which produced the fatal injury.

3. Results

In AP, 304 rural and 76 urban units were selected. Of the total population registered, 98.4% were alive, 0.6% had died, and 1% had migrated at the time of interview (Table 1). Krishna district was the biggest district with 82 units and Vizianagaram district was the smallest district with 44 units. Table 2 shows that from Orissa, 310 rural and 70 urban units were selected. Of the total registered population, 98.7% were alive, 0.5% had died, and 0.8% had migrated at the time of interview. Cuttack district was the biggest district with 94 units and Debagarh was the smallest district with 11 units.

The GMR for AP and Orissa was 636 (95% CI: 610–662) and 616 (95% CI: 588–643) per 100,000 person-years (p-ys) respectively. The difference was not statistically significant ($P = 0.29$). The TMR for AP and Orissa was 76 (95% CI: 67–85) and 41 (95% CI: 34–48) per 100,000 p-ys respectively, and the difference was statistically significant ($P < 0.0001$). Both the GMR and the TMR increased with increasing age (Table 3). Males had higher GMR ($P < 0.0001$) and TMR ($P < 0.0001$) than females in all age groups

Table 1 – Number of sampling units and study participants by selected districts in Andhra Pradesh.

Districts	Total units *n*	Rural units *n*	Urban units *n*	Registered *n*	Alive *n* (%)	Dead *n* (%)	Moved out *n* (%)
All	380	304	76	395,886	389,743 (98.4)	2344 (0.6)	3799 (1.0)
Mahbubnagar	69	62	7	74,203	72,711 (98.0)	448 (0.6)	1044 (1.4)
Khammam	51	41	10	52,602	51,916 (98.7)	276 (0.5)	410 (0.8)
Vizianagaram	44	36	8	45,728	45,013 (98.4)	308 (0.7)	407 (0.9)
Krishna	82	56	26	85,263	84,186 (98.7)	472 (0.6)	605 (0.7)
Prakasam	60	51	9	61,836	60,587 (98.0)	353 (0.6)	896 (1.4)
Chittoor	74	58	16	76,254	75,330 (98.8)	487 (0.6)	437 (0.6)

Table 2 – Number of sampling units and study participants by selected districts in Orissa.

Districts	Total units *n*	Rural units *n*	Urban units *n*	Registered *n*	Alive *n* (%)	Dead *n* (%)	Moved out *n* (%)
All	380	310	70	390,362	385,160 (98.7)	2011 (0.5)	3191 (0.8)
Bargarh	54	50	4	55,169	54,463 (98.7)	333 (0.6)	373 (0.7)
Debagarh	11	10	1	11,263	11,164 (99.1)	66 (0.6)	33 (0.3)
Sundargarh	73	48	25	74,311	73,337 (98.7)	437 (0.6)	537 (0.7)
Kendrapara	52	49	3	53,594	52,319 (97.6)	235 (0.4)	1040 (1.9)
Jagatsinghapur	42	38	4	43,007	42,447 (98.7)	164 (0.4)	396 (0.9)
Cuttack	94	68	26	97,931	97,202 (99.3)	372 (0.4)	357 (0.4)
Gajapati	21	19	2	21,379	20,912 (97.8)	152 (0.7)	315 (1.5)
Rayagada	33	28	5	33,708	33,316 (98.8)	252 (0.7)	140 (0.4)

Table 3 – General and tuberculosis mortality rates per 100,000 person years by age and sex.

State	Age groups in years	Males				Females				Difference between males and females *P* value		Males + Females			
		Person years	Dead	GMR[a]	TMR[b]	Person years	Dead	GMR[a]	TMR[b]	GMR	TMR	Person years	Dead	GMR[a]	TMR[b]
Andhra Pradesh	0–14	53,413	75	140	2	51,188	82	160	6	0.41	0.30	104,601	157	150	4
	15–44	95,814	374	390	43	94,783	200	211	25	<0.0001	0.039	190,597	574	301	34
	45–59	23,052	294	1275	269	22,208	143	644	63	<0.0001	<0.0001	45,260	437	966	168
	60+	13,152	632	4805	715	15,045	544	3616	279	<0.0001	<0.0001	28,197	1176	4171	482
	All	185,431	1375	742	107	183,224	969	529	45	<0.0001	<0.0001	368,655	2344	636	76
Orissa	0–14	48,769	148	303	0	47,011	131	279	9	0.48	0.04	95,780	279	291	4
	15–44	80,729	167	207	38	81,998	136	166	13	0.06	0.002	162,727	303	186	26
	45–59	20,795	180	866	101	18,964	105	554	37	0.0002	0.016	39,759	285	717	70
	60+	14,400	622	4319	285	13,951	522	3742	143	0.013	0.01	28,351	1144	4035	215
	All	164,693	1117	678	56	161,924	894	552	26	<0.0001	<0.0001	326,617	2011	616	41

[a] General mortality rate.
[b] Tuberculosis mortality rate.

in Orissa. In AP also, males had higher GMR ($P < 0.0001$) and TMR ($P < 0.0001$) than females for all the age groups except 0–14 years group ($P = 0.41$).

In general, both the GMR and the TMR increased with increasing age (except the 0–14 year age group in Orissa, which had higher GMR than 15–44 year age group) (Table 4). The rural population had higher GMR and TMR than the urban population for all age groups in both states. The GMR for rural population was higher, but for urban population, it was lower in AP than in Orissa.

The top ten causes of death among males and females in AP are shown in Table 5. Among males, the circulatory system diseases (which included cardiovascular disease) were the top cause of death. The external causes of death (which included accidents and suicides) and infectious and parasitic diseases, respectively were in the second and third places. TB was in the fourth place and accounted for 14.4% of male deaths. Deaths which could not be classified were in the fifth place. Among females, infectious and parasitic diseases were the top cause of death. The circulatory system diseases and the external causes of death respectively were in the second and third places. Deaths which could not be classified were in the fourth place. TB was in the fifth place and accounted for 8.6% of female deaths.

The top ten causes of death among males and females in Orissa are shown in Table 6. Infectious and parasitic disease and deaths which could not be classified were the top two causes of death in both sexes. TB was ranked fifth among males and eighth among females.

Table 4 – General and tuberculosis mortality rates per 100,000 person years by age and area.

State	Age groups in years	Rural				Urban				Difference between rural and urban P value		Rural + urban			
		Person years	Dead	GMR[a]	TMR[b]	Person years	Dead	GMR[a]	TMR[b]	GMR	TMR	Person years	Dead	GMR[a]	TMR[b]
Andhra Pradesh	0–14	84,632	146	173	5	19,970	11	55	0	0.0001	0.33	104,602	157	150	4
	15–44	150,062	480	320	36	40,535	94	232	27	0.004	0.39	190,597	574	301	34
	45–59	36,011	354	983	189	9249	83	897	86	0.45	0.03	45,260	437	966	168
	60+	23,245	989	4255	529	4952	187	3776	263	0.13	0.01	28,197	1176	4171	482
	All	293,950	1969	670	85	74,706	375	502	43	<0.0001	0.0002	368,656	2344	636	76
Orissa	0–14	79,497	255	321	5	16,283	24	147	0	0.0002	0.37	95,780	279	291	4
	15–44	131,124	259	198	24	31,603	44	139	32	0.03	0.47	162,727	303	186	26
	45–59	32,369	232	717	71	7391	53	717	68	0.997	0.92	39,760	285	717	70
	60+	23,906	954	3991	226	4445	190	4274	157	0.38	0.37	28,351	1144	4035	215
	All	266,896	1700	637	42	59,722	311	521	37	0.001	0.55	326,618	2011	616	41

[a] General mortality rate.
[b] Tuberculosis mortality rate.

Table 5 – Top ten causes of death – Andhra Pradesh.

Sl. no.	Sex					
	Male			Female		
	Cause of death	Death *n* (%)	Mortality rate per 100,000 person years (95% CI[a])	Cause of death	Death *n* (%)	Mortality rate per 100,000 person years (95% CI)
1	Circulatory system diseases	329 (23.9)	177 (158–197)	Infectious and parasitic diseases excluding TB	225 (23.2)	123 (106–139)
2	External causes of mortality	256 (18.6)	138 (121–155)	Circulatory system diseases	166 (17.1)	91 (77–105)
3	Infectious and parasitic diseases excluding TB	200 (14.5)	108 (93–123)	External causes of mortality	115 (11.9)	63 (51–74)
4	Tuberculosis	198 (14.4)	107 (92–122)	Symptoms and signs not elsewhere classified	113 (11.7)	62 (50–73)
5	Symptoms and signs not elsewhere classified	100 (7.3)	54 (43–65)	Tuberculosis	83 (8.6)	45 (35–55)
6	Nervous system diseases	65 (4.7)	35 (26–44)	Neoplasm	79 (8.2)	43 (33–53)
7	Neoplasm	60 (4.4)	32 (24–41)	Nervous system diseases	62 (6.4)	34 (25–42)
8	Respiratory system	54 (3.9)	29 (21–37)	Respiratory system	41 (4.2)	22 (15–29)
9	Genito urinary system	48 (3.5)	26 (18–33)	Genito urinary system	30 (3.1)	16 (10–22)
10	Digestive system	31 (2.3)	17 (11–23)	Digestive system	15 (1.5)	8 (4–12)
	All causes	1375	742 (702–782)	All causes	969	529 (495–563)

[a] CI, confidence interval.

4. Discussion

The main findings of this VA survey are that infectious (including TB) and parasitic diseases still remain the most frequent causes of death in both these Indian states. While the GMRs were similar, TB mortality was much higher in Andhra Pradesh, highlighting the importance of local socio-economic and environmental factors, as well as health system differences. Our findings are in broad agreement with the Global Burden of Disease 2013 report, which put TB as the third leading cause of death in India, after ischemic heart disease and lower respiratory tract infections.[5]

TMR could vary between states due to variability in the occurrence of co-morbid conditions (e.g. under nutrition, HIV infection, and diabetes mellitus) and other risk factors (smoking, alcohol intake, and indoor air pollution) which predispose to TB and also aggravate the mortality risk. Therefore, a comprehensive and multisectoral strategy that aims to address these risk factors and reduce their prevalence in the community will be required in order to make a dent in the community prevalence of TB. In addition, identification and effective management of these co-morbid conditions simultaneously with TB treatment will be required to reduce TB mortality. The finding that circulatory system diseases and external causes are the other top causes of death suggests that life style diseases and traffic accidents are increasing as in developed countries and appropriate strategies must be in place to control these.

Table 6 – Top ten causes of death – Orissa.

Sl. no.	Sex					
	Male			Female		
	Cause of death	Death *n* (%)	Mortality rate per 100,000 person years (95% CI[a])	Cause of death	Death *n* (%)	Mortality rate per 100,000 person years (95% CI)
1	Infectious and parasitic diseases excluding TB	230 (20.6)	140 (121–158)	Infectious and parasitic diseases excluding TB	221 (24.7)	136 (118–155)
2	Symptoms and signs not elsewhere classified	213 (19.1)	129 (112–147)	Symptoms and signs not elsewhere classified	216 (24.2)	133 (115–152)
3	Circulatory system diseases	122 (10.9)	74 (61–87)	Respiratory system	72 (8.1)	44 (34–55)
4	External causes of mortality	98 (8.8)	60 (47–72)	Circulatory system diseases	69 (7.7)	43 (32–53)
5	Tuberculosis	93 (8.3)	56 (45–68)	External causes of mortality	47 (5.3)	29 (21–37)
6	Respiratory system	90 (8.1)	55 (43–66)	Neoplasm	46 (5.1)	28 (20–37)
7	Nervous system diseases	58 (5.2)	35 (26–44)	Nervous system diseases	46 (5.1)	28 (20–37)
8	Neoplasm	52 (4.7)	32 (23–40)	Tuberculosis	42 (4.7)	26 (18–34)
9	Perinatal causes	39 (3.5)	24 (16–31)	Digestive system	26 (2.9)	16 (10–22)
10	Endocrine, nutritional and metabolic diseases	34 (3.0)	21 (14–28)	Perinatal causes	22 (2.5)	14 (8–19)
	All causes	1117	678 (638–719)	All causes	894	552 (515–589)

[a] CI, confidence interval.

The main purpose of this study was to collect reliable data on general mortality and TB mortality in two states of India. The conventional method involves prospective follow-up of study population for a period of one year to report on the deaths occurring during the follow-up period. A health worker (HW) is deployed for each village/urban unit. The HW records all deaths occurring in the village during his routine weekly or biweekly visits and carries out VA preferably within 7–10 days after the event has occurred. In this study, a retrospective follow-up methodology was used, in which the enumeration of the population and data collection on deaths from a reference date within the last one year was done simultaneously. The retrospective follow-up methodology requires less time, cost, and manpower than the conventional prospective methodology and it is possible to repeat the surveys at periodic intervals to study the trend of mortality for TB or any other health condition. It has been generally accepted that the recall of the event (death) will be accurate up to one year. In this study, the average duration of recall period was 342 days and 307 days for AP and Orissa states, respectively. It can be safely assumed that the estimates of GMR are comparable to estimates obtained in prospective study design. Thus, the retrospective follow-up method is rapid and economical without compromising the accuracy of estimates of GMR.

The VA was initially developed for childhood and maternal mortality studies, but at present many studies on adult mortality also use the VA tool. The validity of VA is influenced by the cause of death per se and other factors related to interviewer, respondent, recall period, and derivation of diagnoses from narrative forms. Chandramohan et al. concluded that VAs by a panel of physicians performed better than an opinion-based algorithm and the validity of VA diagnosis was highest for acute febrile illness and TB/AIDS.[6] Khan et al. reported that deaths coded as pulmonary TB (among adults aged 15+ years) by VA had 92% sensitivity and 99% specificity when validated against hospital diagnosis.[7] Yang et al. reported that TB deaths diagnosed by VA had 62.2% of sensitivity and 99.3% of specificity.[8] Despite the misclassification errors expected with this method, the cause of death data obtained from this study (especially with respect to TB deaths) contributes significantly to the mortality data currently available from India.

Age is an important risk factor for mortality mainly due to diminishing efficiency of the immune system consequent to aging process. Males had higher GMR than females probably due to higher prevalence of risk factors like smoking and alcoholism. However, the overall GMR in the two states was much lower than crude death rates reported by SRS 2004, which may be an indication that the general health status is improving. Rural areas had higher GMR than urban areas, which can be attributed primarily to the poor accessibility and lack of adequate health care facilities in the rural areas.

The TB mortality rate for AP was 76 per 100,000 p-ys and that in Orissa was lower at 41 per 100,000 p-ys. One or more of the following reasons may explain this large difference in the TMRs between the two states: (a) The prevalence of risk factors for TB (e.g. HIV prevalence, malnutrition, migration) is likely to be different in the two states. (b) The efficiency of health care services may vary significantly between them. For example, the level of registration of medically certified causes of death for the period 2008–2010 was much higher in Orissa than in AP.[9]

In this study, the percentage of deaths of total deaths due to TB was 12% in AP and 6.7% in Orissa. Joshi et al. reported that 4% of total deaths were TB deaths in east and west Godavari districts of AP in 2004.[10] Mahapatra reported 6.3% TB deaths in AP in 1991.[11] Gajalakshmi et al. reported 5.8% TB deaths in Chennai city in 1995–97.[12] These data are not strictly comparable because they did not use person-time rate and were collected at different points in time varying from 1991 and 2004.

In Orissa, infectious and parasitic diseases are ranked number one. In AP, it is ranked number two. However, if we include TB also among the infectious disease group, it becomes number one in AP also. This is expected in a developing country

with lack of adequate health infrastructure especially in rural areas. But this is in contrast to the report from east and west Godavari district study where circulatory system diseases accounted for more than twice the number of deaths attributed to infectious and parasitic diseases including TB.[11] TB itself was the fourth highest cause of death accounting for 12% of total deaths. But 9.1% of deaths were not assigned any specific cause of death which is much lower than 19% reported from east Godavari study. Generally, the percentage of unclassified deaths is considered a measure of quality of data collection and coding of cause of deaths, and the lower the percentage, the higher the quality. In Orissa also, infectious and parasitic diseases were ranked number one cause of death even after excluding TB. The circulatory system diseases were ranked third but contributed less than half of the mortality due to infectious causes. TB was ranked sixth in Orissa. But 21.3% of deaths were unclassified highlighting the limitations of the VA technique in finding out the cause of death.

Limitations: Even though the methodology followed is the same in both the states, training of interviewers was given by different trainers because of difference in the languages used in AP and Orissa. Inter-reader variations between coders of cause of death in the two states is also a limitation.

5. Conclusion

This study has shown that it is possible to do rapid mortality surveys using retrospective follow-up methodology. The GMRs are similar in AP and Orissa states. TB mortality rate is higher in AP than in Orissa. Infectious and parasitic diseases including TB are the topmost cause of death in both the states. Improving the health infrastructure in the rural areas will result in the reduction of deaths due to infectious and parasitic diseases and overall general mortality in the two states. The differences in two states are difficult to explain and that the purpose of this manuscript is to bring out the challenges in mortality survey and the experience gained in the survey suggests the need to further standardize the survey tool.

Conflicts of interest

The authors have none to declare.

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Ethical approval

Not required.

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Original Article

Risk factors associated with development of pulmonary impairment after tuberculosis

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ABSTRACT

Background: Treatment of pulmonary tuberculosis (PTB) focuses on microbiological cure and radiological improvement. However, many patients develop pulmonary impairment after the completion of anti-tubercular therapy (ATT), which affects their quality of life (QoL).

Aim and objective: To study the occurrence and severity of pulmonary impairment after tuberculosis (PIAT), risk factors associated with development of PIAT and QoL after development of PIAT.

Methodology: 146 eligible PTB patients, who completed their ATT during January 2013 to December 2013 at National Institute of TB and Respiratory Diseases (NITRD), New Delhi and peripheral centres were enrolled after informed consent and evaluated. PIAT was graded using spirometric parameters. Severity of dyspnoea was assessed using Borg scale and Medical Research Council (MRC) scale. QoL was assessed using Seattle's Obstructive Lung Diseases Questionnaire (SOLDQ).

Results: 74% (108) had PIAT. On univariate analysis, smoking, education, body mass index (BMI), duration of illness prior to diagnosis of TB and number of prior ATT courses taken were the significant risk factors associated with the development of PIAT. On multiple logistic regression, patients who had taken ATT more than once was the independent risk factor associated with PIAT. Severity of dyspnoea was increased on both Borg scale and MRC scale with the increase in impairment of lung function. QoL was lower in patients with severe impairment.

Conclusion: After bacteriological cure of TB after treatment, significant numbers of patients have poor lung function and poor QoL. There is need for prevention and management of such sequelae under national programme.

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1. Introduction

In 2013, globally, an estimated 9 million people developed Tuberculosis (TB) and 1.5 million people died from the disease (including 400,000 deaths among HIV-positive people).[1,2] India alone accounts for 24% of the world's TB cases. Pulmonary tuberculosis (PTB) can result in residual anatomic and functional changes despite microbiological cure.[3,4] After tuberculosis, bronchial and parenchymal structure changes result in sequelae, including bronchovascular distortion, fibrotic bands, emphysematous changes and bronchiectasis. These sequelae are associated with pulmonary impairment after tuberculosis (PIAT) that occurs frequently and varies from mild to severe. PIAT refers to chronic pulmonary function loss that occurs in persons, who have achieved microbiologic cure of PTB. No study from India has been reported about PIAT as far.

This study was aimed to evaluate occurrence, severity and the risk factors leading to the development of PIAT after TB treatment.

2. Materials and methods

This prospective case–control study was conducted in National Institute of Tuberculosis and Respiratory Diseases (NITRD), New Delhi. All consented PTB patients of age 14 and above and had cognitive ability to comprehend and follow advice were considered for study. Those who completed anti-tubercular therapy (ATT) for PTB during January 2013 to December 2013 from nearby five Directly Observed Treatment (DOT) centres covered by NITRD were included in study. One hundred and sixty two patients were enrolled into the study. After clinic-radiological evaluation, spirometry was performed using a dry rolling seal spirometer (Morgan Transfer Test Model C or Medisoft, Spiro Air model).[5] The results were expressed at BTPS (body temperature and pressure saturated). They were reported in absolute volumes as well as percent of predicted normal based on the regression equations used in our laboratory. Patients were classified into two groups, ''Impairment absent'' and ''Impairment present'' based on FEV_1 ≥80% predicted and <80% predicted respectively.[6] Obstruction was defined as an FEV_1/FVC ratio of ≤70% and an FVC of ≥80% predicted, restrictive defects as an FEV_1/FVC ratio of ≥70% with an FVC of ≤80% predicted, and mixed defects were FVC of ≤80% predicted and an FEV_1/FVC ratio of ≤70%.[4] Six-minute walk test was done according to American Thoracic Society guidelines.[7] Dyspnoea was assessed using Borg scale and Medical Research Council (MRC) scale. Quality of life (QoL) was assessed using Seattle's Obstructive Lung Diseases Questionnaire (SOLDQ) in both the groups.[8] It includes 29 questions, which assess four dimensions of life: physical function, emotional factor, coping skills and treatment satisfaction. The higher score denotes better QoL for all the components of the questionnaire. The chest X-rays were classified using the criteria used by National Tuberculosis Association of the USA.[9]

After doing clinic-radiological evaluation and PFT, the following risk factors were evaluated for the development of PIAT. It included demographic factors such as age, sex and BMI; socio-economic status as assessed by education, monthly income and occupation; clinical factors such as delay in starting treatment, number of ATT courses taken prior, sputum status at the time of initiation of treatment, clinical improvement after starting treatment, history of smoking and X-ray picture at the end of treatment.

3. Statistical analysis

Statistical analysis was done using SPSS ver 20. software. Qualitative data were compared using Chi-square test. $p < 0.05$ was considered as significant. Multiple logistic regression analysis was also done after finding the significant factors on univariate analysis.

4. Results

Out of 162 patients enrolled, 16 patients could not perform spirometry. These were excluded from study and remaining 146 patients were analysed. 74% (108) patients had impairment. Demographic profile and risk factors among the patients enrolled in the study are given in Table 1.

As shown in Table 1, on univariate analysis, smoking, education level, BMI, duration of illness and number of prior ATT courses taken were associated with PIAT significantly. 103 patients had taken ATT once (Cat I), and among them 68% developed PIAT. 43 patients had taken ATT for more than one time (40 had taken twice while 3 had taken thrice); among them 88.4% had developed PIAT ($p = 0.001$). PIAT among the patients, who had taken ATT for more than one time have three times higher chances of getting impairment in comparison to those who had taken ATT only once. On multiple logistic regression, number of prior ATT courses taken was found to be significant independent risk factor for PIAT.

Table 2 describes chest X-ray severity of these patients. As observed from Table 2, pulmonary impairment was significantly associated with the severity of X-ray findings. Table 3 shows dyspnoea scoring among the patients. Dyspnoea scores were higher among the patients with impairment. Table 4 describes pulmonary function tests among the patients enrolled and Fig. 1 shows distribution of PFT pattern among the patients with impairment. Of the 108 patients showing pulmonary impairment, 12 (11.1%) showed obstructive pattern, 64 (59.3%) showed restrictive pattern and 19 (17.6%) patients showed mixed pattern on spirometry. 13 (12%) patients had pulmonary impairment without obstruction or restriction as per the definitions used in the study.

The mean (±SD) 6 min walk distance among all the patients was 478.86 ± 80.80 m (range: 190–690 m). Mean (±SD) six-minute walk distance by patients without impairment was 503.37 ± 63.99, while that with impairment was 478.86 ± 80.80.

QoL using SOLDQ is described in Table 5. Mean scores of the various dimensions of life were lower in patients with pulmonary impairment.

Table 1 – Demographic profile of patients and risk factors evaluated for PIAT among the patients enrolled.

Risk factors		Impairment present (n = 108)	Impairment absent (n = 38)	Total (n = 146)	p value
Sex	Male	69 (71.87%)	25 (28.13%)	96 (100%)	$p = 0.423$
	Female	39 (78%)	11 (22%)	50 (100%)	
Age group	14–24 years	43 (72.8%)	16 (27.2%)	59 (100%)	$p = 0.758$
	25–44	41 (77.35%)	12 (22.65%)	53 (100%)	
	≥45	24 (70.5%)	10 (29.5%)	34 (100%)	
BMI	Undernourished	64 (76.2%)	20 (23.8%)	84 (100%)	$p = 0.0398$
	Normal	40 (76.92%)	12 (23.08%)	52 (100%)	
	Overnourished	4 (40%)	6 (60%)	10 (100%)	
Education	Illiterate	17 (81%)	4 (19%)	21 (100%)	$p = 0.0081$
	Up to high school	66 (81.5%)	15 (18.5%)	81 (100%)	
	More than high school	25 (56.8%)	19 (43.2%)	44 (100%)	
Occupation	Unemployed	46 (68.7%)	21 (31.3%)	67 (100%)	$p = 0.195$
	Semi-skilled workers	21 (87.5%)	3 (12.5%)	24 (100%)	
	Skilled workers	14 (25.45%)	41 (74.54%)	55 (100%)	
Monthly income	<Rs. 8009	61 (81.33%)	14 (18.67%)	75 (100%)	$p = 0.0573$
	Rs. 8010–Rs.12,019	26 (72.22%)	10 (27.78%)	36 (100%)	
	>Rs. 12,020	21 (60%)	14 (40%)	35 (100%)	
Socio-economic status	Upper	11 (55%)	9 (45%)	20 (100%)	$p = 0.104$
	Middle	26 (74.3%)	9 (25.3%)	35 (100%)	
	Lower	71 (78%)	20 (22%)	91 (100%)	
Smoking status	Non-smoker	73 (69.5%)	32 (30.5%)	105 (100%)	$p = 0.049$
	Smoker	35 (85.4%)	6 (14.6%)	41 (100%)	
Sputum status	Negative	21 (72.41%)	8 (27.59%)	29 (100%)	$p = 0.488$
	1+	39 (68.42%)	18 (31.58%)	57 (100%)	
	2+	25 (83.33%)	5 (16.67%)	30 (100%)	
	3+	23 (76.67%)	7 (23.33%)	30 (100%)	
Delay in starting ATT/duration of illness	<2 months	67 (68.36%)	31 (31.63%)	98 (100%)	$p = 0.027$
	>2 months	41 (85.41%)	7 (14.58%)	48 (100%)	
Clinical improvement after ATT	<8 weeks	93 (73.23%)	34 (26.77%)	127 (100%)	$p = 0.59$
	>8 weeks	15 (78.95%)	4 (21.05%)	19 (100%)	
No. of ATT courses taken	Once	70 (68%)	33 (32%)	103 (100%)	$p = 0.001$
	More than once	38 (88.37%)	5 (11.62%)	43 (100%)	

5. Discussion

Currently the national programme for TB focuses on bacteriological cure of TB patients. In the current study, various risk factors were evaluated for the development of PIAT. We found that smoking, education, BMI, duration of illness prior to diagnosis of TB and number of prior ATT courses taken were the significant risk factors.

81% among illiterate and 81.5% among those who studied up to high school had impairment, while 56.8% of those who studied more than high school had impairment ($p = 0.0081$). The majority of the patients were belonging to lower class. 78.01% patients of lower class, 74.3% of middle class and 55% of

Table 2 – Chest X-ray findings among the patients enrolled.

X-ray status		Impairment present (n = 108)	Impairment absent (n = 38)	Total (n = 146)	p value
X-ray finding	Normal	17 (41.5%)	24 (58.5%)	41 (100%)	$p < 0.01$
	Abnormal	91 (86.67%)	14 (13.33%)	105 (100%)	
Cavity in the X-ray	Absent	67 (65%)	36 (35%)	103 (100%)	$p = 0.0001$
	Present	41 (95.43%)	2 (4.65%)	43 (100%)	
Severity of X-ray	Normal	17 (41.5%)	24 (58.5%)	41 (100%)	$p < 0.001$
	Minimal	55 (80.9%)	13 (19.1%)	68 (100%)	
	Moderately advanced + far advanced	36 (97.3%)	1 (2.7%)	37 (100%)	

Table 3 – Dyspnoea scoring of the patients enrolled.

Dyspnoea scale	Grading	Impairment present (n = 108)	Impairment absent (n = 38)	Total (n = 146)
Borg scale	Nothing at all	2	2	4
	Very slight	23	21	44
	Slight	57	12	69
	Moderate	23	2	25
	Somewhat severe	1	1	2
	Severe (Heavy)	2	0	2
MRC grade	Grade I	22	24	46
	Grade II	61	11	72
	Grade III	20	3	23
	Grade IV	5	0	5

upper class developed impairment. Lee et al.[10] found in their study that low income was the risk factor for developing impairment in lung function in the form of obstruction after completion of ATT.

Majority of the patients (71.9%) were non-smokers. 85.4% patients among all smokers developed PIAT, while 69.5% non-smokers had PIAT ($p = 0.049$). Ramos et al.,[11] while comparing the pulmonary function results, did not observe a significant difference between the smokers and non-smokers ($p = 0.926$). Snider and colleagues[12] found that heavy smoking (≥20 cigarettes per day) and more severe TB (Roentgenographic score ≥ 9) independently increased the prevalence of airflow obstruction by approximately twofold, while the effect was additive but not synergistic in the simultaneous presence of the two factors.

Our study observed that among patients who had taken ATT for more than one time 88.37% developed PIAT compared to 68% PIAT among those who had taken ATT once only ($p = 0.001$). Di Naso et al.,[13] reported that patients who had taken multiple ATT showed significantly lower levels of FVC (forced vital capacity) when compared to patients who had taken ATT only once.

In current study, sputum status at the start of treatment did not affect occurrence of PIAT ($p = 0.488$). While, Lam et al.[14] had found that smear-positive patients had a higher risk of obstructive defects after completion of ATT (odds ratio = 2.546, $p = 0.045$).

We observed in our study that a delay in starting ATT was significantly associated with development of PIAT. Similarly, Lee et al.[10] in their study among 3176 pulmonary TB subjects showed that delay in anti-TB treatment was an independent risk factor for development of COPD (HR 1.005 [range, 1.003–1.007]).

Of the 108 patients showing pulmonary impairment, 11.1% showed obstructive pattern, 59.3% showed restrictive pattern and 17.6% patients showed mixed pattern on spirometry. Snider and colleagues[12] found 60% of hospitalised TB patients had an FEV_1 of <80% predicted and evenly distributed patterns of dysfunction (restriction in 24%, Obstruction in 23%, mixed in 19%) among them. Plit et al.[15] studied PFT in 76 patients cured of severe Pulmonary TB. They found that, 28% had obstructive and 24% had restrictive lung diseases.

In our study, we found that mean six-minute walk distance was decreased in patients with impairment than those without impairment.

It was observed in this study (Table 4) that there was inverse relationship between the physical function, emotional factor, coping skill and treatment satisfaction scores and the severity of impairment. In patients with very severe loss of lung functions mean scores were 62.83, 63.90, 68.80% and 50.10% for physical function, emotional factor, coping skill and treatment satisfaction respectively. Similarly, Lee et al.[16] found that delays in the diagnosis of TB lead to the increased in lung damage and more frequent co-morbidities and impairment of QoL. Fan et al.[17] concluded that lower scores on all four scales of the SOLDQ were associated with an increasing risk of hospitalisation and death. Ketalaars et al.[18] found that there was correlation between FEV_1 and FVC % predicted with QoL by St. George's Respiratory Questionnaire. With decreased FEV_1 and FVC % predicted, there was decrease in QoL also.

In this study, among the significant risk factors evaluated by univariate analysis, number of prior ATT courses taken prior was found to be significant independent risk factor for development of PIAT after multivariate analysis (logistic

Table 4 – Pulmonary function test of patients enrolled.

PFT parameter	Impairment present (n = 108) Mean ± SD	Impairment absent (n = 38) Mean ± SD
FVC % predicted	68.06 ± 14.13	93.21 ± 10.94
FEV_1% predicted	58.58 ± 15.07	90.39 ± 8.06
FEV_1/FVC	83.26 ± 7.84	73.83 ± 13.39

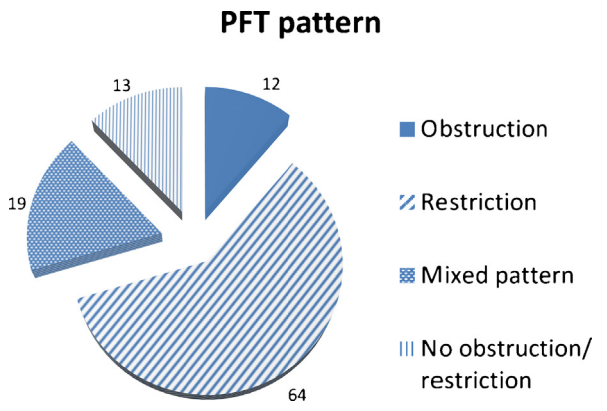

Fig. 1 – PFT pattern among the patients with PIAT (n = 108).

Table 5 – QoL of life assessment of patients enrolled.

SOLLDQ	Impairment present (n = 108) Mean ± SD	Impairment absent (n = 38) Mean ± SD
Physical function	82.18 ± 12.12	89.90 ± 11.89
Emotional factor	80.91 ± 14.35	93.87 ± 12.46
Coping skill	83.92 ± 11.89	93.76 ± 10.85
Treatment satisfaction	66.95 ± 14.65	78.61 ± 17.97

regression). PIAT among the patients who had taken ATT for more than one time have three times higher chances of getting impairment in comparison to those who had taken ATT once.

Our study had a few limitations: The sample size was small. Spirometry and chest X-ray at the time of initiation of treatment were not available. Patients were enrolled only from DOT centres, so the patients belonging to higher socio-economic strata were not involved in the study.

6. Conclusion

After completion of ATT and bacteriological cure of TB, significant numbers of patients have poor lung function and poor QoL. Smoking, lower education, lower BMI, duration of illness/delay in starting ATT and more courses of ATT taken prior are the risk factors for development of PIAT found in this study. Patients who had taken ATT more than once had three times higher chances of developing PIAT than who had taken once and was single independent risk factor for development of PIAT. National programme should focus on issue of PIAT among patients treated for PTB as a holistic approach. There is need for prevention and management of such sequelae under national programme.

Conflicts of interest

The authors have none to declare.

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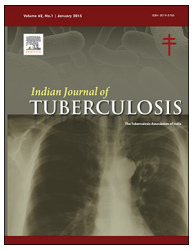

Original Article

Universal access to DOTS in Delhi Prisons: Where do we stand?

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ABSTRACT

Background: Universal access implies that all tuberculosis (TB) patients in the community should have access to early, good quality diagnosis and treatment services that are affordable and convenient to the patient in time, place, and person. To achieve universal access, all affected vulnerable and marginalized population like prison inmates should have access to TB diagnostic and treatment services.

Objectives: To assess the TB control activities in prisons of Delhi, the capital of India, and to suggest interventions for strengthening the program based on the observations.

Materials and methods: Study was conducted at Tihar Prison, Delhi. TB case notification data from the Revised National TB Control Program (RNTCP) between 2008 and 2012 and log process framework were used to assess various parameters.

Results: Mean number of patients initiated on TB treatment was 120.6 annually between 2008 and 2012. The RNTCP has been implemented in Delhi Prisons since 2002; however, gaps were identified in human resource, training needs, case finding, diagnostic and treatment services, and supervision on situational analysis. Coordination between prison authorities and RNTCP authorities in relation to initial screening and discharge process appeared to be weak.

Conclusion and recommendations: Because of the restricted access, vulnerability of the prison population, increase in drug-resistant TB, the TB control activities in the prison require restructuring. Initial screening for early diagnosis and treatment and ''Discharge planning'' needs to be devised so that there is sufficient time before release or transfer of individuals from prison. This needs strong commitment from the prison health authorities and RNTCP staff.

1. Background

The National Strategic Plan (2012–2017) rolled out by Revised National Tuberculosis Control Program (RNTCP) emphasizes the need for Universal Access to quality TB services as there is now global consensus that the twin objectives of 70/85 alone is not enough to achieve adequate reduction of tuberculosis (TB) transmission and reduction in disease burden at the pace with which epidemiological impact is expected.[1]

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Universal access implies that all TB patients in the community should have access to early, good quality diagnosis and treatment services in a manner that is affordable and convenient to the patient in time, place, and person. To achieve universal access, all affected communities, including vulnerable and marginalized population, including women, children, elderly, migrants, homeless people, alcohol and other drug users, prison inmates, people living with HIV, etc., should have access to TB diagnostic and treatment services.

All these populations have a higher risk of developing the disease due to interactions between various factors known and prevalent among them. Our study focused on TB control activities in prison settings as poor access to health services, combined with deterioration in the health and nutritional conditions among prisoners, contribute to delayed diagnosis and poor treatment outcomes. Research has shown that a high burden of TB is observed in prison systems globally. TB prevalence among prisoners is 10–50 times higher than the general population.[2] The congregate environment, poor ventilation, and prolonged duration of infectiousness enhance TB transmission among inmates and prison staff. Prisoners are also more likely to harbor drug-resistant strains of TB.

Documentation on the TB situation in prisons in developing countries is limited, and very few studies have quantitatively evaluated TB control programs in prisons.[3]

1.1. *Objectives*

The objective of this study is to assess the TB control activities in prisons of Delhi, the capital of India, and to suggest interventions for strengthening the program based on the observations.

2. Material and methods

2.1. *Study setting and design*

Study was conducted at Tihar Prison, Delhi that is the largest prison in Asia. It has nine jails in the premises of Tihar in Janankpuri, South West Delhi and one in Rohini, North West Delhi. TB control program in prison has been implemented as a part of routine RNTCP in the prison since 2002 in Delhi. PMDT services were started in Delhi in 2008 and extended to the prison in the year 2011. The Designated Microscopy Centre and DOT Centre is located in Central Jail Hospital (CJH) in Jail no. 3 of Tihar Jail. Situational analysis of RNTC program activities was undertaken between May and July 2013. Programmatic information, particularly information on TB control activities in the prison health system between 2007 and 2012, was collected from the program reports.

2.1.1. *Ethical considerations*

Ethical clearance was obtained from the Institutional Review Board. Permission was sought from the jail authorities. The objective and procedure of the study were explained to the authorities and the participants.

2.2. *Data collection*

Information on the prison population was obtained from the prison authorities. TB case notification data from the RNTCP, between 2007 and 2012, were analyzed. Programmatic parameters that were assessed using the log process framework included human resources available and training needs, case finding and treatment practices, diagnostic and treatment process, infection control practices, advocacy, communication and social mobilization (ACSM) in prison, drugs and logistics management, follow-up after release (referral system), TB/HIV coinfection, case recording, reporting, supervision, and monitoring. Key informant interviews were conducted with prison managers, prison health staff, and RNTCP staff.

2.2.1. *Statistical analysis*

Data were expressed as proportions using MS Excel sheet.

3. Results

Tihar Jail has a total capacity of 6250 inmates but houses 12,417 inmates as on (October 2012). Out of these, 3232 (26.1%) were convicts and 9178 (73.9%) were undertrials. Amongst convicts, majority of 3109 (96.1%) are males and 123 (4%) are females. 8751 and 427 inmates were male and female undertrials, respectively. Majority of the male inmates belonged to the age range of 21–30 years whereas majority (49.8%) of female (274/550) inmates were between 30 and 50 years of age. Experienced medical and paramedical staff, drawn from Delhi Government Health Services, professionally manages the Medical Care in the Delhi Prisons. 78 doctors and 127 paramedical staff are deputed for round-the-clock healthcare of prisoners.

The programmatic data on number of TB cases initiated for treatment in prison and their outcome between 2008 and 2012 are presented in Table 1. Treatment success ranged between 10.4% and 71.5%. ''Transferred out'' was reported to be ranging between 26.8% and 48.1% and ''released'' was reported as outcome ranging from 14% to 44.8% for patients put on treatment from 2008 to 2012. According to operational guidelines of RNTCP, ''transferred out'' means a patient who has been transferred to another Tuberculosis Unit/District and his/her treatment result (outcome) is not known.[4] Under treatment outcome, ''released'' was recorded when the inmate on TB treatment was released before completing treatment and his treatment result (outcome) was not known. Similar findings have been reported by Anderson et al. in their study wherein only 48% of prisoners diagnosed with active TB completed treatment and 20% were lost to follow-up.[5] Another study has also shown that less than half (48%) of the patients diagnosed as having TB in prison completed treatment, with a fifth lost to follow-up.[6]

The assessment of TB control activities was done using log process framework and the results are as follows:

1) **Physical infrastructure** required for running RNTCP services in the jail was assessed. The DMC in Tihar Jail is situated in the Central Laboratory of CJH in Jail no. 3. There

Table 1 – Reported number of TB cases and their treatment outcomes as per TB register (2008–2012).

Year	No. of cases	Sex		Category of treatment*			Type of disease		Treatment outcome**						
	N (%)	M n (%)	F n (%)	I n (%)	II n (%)	III n (%)	Pulmonary n (%)	Extra pulmonary n (%)	Cure n (%)	Treatment completed n (%)	Transfer out n (%)	Died n (%)	Default n (%)	Switch to Cat IV n (%)	Failure n (%)	Released n (%)
2008	201 (100)	194 (96.5)	7 (3.5)	92 (45.8)	66 (32.8)	43 (21.4)	129 (64.2)	72 (35.8)	4 (1.9)	140 (69.6)	54 (26.8)	2 (0.9)	1 (0.45)	–	–	–
2009	130 (100)	126 (97.0)	4 (3.0)	65 (50.0)	22 (17.0)	43 (33)	76 (58.5)	54 (41.5)	8 (6.1)	58 (44.6)	60 (46.2)	1 (0.76)	1 (0.76)	–	1 (0.76)	–
2010	128 (100)	121 (94.5)	7 (5.5)	77 (60.2)	29 (22.7)	22 (17.2)	81 (63.3)	47 (36.7)	12 (9.4)	78 (61.0)	35 (27.3)	1 (0.78)	1 (0.78)	–	1 (0.78)	–
2011	67 (100)	66 (98.5)	1 (1.5)	42 (62.7)	25 (37.3)		60 (89.6)	7 (10.4)	6 (8.9)	25 (37.3)	–	–	–	3 (4.5)	3 (4.5)	30 (44.8)
2012	77 (100)	75 (97.4)	2 (2.6)	29 (37.7)	48 (62.3)		28 (36.4)	49 (63.6)		8 (10.4)	37 (48.1)	2 (2.6)	–	–	3 (3.9)	11 (14.3)

* Cat III discontinued after 2010.
** Not available for 16 (20.7%) cases in the year 2012.

is a separate DMC and DOT Centre in Rohini Jail. There is no definite space designated for sputum collection. In Tihar Jail, DOT Centre is housed in CJH and all male sputum positive patients/MDR cases are admitted in TB ward in CJH. There was no such facility for female smear positive/MDR patients.

2) **Human resources**: Lab technician (LT), DOT provider, and a nodal officer RNTCP are required for smooth implementation of the program. For diagnosis, LTs posted from General Health Services were trained in sputum microscopy when the program was initiated in the jail. However, the pathologist posted in the Central Laboratory, who was not trained in RNTCP, was conducting sputum smear microscopy. LTs of Central Laboratory felt they were overworked, as their laboratory was the only laboratory catering to the needs of all inmates leading to high workload. Secondly, the LTs opined that RNTCP required excessive documentation that hindered them from doing other laboratory activities.

   The DOT Centre was being manned by a staff nurse who organized DOT and maintained the original TB treatment cards and records as per program guidelines. Inmates who were smear negative were given DOTS in their respective wards by the staff nurse posted in the ward, who maintains a duplicate treatment card for every patient.

   The overall incharge for all RNTCP activities in the jail was the designated nodal officer who belonged to the General Duty Medical Officer cadre of Delhi Government. There were two chest specialists who visited each jail on a weekly basis and provided consultation to the patients referred to them through the General OPD of the respective jail.

3) **Training**: The prison health staff was not trained in RNTCP during induction or during on-the-job trainings. According to the prison health staff (all cadres of staff), they felt isolated from their peers and also were forgotten by various training programs. According to an Editorial in IJTLD, raising awareness about TB among prisoners and medical and nonmedical staff through continuing education can strengthen TB control.[7] Effective plans for human resource development need to be implemented and should cover the entire process, including basic education (inservice and preservice), retraining, on-the-job training, and career development.

4) **DOTS services**

   a) *Case finding and treatment practices*

      Symptoms-based screening for TB was being conducted as a part of the initial medical examination once inmates are inducted in the jail. Inmates giving history suggestive of TB were investigated for TB using sputum microscopy and Chest X-ray (CXR). However, only 50% TB symptomatics were investigated due to operational problems in jail like court appointments, mulaquat (meeting), etc. There is no procedure for early detection of TB in prison inmates and following initial screening; the program relies on passive case finding for TB. All TB suspects are referred to Chest OPD through General OPD for further evaluation. Sputum smear microscopy and CXR are the investigations of choice.

b) *Diagnostic and treatment process*

Medical Officer (MO) in the General OPD of their respective jail is the first point of contact for prisoners who seek healthcare. The MO-incharge usually gets sputum microscopy and X-ray done simultaneously. In most of the jails, facility for X-ray is available. For sputum microscopy, the patient is given two sputum containers for collecting morning and spot sputum specimens. The samples from all jails except Jail no. 3 are transported to Central Lab. However, patients from Jail no. 3 present with their morning sample at the lab situated in CJH, and provide the spot specimen there. There is no area defined for sputum collection. The staff nurses informed that it is difficult to ensure the quality of sputum smear and also the source of sample generation, as prisoners tend to exchange or sell samples.

Status paper on prison population has documented that smear microscopy is a challenge that in some prisons there is a market for selling sputum positive for TB, because it leads to transfer to a hospital unit and better conditions.[8] The staff nurses posted in the prison reported similar findings. In addition, because of rapid transmission in prisons, particularly in high HIV burden settings, it is imperative to prioritize the diagnosis of drug-resistant forms of TB, using tools such as Xpert MTB/RIF.[8]

The results of sputum smear microscopy are sent to the respective prisons by the Central Laboratory. The reports of CXR and sputum microscopy usually are made available to the Chest Physician within a week and treatment is initiated as per program guidelines with concurrence of DTO. Extra pulmonary patients were referred to their district hospital, Deen Dayal Uppadhayay Hospital, for further investigations and treatment. The process was reported to be quite lengthy and time taking. All smear positive male patients were shifted to the TB ward in CJH in Jail no.3 and DOTS treatment was initiated. They were shifted back to their original jails after they converted to smear negative. However, female TB patients irrespective of their smear status were initiated on treatment in the ward of Jail no. 6, which housed female inmates.

c) *Contact tracing and chemoprophylaxis*

There was no provision of either screening for TB or chemoprophylaxis for the contacts of sputum positive female patients. However, some female inmates also had children staying with them. Not only the children of sputum positive females but children of other female inmates were at risk of acquiring TB infection as they shared the same accommodation. Even HIV-infected female inmates, who are at a higher risk, shared the same premises.

5) **Quality assurance of diagnostic services:** Quality assurance for sputum microscopy is done as per program guidelines but requires strengthening. On site evaluation and RBRC reports showed discrepancies implying need for training the LTs or the person involved in conducting smear microscopy for improvement of their performance.
6) **ACSM**: It was reported by the health staff that there was no system of dissemination of information regarding TB among inmates. No ACSM activities are specifically conducted to generate awareness about TB. Even RNTCP staff failed to conduct such activities. However, TB patients are counselled and educated about various aspects of TB once they are initiated on treatment through patient–provider interactions. Status paper has recommended that during screening on entry to prison, it is crucial that medical staff provide prisoners with general information on TB, as well as information on the main signs and symptoms to facilitate early diagnosis at a later stage and the availability of TB diagnostic and treatment services in the prison.[7]
7) **Drugs and logistics management**: Staff nurse (nodal) was responsible for managing the drug stock. The drugs are provided through RNTCP. However, in case of short supply, the prison authorities procured the medicines.
8) **Case recording and reporting**: Nodal staff nurse maintains the records and reports related to treatment. The records and reporting was being done as per RNTCP guidelines under the supervision of the nodal officer.
9) **TB/HIV coinfection**: All TB patients have to be referred for HIV testing. It was observed that all the TB patients were referred to the Integrated Counselling and Testing Centre in CJH for HIV testing and HIV test results were available for more than 90% patients. Staff also informed that few patients refused to get their HIV test done.
10) **Infection control practices:** (*Administrative, Environmental and PPE*): Natural ventilation was found to be poor in the barracks. All male sputum positive patients were admitted in the TB ward till they converted smear negative. The staff informed that the patients were counselled on cough etiquette; however, they did not comply to these instructions. Therefore, isolation was a preferred choice. On the contrary, isolation for smear positive/MDR female patients during initial phase of treatment was lacking. Patients were neither counselled about sputum disposal nor provided any container or disinfectant for proper sputum disposal.
11) **Follow-up after release (referral system)**: As per programmatic data, treatment outcome, ''transfer out,'' or ''released'' ranged between 14% and 45% for patients put on treatment from 2008 to 2012. On enquiring the senior treatment supervisor and the nodal staff nurse at jail hospital, it was found that almost nil feedback was received for ''transfer out'' cases on continuation of treatment after release from prison. Patient mobility is one of the biggest risk factors for incomplete treatment inside or outside prisons. Incomplete treatment leads to a lower chance of cure and therefore increased transmission of TB.[3] Decisions to transfer, release, or amnesty, were often made and implemented within hours by administrators without the knowledge of health staff. Therefore, it was difficult to follow the referral process as per RNTCP guidelines and many patients might not be completing treatment once they were out of prison. When discussed with the staff, poor registration and false addresses given by prisoners made tracing of the released prisoner patient more difficult. Therefore, even if there was a TB service

available in the area where the prisoner goes after release, it was often difficult to notify this service or to prepare a thorough, planned discharge. The referral process as envisaged under the program was found to be missing because of unplanned discharges/releases. Therefore, it is the joint responsibility of the prison administrators and health staff of prison and national program to ensure that the continuity of treatment is achieved.[9] While guidelines exist, they are difficult to implement in practice as illustrated by Anderson et al., who showed that only 48% of prisoners diagnosed with active TB completed treatment and 20% were lost to follow-up.[5]

12) **Supervision and monitoring** needs strengthening at a large scale. As the access to prison premises is restricted, the RNTCP staff found it difficult to monitor the activities completely as per guidelines especially related to diagnostic services.

4. Conclusion and recommendations

RNTCP has come a long way in provision of diagnostic and treatment services for TB amongst prison inmates, as the services were initiated in the year 2002. The services have been running successfully for the last 12 years. However, because of the restricted access, vulnerability of the prison population, and increase in DR TB, the TB control activities in the prison require restructuring. This needs strong commitment from the prison health authorities and RNTCP staff.

In order to achieve the goals of reaching the unreached as envisaged by the NSP, the definition of presumptive TB for prison inmates has been revised and needs to be operationalized at the level of initial medical examination on entry to the prison. An operational framework for tracking of inmates who miss TB screening during initial examination should be designed so that early diagnosis and treatment is available for all inmates. For enhancing the quality of diagnostic services, trained RNTCP staff should conduct sputum microscopy or the prison staff needs training on priority basis. Sputum collection needs to be done under direct supervision (directly observed sputum collection) and front loading of samples using LED microscopy may be introduced to prevent exchange of samples among prisoners. The medical officers and paramedic staff need to be trained on the recent updates in RNTCP and Programmatic management of drug resistant TB (PMDT) through Continued Medical Education (CME) programs arranged at the prison premises. Referral linkages for PMDT services need to be streamlined so that no time is wasted to initiate treatment, otherwise, the patient will keep on transmitting the disease. There is an urgent need to link all the releases and transfers of jail inmates on TB treatment through RNTCP to minimize loss to follow-up after release. Mechanism for ''Discharge planning'' needs to be devised so that there is sufficient time before release or transfer of individuals from prison. It is suggested that the patient should be given TB information leaflets and a discharge letter that states the TB results, treatment accorded, and address of the local TB referral clinic.

Supervision, monitoring, and evaluation should be carried out on a regular basis as per RNTCP guidelines for TB control activities in prison. The failure of TB control in prisons consequentially impacts on the community in general through visitors to prisons, prison staff, and prisoners discharged into the community; therefore, improving TB control in prisons impacts TB control in the community.[10]

Effective plans for human resource development need to be implemented. NTPs should always be actively involved with the prison medical services, not only for training the staff about TB but also for supervision of laboratory work, case-finding, reporting, supplies, and supervision.

Conflicts of interest

The authors have none to declare.

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Original Article

Etiology of hemoptysis: A retrospective study from a tertiary care hospital from northern Madhya Pradesh, India

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ABSTRACT

Objective: To evaluate the various etiologies of hemoptysis and outcome in an Indian cohort.
Material and methods: Retrospective analysis of patients admitted with complaints of hemoptysis in the department of Pulmonary Medicine between April 2010 and March 2013. We categorized the patients according to various etiologies and according to the grades of hemoptysis.
Results: Three hundred and forty-six patients were included in the study. Of these, 214 (67%) were men and 142 (33%) were women. Tuberculosis (79.2%) accounted for majority of cases of hemoptysis. Other causes of hemoptysis were lung cancer (7.2%), bronchitis (4.6%), and bronchiectasis (3.5%). Moderate grade (73.4%) of hemoptysis was the frequent mode of presentation.
Conclusion: Hemoptysis is the most frequent presentation of tuberculosis in India. It may be the presentation of healed pulmonary tuberculosis. Moderate amount of hemoptysis is commonly seen in the general population.

1. Introduction

Bleeding from the lungs or from tracheobronchial tree results in the coughing out of blood from the mouth and is referred as hemoptysis. It is the symptom per se not the disease and it required further evaluation to identify the disease that causes it. The level of mildness the hemoptysis may be is always of concern for the patient. Disease may range from infection to malignancy.

Various diseases like bronchiectasis, pulmonary tuberculosis, and lung cancer may cause hemoptysis. It is the geographical boundaries that result in the variation of the causes of the hemoptysis. Pulmonary tuberculosis is still the commonest cause of hemoptysis in developing countries like India,[1] while in developed countries, bronchitis and bronchiectasis are topping the charts in the causes of hemoptysis.

Hemoptysis is also classified as mild, moderate, and massive. This division is based on the amount of blood expectorated in the last 24 h i.e., mild (<100 ml/24 h), moderate (100–400 ml/24 h), and severe (>400 ml/24 h or >30 ml/h).[1] But any amount of hemoptysis that endangers the life of patient should be referred as massive or severe hemoptysis.

The purpose of the study was to evaluate the relative frequency of the causes of hemoptysis in an Indian cohort and to see whether the disease pattern has shown changes in the

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same progression as they were calculated in the past few decades in other developed countries.

2. Material and methods

This was a retrospective study. We analyzed the data of a patient who was admitted with complaints of hemoptysis in the Department of Pulmonary Medicine of Gajra Raja Medical College, Gwalior, India from April 2010 to March 2013. The study was approved by the ethical committee of the college.

Based on the examination of the medical record, patient's demographic characteristics, including age and sex, were noted. Medical records were analyzed to know the etiology of disease, smoking history, chest radiography and CT scan, sputum smear test and culture, and bronchoscopic and histopathological examination. Pulmonary neoplasm was diagnosed on the basis of histopathological examination. Patients were divided into three groups according to the amount of hemoptysis they had produced i.e., mild (<100 ml), moderate (100–400 ml), and severe (>400 ml). On the basis of etiology of hemoptysis, patients were further divided into tubercular and nontubercular group. Nontubercular group included pulmonary neoplasm, bronchitis, bronchiectasis, and other causes.

All patients were treated conservatively for the hemoptysis. Conservative treatment included the cough suppressant, along with absolute bed rest, mild sedatives if needed, and other supportive measures (protection of airways, endotracheal intubation, whole blood/blood products transfusion, lateral decubitus positioning making the bleeding site in lower position, and tranexamic acid) were given. Along with it, the primary cause was treated according to the management protocol for that disease.

3. Results

During the study period, 346 cases of hemoptysis were admitted. Of these, 214 (67%) were men and 142 (33%) were women. Mean age of the patients was 40 ± 12.6 years. Two hundred and seventy-four (79.2%) patients were diagnosed to have tuberculosis. There were 208 patients of active tuberculosis, out of which, 174 patients had sputum for AFB positive.

Table 1 – Etiology of hemoptysis in tubercular patients.

Diagnosis	No. of patients
Active tuberculosis	208 (60.1%)
AFB positive	174 (50.28%)
AFB negative	34 (9.8%)
Inactive tuberculosis	66 (19.1%)
Total	274 (79.2%)

Table 2 – Etiology of hemoptysis in nontubercular patients.

Diagnosis	No. of patients
Lung cancer	25 (7.2%)
Bronchitis	16 (4.6%)
Bronchiectasis	12 (3.5%)
ABPA	2 (0.6%)
Pneumonia	9 (2.6%)
Lung abscess	2 (0.6%)
Idiopathic	2 (0.6%)
Cardiac	2 (0.6%)
Antiplatelet drugs	1 (0.3%)
Pulmonary hypertension	1 (0.3%)
Total	72 (20.8%)

However, 66 patients had inactive tuberculosis (Table 1). There were 18 cases of tuberculosis that developed hemoptysis during the course of antitubercular treatment. All of them were bacteriologically negative cases of tuberculosis at the time of hemoptysis. Lung malignancy is the second commonest cause of hemoptysis, and all the cases were of primary malignancy. One case was diagnosed to have pulmonary hypertension on the basis of Doppler echocardiography with normal chest CT report.

Hemoptysis in majority of the patients was of moderate degree (Table 2). Severe hemoptysis was seen in 5.2% cases only. Mean duration of the stay for the hemoptysis patients was 12 ± 5.3 days. Mortality rate among hemoptysis patients was 3.4% (12); apart from 3 cases all of the other deaths were related to primary disease process. All patients were treated conservatively. Six patients required whole blood transfusion, while in 10 cases, packed red blood cells were used. None of the patients underwent bronchial artery embolization or surgery (Table 3).

Table 3 – Grading of hemoptysis.

Diagnosis	Mild	Moderate	Severe	Total
Tuberculosis	22 (8%)	237 (86.5)	15 (5.5%)	274 (100%)
Lung cancer	21 (84%)	3 (12%)	1 (4%)	25 (100%)
Bronchitis	11 (68.8%)	4 (25%)	1 (6.2%)	16 (100%)
Bronchiectasis	10 (83.3%)	2 (16.7)	0 (0%)	12 (100%)
ABPA	2 (100%)	0 (0%)	0 (0%)	2 (100%)
Pneumonia	4 (44.4%)	4 (44.4%)	1 (11.1%)	9 (100%)
Lung abscess	0 (0%)	2 (100%)	0 (0%)	2 (100%)
Idiopathic	2 (100%)	0 (0%)	0 (0%)	2 (100%)
Cardiac	2 (100%)	0 (0%)	0 (0%)	2 (100%)
Antiplatelet drugs	0 (0%)	1 (100%)	0 (0%)	1 (100%)
Pulmonary hypertension	0 (0%)	1 (100%)	0 (0%)	1 (100%)
Total	74 (21.4%)	254 (73.4%)	18 (5.2%)	346 (100%)

4. Discussion

Causes of hemoptysis depend on the geographic area and the time of the study conducted in the same geographic area. This is a symptom that was previously considered as the diagnostic feature of tuberculosis, which has now been replaced by the lung malignancy, bronchitis, and bronchiectasis in the developed countries.[2] However, in developing countries, tuberculosis is still the leading cause of hemoptysis. Our study also showed that 79.2% of the patients were diagnosed with tuberculosis. Rao[3] in 1960 reported tuberculosis as the leading cause of hemoptysis and it still continues to be the same as reported in our study. Tuberculosis had been reported in the developed countries in the older studies.[4,5] It is not only the active tuberculosis that causes hemoptysis, it can also develop in patients who were treated for tuberculosis in the past. Hemoptysis is not only the initial feature of tuberculosis but might also develop during the course of treatment,[1] and does not denote that the patient had failed the treatment. In our study we had seen that 18 (5.2%) patients developed hemoptysis while they were on the antitubercular treatment.

Incidence of bronchogenic carcinoma was found to be 7.2% and it was the second commonest cause of hemoptysis in our study. It was similar to the study done by Prasad et al.[1] where it was 5.2%. Rate of lung malignancy in the hemoptysis patient was found to be 6–19% in the recently published studies.[6–10] It was the third commonest cause of hemoptysis in these studies after bronchiectasis and bronchitis.

As stated earlier, bronchiectasis was the leading cause of hemoptysis in the developed world. Swanson et al.[11] reported bronchiectasis as the most frequent (17%) cause of hemoptysis followed by pulmonary arterial hypertension and malignant tumor. Similar trend of bronchiectasis was seen in studies like Lundgren et al.[12] (38%), Abal et al.[7] (21%), Hirshberg et al.[10] (20%), and McGuinness et al.[8] (25%). In our study, it was the fourth leading cause of hemoptysis (3.5%). It was similar to the trend found in India.[1]

Majority of the patients in our study had moderate amount of hemoptysis (73.4%). Classifying the severity of hemoptysis by various ways in literature, the finding continues to be the

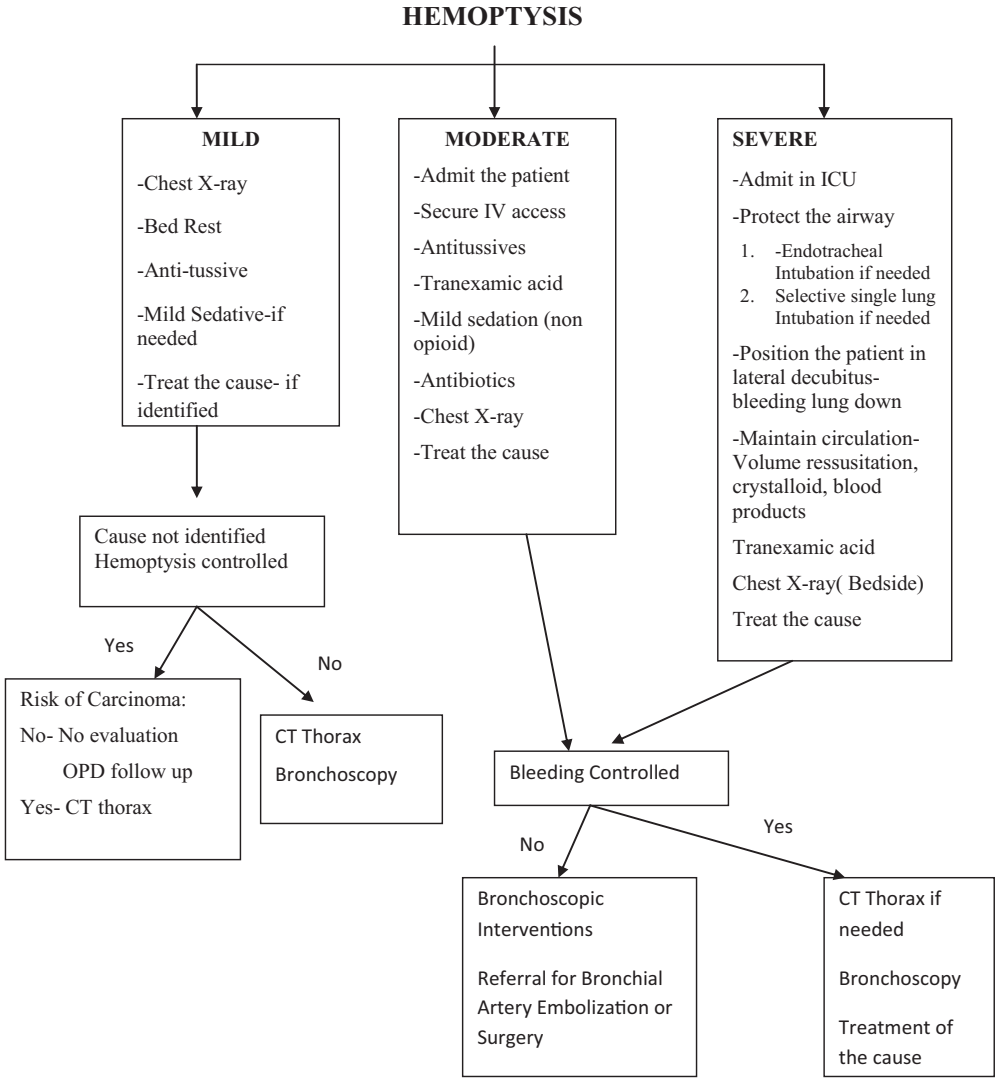

Fig. 1 – Algorithmic approach for management of hemoptysis.

same. It is moderate amount of hemoptysis that was most frequently assessed in literature. Hirshberg et al.[10] divided the patients into three groups based on the amount of hemoptysis into trivial (drop of blood, bloody sputum), moderate (<500 ml/24 h, 1–2 cups), and massive (>500 ml/24 h, more than 2 cups) and they found moderate hemoptysis in 48% of cases. Lundgren et al.[12] classified the hemoptysis as mild, moderate, or massive, depending on the amount of blood expectorated: <100 ml in 24 h (mild); 100–600 ml in 24 h (moderate); and >600 ml in 24 h or >30 ml/h (massive). They found moderate amount of hemoptysis in 56% of cases. In our study, moderate amount of hemoptysis was the frequent mode of presentation in the patients with tuberculosis. However, mild amount of hemoptysis was seen in majority of the cases of lung malignancy. It was similar to studies done in the past where majority of the lung cancer patients had shown mild hemoptysis.[10]

In our study, all the patients were treated conservatively. No advance procedure was done due to the nonavailability of the facility in our center. Still the mortality rate in our study is 3.4% (12) only. It is somewhat lower to the rate reported in the literature. Hirshberg et al.[10] reported 9% mortality rate in 208 patients similar to the mortality rate in Knott-Craig et al.[13] study. This difference may be due to the difference in the study group. The study from India has reported mortality rate of 8.2%.[1].

5. Conclusion

In developing countries like India where tuberculosis is still prevalent, it is the commonest cause of hemoptysis. It not only denotes that the patients have active disease but it may also develop when the patient is undergoing antitubercular treatment. It might also present in treated cases of tuberculosis, and in such cases, antitubercular treatment is not required if they do not show any clinicoradiological evidence of tuberculosis. Development of hemoptysis in patient undergoing antitubercular treatment does not require change of therapy until it proved to be a resistant case. Approach for the management of hemoptysis in the resource-limited setting is shown in Fig. 1.

5.1. *Limitations*

The limitation of our study was that it was a retrospective study that was conducted in resource-limited conditions where the advance facilities for the treatment of massive hemoptysis were not available.

5.2. *Key messages*

In a developing country, tuberculosis is the leading cause of hemoptysis. In the presence of limited resources, can be diagnosed and managed properly.

Conflicts of interest

The authors have none to declare.

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Original Article

Innovatively addressing the challenge of maintaining binocular microscopes under Tuberculosis Programme in India – Is this feasible?

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ABSTRACT

Background: India is a high TB burden country. The preferred first line diagnostic tool under National TB Programme is sputum smear microscopy through binocular microscopes (BMs) from 13,000 designated microscopy centres across the country. The programme had devised innovative strategy for maintenance of BMs. A study was conducted to look into the operational feasibility of an external agency to provide maintenance services for BMs engaged through newer strategy.

Methods: A cross-sectional study was conducted in the states of Uttar Pradesh, Bihar and Rajasthan during 2010–2013.

Results: A total of 9314 BMs were serviced during the period 2011–2013, of which 1104 (11.8%) had major repairs, 2204 (23.6%) had minor repairs, 1054 (11.3%) were provided emergency breakdown services and 223 (2.4%) were condemned.

Conclusion: The bold initiative and newer strategy of the programme to engage agencies for BMs maintenance services is worthwhile and should be continued and could be considered for replication across the country.

1. Introduction

In India, tuberculosis (TB) continues to be a serious public health problem. Sputum smear microscopy through binocular microscopes (BMs) is currently the preferred first line diagnostic tool for TB under the national programme. By 2013, the programme has established a network of over 13,000 quality assured microscopy centres (MCs) across the country which examines over 8 million presumptive TB cases annually[1] diagnosing nearly 1 million cases, i.e. ~8.5 presumptive TB cases were examined to diagnose a sputum smear positive TB case.[1] Apart from diagnosis, the MCs also conduct follow-up examinations of patients on treatment.

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With the emphasis on early diagnosis and universal access to TB care, ensuring functionality of BMs is of paramount importance to reduce delay and prevents false results that can have profound consequences on patient management and disease epidemiology in the country. To maintain the efficiency and continuous functionality of BMs, the programme has devised guidelines for states to secure maintenance of BMs which are out of manufacturer's warranty through an external agency. However, programme managers have encountered many challenges while engaging agencies which are enumerated below:

(a) *Limited availability of maintenance agencies:* The numbers of agencies that provide annual maintenance services which meet the standard technical and operational requirements of the programme are limited at states. Even when available, the agencies do not find the current norms attractive (25 USD annually per microscope[2]) as it necessitates maintenance of robust logistics supply chain management that needs additional capital and human resource investment for effective operationalisation. Any flexibility in the requirements may compromise the quality of services.
(b) *Delivery of services:* Agencies hired by states do not provide onsite maintenance and instead, recall the microscopes from the distantly located MCs to centralised locations (e.g. cities or district headquarters) and the onus of getting the BMs lies on the programme staff or laboratory technician. This directly or indirectly costs the programme in terms of loss of at least 2–3 working days for a MC besides the travelling cost involved for the staff.
(c) *Monitoring of services:* The state and district programme managers are unable to monitor the services of the agency due to competing priorities and lack of monitoring tool and indicators to assess the performance.
(d) *Delayed disbursement and renewal of services:* There is usually delay in disbursement of funds to the agencies and renewal of contracts due to administrative reasons. This results in demotivation of the agency and discontinuity of services.

Complexities in engaging agencies at field level have precluded the Revised National Tuberculosis Control Programme (RNTCP) to adopt newer strategies at national level for engagement. The International Union against Tuberculosis and Lung Disease (The Union) was delegated to support the maintenance services of BMs, on a pilot basis under the Global Fund supported project Axshya, in 3 large states (Uttar Pradesh, Bihar and Rajasthan) that were facing challenges in securing maintenance services. Through an open competitive bidding process, the Union identified five private agencies and awarded the maintenance contract to the one adjudged the best based on strict technical and financial criteria. This paper is an effort to describe the process and output of this newer strategy, i.e. public private (not for profit) partnership (PPP) and further sub-contracting to private (for profit) agency.

The Process: Due feedback from state programme managers was obtained by The Union through series of consultative meetings. The criteria for comprehensive delivery of services were laid down to the provider agency which included

1. Quarterly onsite preventive maintenance of the BMs
2. Addressing onsite emergency breakdown of BMs within 72 h from receipt of complaint
3. Replacement of replaceable non-functional parts of the BMs wherever required

2. Methods

A cross-sectional study was conducted in the states of Uttar Pradesh, Bihar and Rajasthan during 2010–2013. Initially, the agency conducted a baseline onsite assessment of BMs at respective districts. The available BMs were classified as (1) functional BMs, (2) non-functional BMs (BMs that require minor or major repairs or both) and (3) irreparable BMs. The items included as minor and major repairs are listed in Box 1. The irreparable BMs were listed and a certificate was issued for their condemnation and replacement as per programmatic procedures.

For each BMs serviced under quarterly maintenance or emergency breakdown, a service report was prepared by the agency technician using a standardised format mentioning the details of the repairs undertaken including the spare parts replaced. The service report was verified by respective laboratory technician of the MC and certified by the district programme manager. The cumulative service records and reports from districts and states formed the basis for quarterly release of funds to the provider agency by the Union. All the RNTCP BMs at the states were covered for annual maintenance and the service reports generated during the process were further analysed in the study. The renewal of the annual contract with the agency is done after a thorough review of the performance in consultation with the state programme manager.

3. Results

A total of 9314 BMs were serviced during the period 2011–2013, of which 1104 (11.8%) had major repairs, 2204 (23.6%) had minor repairs, 1054 (11.3%) were provided emergency breakdown services (Table 1) and 223 (2.4%) were condemned. The main reasons for condemnation were (a) distortion of optical alignment and prism damage due to wear and tear, (b) older microscopes of more than 20 years and (c) non-availability of

Box 1. List of minor and major repairs performed for BMs

Minor repairs:
- Problems in coarse adjustment
- Problems related to rack and pinion tubes
- Dropping of stage and electrical problems

Major repairs: Replacement of,
- Eye piece
- High powered lenses
- Complete stage
- Bulb
- Mirror assembly and electrical circuit

Table 1 – Types of repairs and emergency services undergone by BMs in different states, 2011–2013.

Year	States	No. of microscopes serviced	Major repairs, N (%)	Minor repairs, N (%)	Condemned microscopes, N (%)	Emergency breakdown services, N (%)
2011	Uttar Pradesh and Bihar	2521	491 (19)	783 (31)	137 (5)	245 (10)
2012	Uttar Pradesh, Bihar and Rajasthan	3373	287 (9)	662 (20)	55 (2)	392 (12)
2013	Uttar Pradesh, Bihar and Rajasthan	3420	326 (10)	759 (22)	31 (1)	417 (12)

Table 2 – Proportion of BMs covered in different rounds of maintenance services, 2013.

State	Number of BMs	Round of service			
		First, N (%)	Second, N (%)	Third, N (%)	Fourth, N (%)
Uttar Pradesh	1870	1870 (100)	1864 (99.7)	1834 (98.4)	1682 (91.7)
Bihar	770	770 (100)	760 (98.7)	770 (100)	770 (100)
Rajasthan	792	792 (100)	792 (100)	792 (100)	792 (100)

microscope spares like lens, stage and circuit. The performance of 2013 was analysed for proportion of BMs that underwent quarterly maintenance services and almost all BMs underwent four services during the year (Table 2).

4. Discussion

The study findings suggest operational plausibility of an external agency providing maintenance services for BMs engaged through this newer strategy. The performance of the agency, which is periodically reviewed, is found to be optimal with good acceptability at field. This newer strategy has following programmatic implications. First, the state or district programme managers are saved the unnecessary administrative processes of identifying and contracting suitable agencies that provide these services. Secondly, the performance of the agency is monitored by a technical partner with systematic feedback from the programme personnel who indirectly maintains control through verification and certification of the service reports submitted by the agency. This enhances the transparency and ownership of the health system. Thirdly, the disbursement of funds to the agency and process of renewal of annual contract, based on the objective performance of the agency in the field, is timely and streamlined. The programme at national level and the donor agency also has an edge to monitor and supervise the activity closely at field level.

The following reinforces the transparent mechanism at service delivery that exists at district, state and national level. The agency generally advocates and delivers the services under the direct supervision of RNTCP staff or District TB Officer or any other health personnel. The place of service delivery is dependent on the geography of the district, availability of transport facility and laboratory technician. The BMs maintenance services are provided on-site at the respective MCs. The services provided during emergency breakdown enable the MCs to resume their services almost instantaneously. General orientation regarding routine care of the BMs is also provided to the laboratory technicians during the visits. The irreparable microscopes, certified by the agency, get replaced and the agency also provides solutions through phones to the laboratory technicians on minor technical problems. There remains no scope for the hired agency to get its contract renewed on non-performance. To conclude, the bold initiative and newer strategy of the programme to engage agencies for BMs maintenance services is worthwhile and should be continued and could be considered for replication across the country. The credibility of newer strategy should prompt programme to widen its area to laboratory equipments at RNTCP accredited culture and drug susceptibility testing laboratory facilities.

Authors' contribution

The idea was conceived by SK, SBN, SSC and SS; SBN, SK, SSC, SS, BMP and KSS have contributed in writing, while all other authors have approved the final manuscript.

Conflicts of interest

The authors have none to declare.

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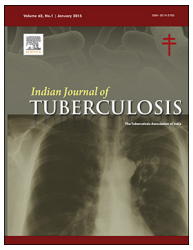

Original Article

A case–control study identifying the characteristics of patients providing incorrect contact information at registration for DOTS in Pune, India

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ABSTRACT

Background: Provision of incorrect contact information by the patient at the time of registration for treatment is a deterrent to treatment adherence.

Objective: To determine the characteristics of patients providing incomplete contact information at the time of registration for Directly Observed Treatment Short course (DOTS) at the tuberculosis units (TUs) in Pune, India.

Methods: A nested case–control study was conducted where the characteristics of patients who had provided incorrect contact information (cases) were compared with the characteristics of patients who could be traced (controls). Cases and controls were identified from a cohort of 3802 tuberculosis patients registered at the DOTS centres in Pune. Correct or incorrect contact information was ascertained by visiting each address provided at the time of registration. Characteristics associated with providing incorrect contact information were determined through multinomial regression analysis.

Results: There were 406 (10.7%) patients who could not be traced due to incorrect address provided at the time of registration at the DOTS centres. Registration at the TUs in the peripheral areas of the city (odds ratio (OR) = 3.57, 95% confidence interval (CI) = 2.64–4.84) and engagement in migration prone occupation (OR = 1.83, 95% CI = 1.47–2.26) were associated with odds of providing incorrect information at the time of registration.

Conclusion: Untraceable patients were more likely to be engaged in occupations with a potential for migration. DOTS centres located in developing areas of cities should reinforce validation of contact information of patients.

1. Introduction

India reports an annual burden of 2.1 million tuberculosis cases and an estimated incidence of tuberculosis of 171 per 100,000 population.[1] Compliance to Directly Observed Treatment Short (DOTS), wherein patients are put on 2 months of intensive treatment followed by 4 months of continuous treatment (or 3 months of intensive treatment followed by 5 months of continuous treatment in case of patients with a

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history of tuberculosis), is ensured by a number of activities of the Revised National Tuberculosis Control Programme (RNTCP). These include verification of contact addresses provided by patients at the time of registration for treatment by the Tuberculosis Health Visitor,[2] and follow-up of patients not presenting for treatment. In these instances, provision of incorrect contact information becomes a matter of concern for programme managers. In addition to issues relating to treatment compliance, provision of incorrect addresses is challenging for research studies, where a cohort of patients may need to be periodically contacted, such as for studies measuring efficacy of treatment or studies measuring survival of patients after treatment. As a part of a larger study to estimate the survival of patients after completion of DOTS, we determined the proportion and characteristics of patients providing incorrect contact information at the time of registration for DOTS.

2. Method

2.1. Study design and setting

The study was a nested case control study. The study setting was the six tuberculosis units (TUs) situated within the limits of Pune Municipal Corporation and catering to 3,000,000 population.[3] Among the six TUs, two (designated as TU 3 and TU 5) were located in the newly developing areas of the city witnessing significant construction activities, while the remaining four (TU 1, 2, 4 and 6) were located within the residential areas of the city.

2.2. Participants

The study included a cohort of 3802 adult patients diagnosed with pulmonary tuberculosis as per the RNTCP diagnostic protocol[4] and registered between January 2009 and December 2010. All 3802 patients were contacted at the address provided at the time of registration for treatment. Cases were defined as those patients who could not be located at the address provided at the time of registration for DOTS despite three visits at the interval of 3 months from the first visit, and who could not be identified by neighbours. Controls were patients who could be located at the reported address or erstwhile patients who were known to neighbours but who were reported as migrated to a new location at the time of visit for confirming the contact address.

2.3. Variables and data collection

The variables analysed in the study included demographic characteristics (age, sex, residential address, occupation), clinical characteristics (type of case, baseline sputum smear status, HIV status) and treatment related (date of initiation of treatment, date of last contact with the DOTS centre, treatment outcome and regularity in treatment). The variable, migration prone occupation included patients involved in construction or who were farm labourers. Based on their location in the peripheral parts of the city, patients registered with TU 3 and TU 5 were designated as TUs in newly developing areas. Data on patient characteristics were collected from the RNTCP records using a structured data collection format.

2.4. Ethical consideration

For patients who could be contacted, verbal consent was obtained by the researcher. In case of lack of contact, the researcher visited the given address and made enquiries about the patient without divulging the reason for the visit to neighbours. The study was approved by the Institutional Ethics Committee of Savitribai Phule Pune University.

2.5. Statistical analysis

Univariate analysis using Statistical Package for Social Sciences (SPSS) version 20 was carried out to determine the significant differences in demographic, clinical and treatment-related characteristics between cases and controls. Factors significantly associated with the outcome variable in the univariate analysis were included in the multinomial regression analysis to identify the significant characteristics associated with patients providing incorrect contact information at the time of registration for DOTS.

3. Results

Between January 2009 and December 2010, 3802 pulmonary tuberculosis patients had registered at the six TUs in Pune city. Of these, 406 (10.7%) patients could not be traced to the provided address. The remaining 3396 (89.3%) patients constituted the control group in the study and included patients who could be contacted at their residence (n = 3224) or patients whose information on migration status could be obtained (n = 172). Table 1 shows the characteristics of cases and controls. There was no significant difference in the distribution of patients by age, sex, baseline sputum smear status and type of case (that is new cases or cases with history of tuberculosis). There was also no difference in the treatment outcome between cases and controls. There was, however, a difference in occupation between patients registered in the two TUs located in the newly developed areas of the city (TU 3 and TU 5) and the remaining TUs. Patients registered at TU 3 and TU 5 were more likely to be in migration prone occupations as compared to patients registered in the remaining TUs (61.4% versus 45.3%, odds ratio (OR) = 1.93, 95% confidence interval (CI) = 1.59–2.34) (Fig. 1).

Upon univariate analysis, two variables were significantly associated with provision of incorrect contact information at the time of registration. Patients registered at the two TUs located in the newly developing areas of the city (TU 3 and TU 5) were more likely to provide incorrect information at the time of registration (65.8%) as compared to patients registered in the remaining TUs (65.8% versus 33.8%, OR = 3.76, 95% CI = 3.03–4.67). The other associated characteristic was a greater number of patients in the case group who had unknown HIV status (47.3%) as compared to patients in the control group (32.1%) (OR = 1.83, 95% CI = 1.47–2.27) (Table 1).

Table 1 – Characteristics of cases (untraceable patients) and controls.

Characteristics	Cases (N = 406)	Controls (N = 3396)	OR (95% CI)
Socio-demographic characteristics			
Age group (N = 3799)			
Less than or equal to 20	10.8 (44)	11.4 (387)	0.83 (0.52–1.32)
21–30	32.8 (133)	29.2 (990)	0.98 (0.66–1.45)
31–40	22.2 (90)	24.5(831)	0.79 (0.52–1.19)
41–50	16.5 (67)	16.5 (561)	0.87 (0.56–1.34)
51–60	9.1 (37)	10.9 (370)	0.73 (0.45–1.18)
61 and above	8.6 (35)	7.5 (254)	Ref.
Sex (N = 3802)			
Male	69.7 (283)	65.6 (2228)	1.21(0.96–1.51)
Female	30.3 (123)	34.4 (1168)	Ref.
Place of registration (N = 3802)			
TUs in newly developing areas	65.8 (267)	33.8 (1149)	3.76 (3.03–4.67)
Rest of the city	34.2 (139)	66.2 (2247)	Ref.
Clinical characteristics			
Baseline sputum smear status (N = 3801)			
Positive	74.6 (303)	74.0 (2513)	1.03 (0.82–1.31)
Negative	25.4 (103)	26.0 (882)	Ref.
Type of case (N = 3802)			
New	84.0 (341)	81.2 (2759)	Ref.
With history of tuberculosis	16.0 (65)	18.8 (637)	0.83 (0.63–1.09)
HIV status (N = 3802)			
Positive	6.9 (28)	11.2 (379)	0.76 (0.51–1.15)
Negative	45.8 (186)	56.7 (1927)	Ref.
Unknown	47.3 (192)	32.1 (1090)	1.83 (1.47–2.26)
Treatment outcome (N = 3522)			
Treatment completed	86.5 (327)	88.3 (2776)	Ref.
Defaulted	13.0 (49)	10.4 (328)	1.27 (0.92–1.75)
Treatment failure	0.5 (2)	1.3 (40)	0.43 (0.10–1.77)

After multinomial logistic regression analysis, individuals registering with the TUs located in the newly developing areas (adjusted odds ratio (AOR) = 3.57, 95% CI = 2.64–4.84) were found to be more likely to provide incorrect contact information at the time of registration at the TUs (Table 2).

4. Discussion

The importance of correct contact information is significant not only for ensuring treatment completion, but also for conducting studies requiring periodic follow-up of patients.[5,6] The current study attempted to identify factors associated with patients who provide incorrect contact information at the time of registration at the DOTS centres. Comparison of characteristics of patients providing incorrect addresses identified an association with registration at TUs located in the newly developing areas of the city, where patients were primarily engaged in migration prone occupations such as construction. Another characteristic significantly associated with patients providing incorrect address was unknown HIV status, due to refusal to undergo voluntary HIV testing. In multinomial regression analysis, only one variable,

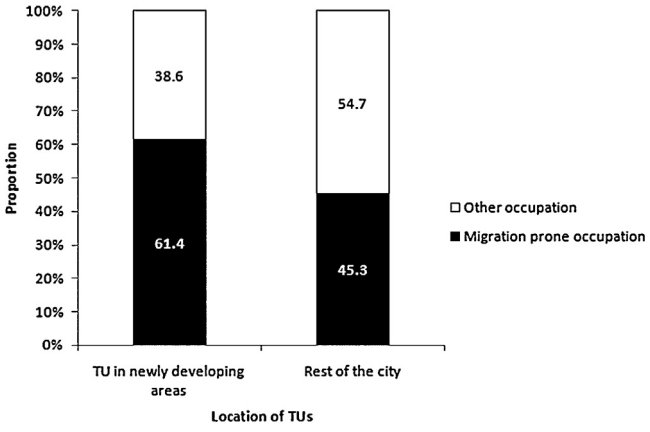

Fig. 1 – Distribution of patients engaged in migration prone occupation in TUs located in newly developing areas and rest of the city.

Table 2 – Multinomial logistic regression analysis to characterise patients likely to provide incorrect personal information during registration.

Characteristics	AOR (95% CI)
Place of registration	
Peripheral TUs	3.57 (2.64–4.84)
Rest of the city	Ref.
Occupation	
Occupation prone to migration	0.99 (0.74–1.32)
Other employment	Ref.
HIV status	
HIV positive	1.02 (0.59–1.75)
HIV status unknown	1.28 (0.95–1.74)
HIV negative	Ref.

registration in TUs located in the newly developing areas, was significantly associated with the characteristics of patients who had provided incorrect contact information. Thus, the results of our study also support earlier studies identifying migration as a major variable, which is known to be associated with treatment compliance, outcome, re-infection and mortality risk.[7–18]

The main conclusion of our study is that programme managers at TUs where patients are likely to be in migration prone occupations need to be vigilant and ensure validation of addresses at the time of patient registration. It is, however, worth noting that there was no difference between cases and controls in terms of treatment outcome, suggesting that while the case patients were willing to complete treatment, they were unwilling to divulge contact details. The reasons for this are not apparent from our study, but needs to be investigated further through qualitative studies.

5. Conclusion

Correct contact information is necessary not only for a successful tuberculosis control programme, but also for the purpose of conducting follow-up studies. The results of this study identify that peripherally situated TUs are more likely to receive patients in migration prone occupations, who are more likely to provide incorrect residential information.

Conflicts of interest

The authors have none to declare.

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Case Report

Successful removal of self-expanding metallic stent after deployment for tubercular bronchostenosis

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ABSTRACT

The use of metallic stents is traditionally not recommended for benign tracheobronchial conditions. With advances in the field of interventional bronchoscopy, metal tracheobronchial stents have occasionally been used to treat benign disease. However, the removal of these stents from the airway is technically difficult. We are reporting the case of a young female subject who received a self-expanding metallic stent for alleviation of post-tubercular bronchostenosis, which was successfully removed after two months without complications. Metal stents can be used in benign tracheobronchial conditions but require meticulous follow-up to monitor complications. Experienced operators can remove them without major complications and this may be life-saving in emergencies. We are reporting this case for the rarity of such procedures in India.

1. Introduction

Traditionally, tracheo-bronchial self-expanding metallic stents (SEMS) are not recommended for use in benign conditions of the airway since there are complications such as granulation tissue formation, migration, and technical difficulty in removal of these stents in the event of resolution of the benign etiology. However lately, SEMS have been used not only in malignant, but also for the management of benign tracheo-bronchial conditions. There are few reports of successful removal of metallic endobronchial stents used for benign indications.[1–3] A couple of case reports have been published by Indian authors documenting the removal of SEMS.[4,5] We report our successful experience of removing metallic stent from the airway of a subject with post-tubercular bronchostenosis.

2. Clinical record

A 26-year-old female, a known asthmatic presented with complaints of dry cough and significant weight loss (6 kg) over preceding seven months. She had been evaluated elsewhere

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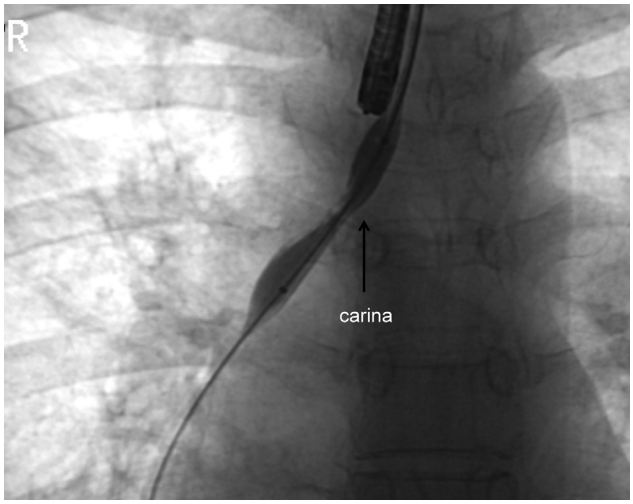

Fig. 1 – Fluoroscopy picture at the onset of balloon bronchoplasty shows severe narrowing of proximal RMB as seen by the constricted balloon at this region.

and diagnosed to have right main bronchus (RMB) stenosis for which she was referred to a tertiary center. At presentation, her general examination and vital signs were normal. Respiratory system examination revealed a central trachea, with decreased air entry on the right side and coarse inspiratory crackles over right interscapular and infraaxillary region. Chest radiograph showed a right lung consolidation with nodular infiltrates. A computed tomographic scan of the thorax showed gross narrowing of RMB, a cavity with air-fluid level in the right upper lobe, cylindrical bronchiectasis in right middle lobe, extensive consolidation in right lower lobe, and significant right lower paratracheal and subcarinal adenopathy.

Bronchoscopy was done, which showed normal vocal cords and trachea, but the RMB was invisible and on gentle prodding of the region of the RMB, pus poured out from the bronchus, which became barely visible. Bronchial wash and biopsy were taken and this revealed scanty AFB, and she was subsequently started on anti-tubercular therapy. In the same sitting, balloon bronchoplasty was done with a 8 mm × 4 mm balloon. While inflating the balloon, the severe proximal RMB stenosis was re-demonstrated (Fig. 1). The bronchoscope could be passed easily into the RMB after the procedure. The procedure was then repeated with a 10 mm balloon. The size of the lumen had increased and CT scan also showed improved right lung expansion after the procedure. However, when bronchoscopy was done a month later, the stenosis had recurred. Thus dilatation was repeated. The same sequence followed once more.

Since the stenosis had a tendency to recur after dilatation and the patient wanted respite from procedures, it was decided to plan a stent in place that will help to keep it patent. Since the silicon stent was not in stock, a covered SEMS placement was planned after obtaining informed consent. After dilating the RMB to 10 mm, a 12 mm × 3 cm covered self-expandable nitinol metallic stent (Niti-S) was deployed across the stenosis (Fig. 2a–c). A repeat bronchoscopy was done on

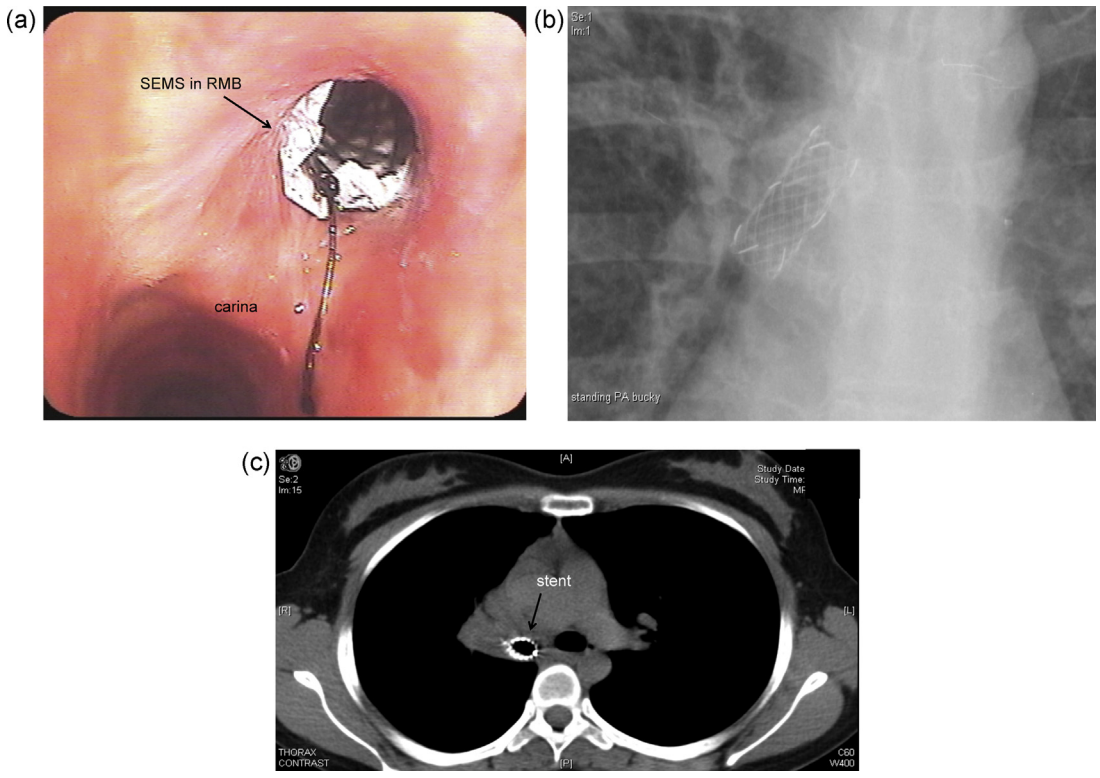

Fig. 2 – (*a*) Bronchoscopic image at carina with SEMS (self-expanding metallic stent) in the RMB. (b) X-ray image post-stenting, showing the fully expanded SEMS keeping the RMB patent. (c) Computed tomography confirming the SEMS in the correct position.

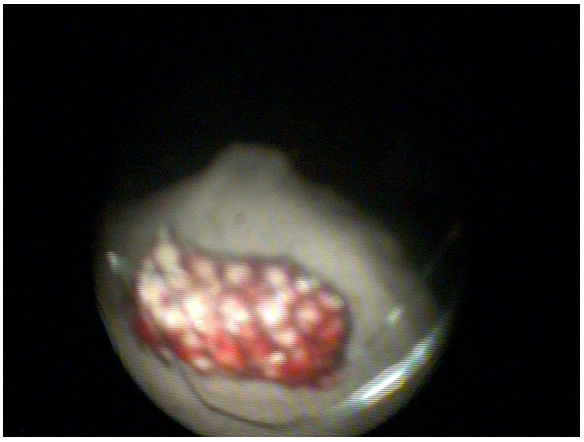

Fig. 3 – Picture of the SEMS (self-expanding metallic stent) that was removed in toto.

the next day to inspect the position of stent, and it was found to be partially covering the right upper lobe bronchus opening. Hence, it was cautiously pulled up by a few millimeters and repositioned appropriately. There were no immediate post-procedure complications and the patient was discharged in stable condition.

Being wary of the likely difficulties with delayed stent removal, the procedure was planned under general anesthesia after 2 months, with the hope that it may be replaced with a silicone stent of appropriate size. The SEMS was removed in toto (Fig. 3), using rigid bronchoscopy and stent removing forceps. After stent removal, the RMB was patent, allowing the passage of the 6.2 mm bronchoscope freely through it. The distal segments were all patent. Hence, it was decided to keep her under surveillance. There were no post-operative complications and the patient was discharged the following day. However, at review in 2 months, there was recurrence of stenosis of proximal RMB. This warranted re-stenting. As the patient wanted a permanent solution, in discussion with the thoracic surgeons, she was advised to come prepared to explore surgical options.

3. Discussion

SEMS are inserted with increasing frequency in patients with benign and malignant airway stenosis.[6,7] They are generally not preferred in benign disease, since they have been shown to make potentially operable post-intubation tracheal stenosis (PITTS) inoperable because of the severe complications associated with the technique. This prompted the US Food and Drug Administration to publish recommendations to limit the use of SEMS in benign tracheal stenosis. Silicone stents are more suitable because of their easy removal and are not likely to jeopardize a future surgery, as they do not get epithelialized. SEMS, on the other hand, become epithelialized, which supposedly prevents migration and permits ciliary activity to continue. However, significant complications can occur, including airway inflammation, stent migration, airway erosion, stent fracture and collapse, but more serious complications are uncommon.[8] SEMS were mostly used for large airway stenting, and the most frequent indication is palliative treatment for malignant disorders. However, more recently, SEMS have been used to treat benign airway obstruction caused by anastomotic narrowing after lung transplantation, infection, congenital lesions, tracheobronchomalacia, and inflammatory conditions including relapsing polychondritis, Wegener granulomatosis, acquired immunodeficiency syndrome, and external compression from benign mediastinal masses or fibrosis.[8] Considering the frequent complication of blockage of tracheal stents, it is questionable whether the use of tracheal stents, especially in the proximal trachea, is justified, particularly when the patient presents in the emergency with a compromised airway.[4] In a study,[7] the following complications of tracheal stents were looked at: granulation tissue formation (27%), restenosis (19%), migration (10%), fracture (8%), erosion (4%), and bleeding (1%).

Granulation tissue formation may be mild enough to remain asymptomatic, moderate to produce stridor, or severe enough to present as life-threatening respiratory distress.[9] Covered stents prevent tumor or granulation tissue from proliferating through the stent. However, the presence of a covering hampers expectoration of sputum, thus increases infection. Uncovered stents allow granulation tissue to proliferate within the stent, thus blocking its lumen and causing difficulty in stent removal. Metallic stents are more prone to develop granulations[10] when compared to silicone stents, especially at the proximal segment, as they are more rigid with multiple edges and produce circumferential pressure on tissues, leading to airway irritation. The granulation tissue that forms around metal stents also leads to epithelialization of the stent, making its removal extremely difficult. Once the stent becomes mucosalised, it may require destruction and piecemeal removal.[4,10] Their placement used to be considered as permanent, with open surgery as the only way to remove the stent. There are few recent case reports about their removal with the bronchoscope, but the complications after their removal are very high.[5]

We report the successful removal of a covered SEMS (ultraflex nitinol stent) from the airways of a patient without significant complications. The case is being reported for the rarity of the instances of complete removal of SEMS from airways without complications. This offers a ray of hope for patients with benign tracheobronchial disease who might require placement of metallic stents in life-threatening emergencies when silicone stents are not immediately available or the technical support and know-how to place silicon stents using rigid bronchoscopes are not available. The major dilemma while placing metallic stents for benign disease is the question – will removal pose problems? This experience has been reassuring that metallic stents, in such cases, can and have been successfully removed in the short term. It is prudent to reiterate that it is a short-term or bridging option to something more permanent in benign disease.

Conflicts of interest

The authors have none to declare.

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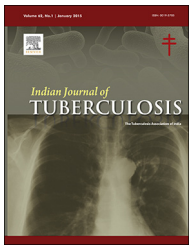

Case Report

Hematemesis: Unusual presentation of isolated gastric tuberculosis

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ABSTRACT

A 25-year-old male presented with hematemesis, epigastric pain, and melena. He had dyspepsia with significant weight loss for 3 months period. On clinical examination, he was pale with no organomegaly or lymphadenopathy. The X-ray chest was normal, and ultrasound abdomen was normal. Upper GI endoscopy revealed nodularity and ulceration along proximal part of lesser curvature of the stomach. CT scan abdomen showed thickening of lesser curvature just below gastro-esophageal junction. The biopsies were negative for malignancy. Repeat upper GI endoscopy showed a nonhealing ulcer, on repeat well biopsies taken from the base of ulcer primary gastric tuberculosis was diagnosed. It showed many epithelioid cell granulomas and multinucleated giant cells with caseous necrosis on histology. Acid-fast bacilli on Zeil Neelsen staining and TB PCR were positive for *Mycobacterium tuberculosis*. He was put on four-drug anti-tuberculous treatment. On follow-up, the patient gradually improved and regained weight. Repeat upper GI endoscopy done after 8 weeks showed healing of the ulcer with decrease in nodularity.

1. Case report

A 25-year-old male presented with two bouts of hematemesis, 2 days prior to admission, containing about 200 ml of blood per bout, blackish in color mixed with few clots followed by episodes of malena for next 2 days. He also had complaints of pain in upper abdomen, occasional vomiting, and dyspepsia for 3 months. Pain was in epigastric region, dull aching, aggravated after meal and partially relieved by vomiting. There was a history of significant weight loss over this period. There was no history of smoking, alcohol intake, analgesic use, cough, hemoptysis, and risk factors for chronic liver disease. He was treated by proton pump inhibitors, but symptoms were not relieved. General examination was normal except pallor. Systemic examination did not reveal any abnormality. X-ray chest, complete blood count, renal, and liver function tests were normal. ESR was 40 mm per hour. HIV, HBsAg, and HCV status were negative. Upper GI endoscopy revealed unhealthy mucosa with nodularity and ulceration along proximal lesser

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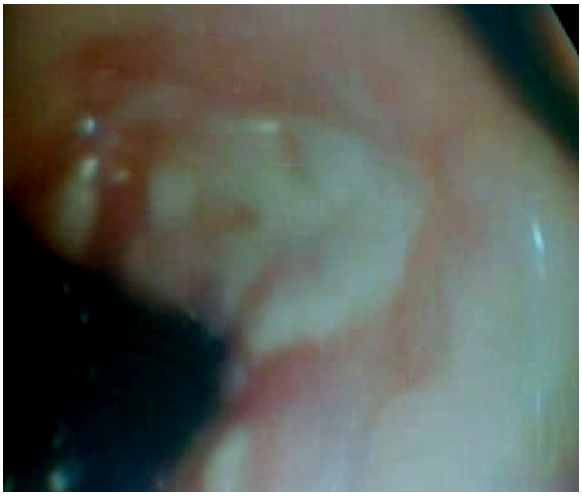

Fig. 1 – Endoscopy image showing gastric ulcer along proximal lesser curvature.

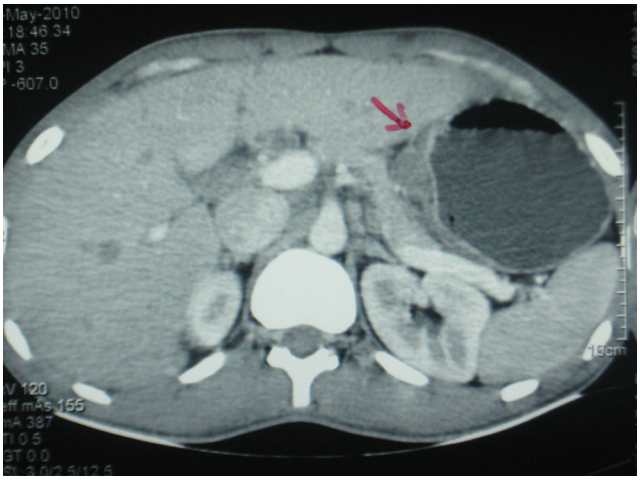

Fig. 2 – CT abdomen showing thickened gastric wall along lesser curvature.

curvature of the stomach (Fig. 1). Esophagus, rest of stomach, and duodenum were normal. Colonoscopy up to terminal ileum was normal. CT scan abdomen showed thickening along the lesser curvature of the stomach just below gastro-esophageal junction (Fig. 2).

A diagnosis of tuberculous gastric ulcer was made based on the findings of biopsy taken from the base of ulcer, which showed many epithelioid cell granulomas and multinucleated giant cells with caseous necrosis. Acid-fast bacilli on Zeil Neelsen staining and TB PCR were positive for *Mycobacterium tuberculosis*. He was put on four drug antituberculous treatment. On follow-up, the patient gradually improved and regained weight. Repeat upper GI endoscopy done after 8 weeks showed decrease in nodularity with healing of the previously seen ulcers of the high lesser curvature below gastro-esophageal junction (Fig. 3).

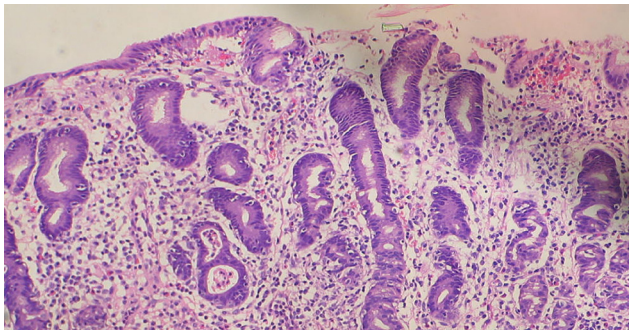

Fig. 3 – Gastric biopsy showing inflammatory infiltrate with granuloma.

2. Discussion

Within the gastrointestinal tract, the ileo-caecal region is the most common site for intra-abdominal tuberculosis.[1] The incidence of gastric tuberculosis is 0.03–0.21% of all routine autopsies.[2] The possible routes of infection include direct infection of the mucosa, hematogenous spread, or extension from a neighboring tuberculous lesion. The antrum and prepyloric regions are the most common sites of tuberculous lesions in the stomach.[3] Primary and isolated gastric tuberculosis without evidence of lesions else where is exceedingly rare due to the bactericidal properties of gastric acid, the scarcity of lymphoid tissue in the mucosa, and the rapid emptying of gastric contents.[4] However, the gastrointestinal tract is the sixth-leading location of extrapulmonary tuberculosis, following nodal, genitourinary, bone and joint, miliary, and meningeal locations.[5] In decreasing order, gastrointestinal localizations include the ileo-cecal region, the ascending colon, the jejunum, the appendix, the duodenum, the stomach, the esophagus, the sigmoid colon, and the rectum. Based on endoscopy, lesions may be described as, single or multiple ulcers with or without hypertrophic nodular lesions surrounding a stenotic pyloric channel. Ulcerative lesions are the commonest, and typically centers in the antrum and along the lesser curvature, as seen in our patient. Presenting symptoms may be similar to peptic ulcer or are often related to gastric outlet obstruction. Hematemesis is rare.[6] Failure to respond to traditional ulcer therapy should arouse high index of suspicion confirmatory diagnosis mainly is histopathological examination of the lesion. But microbiological proof is not always possible. Acid-fast bacilli are detected in only 4–6% of cases and granulomas are found only in 40% of cases. Endoscopic biopsy is positive in only one third of cases. Tubercular granulomas are submucosal and endoscopic biopsies do not include submucosa routinely. Polymerase chain reaction amplification of mycobacterium DNA from gastric biopsy increases the sensitivity up to 95% and specificity 100%.[5,6] Treatment is mainly medical with antitubercular drugs, but surgery may be needed in complicated cases.

In conclusion, our case highlights the diagnostic challenge of gastric tuberculosis in developing countries. A high index of suspicion is required in order to diagnose this rare condition, as it can present in patients with no particular risk factors or symptoms. Therefore, in patients residing in endemic areas, who have history mimicking peptic ulcer symptoms and not

responding to anti-ulcer therapy, gastric tuberculosis should always be part of the differential diagnosis.

Conflicts of interest

The authors have none to declare.

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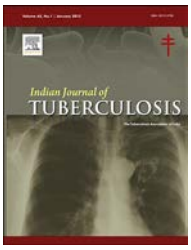

Abstracts

Risk of active tuberculosis in the five years following infection... 15%?

Trauer JM, Moyo N, Tay E-L, Dale K, Ragonnet R, McBryde ES, Denholm JT. *Chest* 2016;149(2):516–525. http://dx.doi.org/10.1016/j.chest.2015.11.017

Background: It is often stated that the lifetime risk of developing active TB after an index infection is 5–10%, one-half of which accrues in the 2–5 years following infection. The goal of this study was to determine whether such estimates are consistent with local programmatic data.

Methods: This study included close contacts of individuals with active pulmonary TB notified in the Australian state of Victoria from 1 January 2005 to 31 December 2013, who we deemed to have been infected as a result of their exposure. Survival analysis was first performed on the assumption of complete follow-up through to the end of the study period. The analysis was then repeated with imputation of censorship for migration, death, and preventive treatment, using local mortality and migration data combined with programmatic data on the administration of preventive therapy.

Results: Of 613 infected close contacts, 67 (10.9%) developed active TB during the study period. Assuming complete follow-up, the 1650-day cumulative hazard was 11.5% (95% CI, 8.9–14.1). With imputation of censorship for death, migration, and preventive therapy, the median 1650-day cumulative hazard over 10,000 simulations was 14.5% (95% CI, 11.1–17.9). Most risk accrued in the first 5 months after infection, and risk was greatest in the group aged <5 years, reaching 56.0% with imputation, but it was also elevated in older children (27.6% in the group aged 5–14 years).

Conclusions: The risk of active TB following infection is several-fold higher than traditionally accepted estimates, and it is particularly high immediately following infection and in children.

Conflicts of interest

The authors have none to declare.

http://dx.doi.org/10.1016/j.ijtb.2016.05.003

Market assessment of tuberculosis diagnostics in India in 2013

TB Diagnostics Market Analysis Consortium. *Int J Tuberc Lung Dis* 2016;20(3):304–313

Background: India represents a significant potential market for new tests. We assessed India's market for tuberculosis (TB) diagnostics in 2013.

Methods: Test volumes and unit costs were assessed for tuberculin tests, interferon-gamma release assays, sputum smear microscopy, serology, culture, speciation testing, nucleic-acid amplification tests (i.e., in-house polymerase chain reaction, Xpert® MTB/RIF, line-probe assays) and drug susceptibility testing. Data from the public sector were collected from the Revised National TB Control Programme reports. Private sector data were collected through a survey of private laboratories and practitioners. Data were also collected from manufacturers.

Results: In 2013, India's public sector performed 19.2 million tests, with a market value of US$22.9 million. The private sector performed 13.6 million tests, with a market value of US$60.4 million when prices charged to the patient were applied. The overall market was US$70.8 million when unit costs from the ingredient approach were used for the 32.8 million TB tests performed in the entire country. Smear microscopy was the most common test performed, accounting for 25% of the overall market value.

Conclusion: India's estimated market value for TB diagnostics in 2013 was US$70.8 million. These data should be of relevance to test developers, donors and implementers.

Conflicts of interest

The author has none to declare.

http://dx.doi.org/10.1016/j.ijtb.2016.05.004

Challenges in diagnosing tuberculosis in children: A comparative study from Sudan

Elhassanv MM, Elmekki MA, Osman AL, Hamid ME. *Int J Infect Dis* 2016;43:25–29

Highlights

- The diagnosis of tuberculosis (TB) in children is challenging due to insufficient specimen material and the scarcity of bacilli in specimens.
- This study aimed to evaluate diagnostic methods for diagnosing childhood TB in Sudan.
- The situation regarding pediatric TB in Sudan and its prevalence are discussed, since Sudan is known as one of

the developing countries that suffers from the emergence of such fatal disease due to the lack of policies and regulations to control outbreaks of community-based infections.

Objectives: The diagnosis of tuberculosis (TB) in children is challenging due to insufficient specimen material and the scarcity of bacilli in specimens. This study aimed to evaluate methods for diagnosing TB in children in Sudan.
Methods: Patients (N = 197) were subjected to the tuberculin skin test (TST). Gastric lavage or sputum specimens were then collected, processed, and cultured as per standard procedures.
Results: Culture on Löwenstein–Jensen medium, the reference standard, revealed growth in 16.2% of the specimens. Comparative analysis showed that 43.7% were positive for the TST (sensitivity 100%, specificity 67.3%), 8.1% were positive by Ziehl–Neelsen stain (sensitivity 43.8%, specificity 98.8%), 11.2% by auramine stain (sensitivity 56.3%, specificity 98.8%), and 17.8% were positive for PCR amplification of the IS*6110* sequence (sensitivity 100%, specificity 98.8%).
Conclusions: It is concluded that whilst TST and IS*6110* achieved 100% sensitivity based on the reference standard of culture, the latter was more specific. The TST is recommended for routine diagnosis and the use of PCR for particular cases, depending on the facilities and the urgency.

Conflicts of interest

The authors have none to declare

http://dx.doi.org/10.1016/j.ijtb.2016.05.005

Natural remedies against multi-drug resistant *Mycobacterium tuberculosis*

Pandit R, Singh PK, Kumar V. *J Tuberc Res* 2015;3(4):171–183
Tuberculosis (TB), caused by *Mycobacterium tuberculosis* is an infectious deadly disease and the treatment of which is one of the most severe challenges at the global level. Currently more than 20 chemical medications are described for the treatment of TB. Regardless of availability of several drugs to treat TB, the causative agent, *M. tuberculosis* is nowadays getting resistant toward the conventional drugs and leading to conditions known as multidrug-resistant tuberculosis (MDR-TB) and extensively drug resistant tuberculosis (XDR-TB). This situation has terrified the global health community and raised a demand for new anti-tuberculosis drugs. Medicinal plants have been used to cure different common as well as lethal diseases by ancient civilizations due to its virtue of variety of chemical compounds which may have some important remedial properties. The aim of the present review is to focus on the anti-tubercular medicinal plants native to India as well as the plants effective against MDR or XDR-TB across the globe. In the present review, we have addressed 25 medicinal plants for TB and 16 plants effective against MDR-TB testified from India and 23 herbal plants described for MDR-TB across the world during 2011–2015. These herbal plants can serve as promising candidates for developing novel medications to combat multidrug resistant *M. tuberculosis*.

Conflicts of interest

The authors have none to declare

http://dx.doi.org/10.1016/j.ijtb.2016.05.006

The influence of various intervention types on treatment success rates among category II tuberculosis patients

SenGupta B, Burrus CJ, Tirmizi N, Rooj B, Moshman HS, Pandey S, Jaamaa G, Roy K. *J Tuberc Res* 2015;3(2):43–49
Background: Category II tuberculosis (TB) patients (i.e. re-treatment TB patients) are at an increased risk for defaulting on treatment compared to category I TB patients. Therefore, extra steps need to be taken to help category II TB patients follow through with their treatment. The goal of this study was to examine the effectiveness of three different types of interventions to help improve treatment success rates among category II patients.
Materials and methods: Three different interventions that were implemented among category II TB patients in the Bardhaman, Hugli, Malda and Murshidabad districts in West Bengal, India, were: (1) setting up group patient provider meetings (PPMs), (2) making home visits and reinforcing the message of full course of treatment, and (3) linking poor TB patients to social welfare schemes (SWSs) to incentivize them to complete treatment.
Results: PPMs and SWSs improved treatment success rates among category II patients. The treatment success rates for patients who received PPMs and patients who received SWSs were 94.2% and 90.7%, respectively, compared to the 74.5% treatment success rate of patients who received no intervention. The effectiveness of home visits, however, depended on the number of home visits the patient received.
Conclusion: PPMs and SWSs improve treatment success among category II TB patients and may easily be incorporated in Directly Observed Treatment, Short-Course programming as feasible ways. A conclusion regarding home visits, however, could not be drawn from this study.

Conflict of interest

The authors have none to declare.

http://dx.doi.org/10.1016/j.ijtb.2016.05.007

Identification of novel loci associated with mycobacterial isoniazid resistance

Viswanathan G, Yadav S, Raghunand TR. *Tuberculosis* 2016:96:21–26
Despite the known association of several genes to clinical isoniazid (INH) resistance, its molecular basis remains unknown in ~16% of clinical isolates of *Mycobacterium tuberculosis* (*M. tb*). While screening a set of *Mycobacterium smegmatis* (*M. smegmatis*) transposon mutants with altered colony morphology for differential susceptibility to INH, we found six resistant mutants and mapped their transposon insertion sites. The disrupted genes in six INH resistant mutants were homologs of *M. tb ctaE*, *rplY*, *tatA*, *csd* and *tatB* with one insertion mapping to the promoter region of *M. smegmatis ctaE*. MIC measurements indicated a wide spectrum of INH resistance in these mutants, with complementation analyses of four selected mutants with the cognate *M. smegmatis* genes and their *M. tb* homologs confirming the association of the disrupted genes with INH resistance. Our discovery of novel genes associated with INH resistance could lead to the identification of novel INH resistance mechanisms and possibly new diagnostic modalities as well.

Conflict of interest

The authors have none to declare.

http://dx.doi.org/10.1016/j.ijtb.2016.05.008

Presumptive treatment of multidrug-resistant tuberculosis in household contacts

Parr JB, Rich ML, Keshavjee S, Franke MF, Mitnick CD, Bayona J, Becerra MC. *Int J Tuberc Lung Dis* 2016;20(3):370–375

Setting: Multidrug-resistant tuberculosis (MDR-TB) is a growing global health threat that often requires presumptive treatment in the absence of drug susceptibility testing (DST) results.
Objective: To compare two approaches to the treatment of MDR-TB contacts with no DST results who develop TB disease.
Design: We conducted a retrospective cohort study of adults treated for TB disease who were contacts of patients living with MDR-TB. Subjects had been treated according to one of two presumptive treatment strategies: (1) regimens containing exclusively first-line drugs, and (2) regimens that included both first- and second-line drugs that were adjusted if and when DST results became available. The primary endpoint was a composite of death and treatment failure.
Results: Household contacts of MDR-TB patients who developed TB disease and were treated with first-line regimens were significantly more likely to experience unfavorable end-of-treatment outcomes than those treated with presumptive MDR-TB regimens (RR 2.88, 95% CI 1.24–6.68).
Conclusion: Household contacts of MDR-TB patients who develop TB disease but have no DST results should receive regimens containing second-line drugs selected based on the infecting strain of the index patient. Regimens containing only first-line anti-tuberculosis drugs significantly increase the risk of unfavorable outcomes.

Conflicts of interest

The authors have none to declare

http://dx.doi.org/10.1016/j.ijtb.2016.05.009

The effect of HIV coinfection, HAART and TB treatment on cytokine/chemokine responses to *Mycobacterium tuberculosis* (*Mtb*) antigens in active TB patients and latently *Mtb* infected individuals

Kassa D, de Jager W, Gebremichael G, Alemayehu Y, Ran L, Fransen J, Wolday D, Messele T, Tegbaru B, Ottenhoff THM, van Baarle D. *Tuberculosis* 2016;96:131–140

Identification of *Mtb* specific induced cytokine/chemokine host biomarkers could assist in developing novel diagnostic, prognostic and therapeutic tools for TB.
Levels of IFN-γ, IL-2, IL-17, IL-10, IP-10 and MIP-1α were measured in supernatants of whole blood stimulated with *Mtb* specific fusion protein ESAT-6/CFP-10 using xMAP technology. The study groups were HIV positive TB patients (HIV^+TB^+), HIV negative TB patients (HIV^-TB^+), HIV positive tuberculin skin test positive (TST+) (HIV^+TST^+), HIV negative TST+ (HIV^-TST^+), and HIV^-TST^- individuals.
Compared to HIV^-TST^-, latent TB infection led to increased levels of IP-10, IFN-γ and IL-17, while levels of IL-2 and IP-10 were increased with active TB. Levels of IFN-γ, IL-17, MIP-1α, and IL-10 were increased in HIV^-TST^+ individuals compared to HIV^-TB^+ patients. HIV coinfection decreased the level of IFN-γ, IL-17, IP-10 and IL-2. After 6 months (M6) of anti-TB treatment (ATT) in HIV^-TB^+ patients, IFN-γ, IL-10, and MIP-1α levels normalized. After M6 and M18 of ATT plus HAART in HIV^+TB^+ patients, levels of MIP-1α and IL-10 normalized, while this was not the case for IFN-γ, IL-2, IL-17, and IP-10 levels. In HIV^+TST^+ patients on HAART, levels of IFN-γ, IL-17, IL-10 and MIP-1α normalized, while no change in the levels of IL-2 and IP-10 were observed.
In conclusion, the simultaneous measurement of IFN-γ, IL-17 and IP-10 may assist in diagnosing LTBI; IL-2 and IP-10 may assist in diagnosing active TB while IFN-γ, IL-17, MIP-1α, and IL-10 levels could help to discriminate LTBI and active TB. In addition, IL-10 and MIP-1α levels could help to monitor responses to TB treatment and HAART.

Conflicts of interest

The authors have none to declare

http://dx.doi.org/10.1016/j.ijtb.2016.05.010

Setting priorities for a research agenda to combat drug-resistant tuberculosis in children

Velayutham B, Nair D, Ramalingam S, Perez-Velez CM, Becerra MC, Swaminathan S. *Public Health Action* 2015;5(4):222–135

Setting: Numerous knowledge gaps hamper the prevention and treatment of childhood drug-resistant tuberculosis (TB). Identifying research priorities is vital to inform and develop strategies to address this neglected problem.
Objective: To systematically identify and rank research priorities in childhood drug-resistant TB.
Design: Adapting the Child Health and Nutrition Research Initiative (CHNRI) methodology, we compiled 53 research questions in four research areas, then classified the questions into three research types. We invited experts in childhood drug-resistant TB to score these questions through an online survey.
Results: A total of 81 respondents participated in the survey. The top-ranked research question was to identify the best combination of existing diagnostic tools for early diagnosis. Highly ranked treatment-related questions centred on the reasons for and interventions to improve treatment outcomes, adverse effects of drugs and optimal treatment duration. The prevalence of drug-resistant TB was the highest-ranked question in the epidemiology area. The development type questions that ranked highest focused on interventions for optimal diagnosis, treatment and modalities for treatment delivery.
Conclusion: This is the first effort to identify and rank research priorities for childhood drug-resistant TB. The result is a resource to guide research to improve prevention and treatment of drug-resistant TB in children.

Conflict of interest

The authors have none to declare.

http://dx.doi.org/10.1016/j.ijtb.2016.05.011

Multidrug-resistant pulmonary and extrapulmonary tuberculosis: A 13 years retrospective hospital-based analysis

Raveendran R, Oberoi JK, Wattal C. *Indian J Med Res* 2015;142 (5):575–582

Background and objectives: Multidrug-resistant tuberculosis (MDR-TB) is a public health problem of great significance in India. In the present study an attempt was made to analyse the progression of MDR-TB pattern during a course of 13 years (2000–2012) among the patient population at a tertiary care centre in New Delhi, India.

Methods: Mycobacterial isolates obtained on Lowenstein-Jensen (L-J) medium/BacT/ALERT 3D were identified using AccuProbe molecular identification system, routine biochemical tests or GenoType Mycobacteria CM. Antimycobacterial susceptibility testing was performed using resistance ratio method on L-J medium (2000–2004) and 1% proportion method on BacT/ALERT 3D system (2005–2012).

Results: Of the total 14,849 samples subjected to mycobacterial culture, 6569 pulmonary and 8280 extrapulmonary, 2364 were detected positive for mycobacteria. The average percentage positivity rate was 15.9% (18.9 and 13.6% in case of pulmonary and extrapulmonary samples, respectively). Our study revealed a significant increase ($P < 0.001$) in multidrug resistance by 12% (4.7% in 2000 to 19.8% in 2012). MDR-TB was more in case of pulmonary (28.2%) than extrapulmonary (11.6%) TB ($P < 0.001$). Only 6.5% (154) of mycobacterial isolates were non-tuberculous mycobacteria and rapid growers represented by *Mycobacterium fortuitum* and *M. abscessus* were the most commonly isolated species.

Interpretation and conclusions: Increase in prevalence of MDR-TB by 12% in the past 13 years is alarming. Policy modifications may have to be done to strengthen the existing TB control programmes to encourage contact tracing and culture and drug susceptibility testing for all smear positive pulmonary cases to ensure early and appropriate therapy.

Conflict of interest

The authors have none to declare.

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