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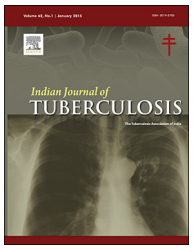

Editorial

Enhancing TB surveillance with mobile technology: Opportunities and challenges

India has taken a bold step towards ending TB, by committing to achieve the END TB Targets five years ahead of the original timeline with the implementation of its new National Strategic Plan (NSP 2017–2025).[1] A strong surveillance mechanism, able to detect all events related to TB disease, with coverage extending to all types of healthcare providers is key to achieving this. The NSP calls for the development and implementation of such a strong surveillance system to achieve India's dream to END TB.

Developing a strong surveillance system has many challenges. This is due to the nature of TB as a prolonged disease and the uncertainty involved in relation to risk factors, complete diagnosis and effective treatment. To address these challenges, WHO has recommended country TB control programmes to implement reporting systems and upgrade themselves over several parameters and quality indicators.[2] This includes moving from aggregate reporting to case-based reporting and eventually being able to track individuals through time. The current standard in reporting systems is electronic information systems over the internet, able to collect real time information, Data should be validated and cleaned from the point of data collection using automated systems.[2]

Historically, supervision and monitoring in RNTCP was based on aggregate numbers reported by TU. As per the recommended standards the programme needed to be able to track individual cases from diagnosis to treatment completion, at national level. With this objective in mind, the programme launched its centralised online case-based information system in 2012, and christened it Ni-kshay. At the time, in Nikshay and throughout the programme, only cases that sought treatment in the public sector, were systematically tracked till treatment completion. Cases in the private sector could be notified to the programme through Nikshay. In 2017, based on the revised Technical and Operational Guidelines 2016,[3] Nikshay was upgraded from the case-based system to a person-centric system, able to track individuals through their entire struggle with TB. This new system supports the monitoring of all types of patients, supporting equally the government and private health systems to detect and follow up people affected with TB throughout their lifetime. This includes from identification as person vulnerable to TB, diagnosis, treatment initiation, treatment completion, long term follow-up and even if they experience a recurrence of TB. This system is the platform on which the new surveillance system is built in RNTCP.

To improve access to and use of this novel system, the programme has developed mobile-friendly web and android applications and has been continuously improving them. These applications assist providers to notify TB cases, manage their treatment and follow them up to treatment completion and beyond. They assist patients by supporting them to self-report treatment adherence, while enabling the health system to maintain a supportive supervisory role. This editorial seeks to inform the reader about the opportunities for patients, and healthcare providers and the challenges the system has to overcome to eliminate the burden of TB.

Opportunities for patients: The programme is trying to increase active involvement of patients in the programme. It has now empowered patients to self report whether they have consumed their daily dose of drugs, with the health system providing a supportive supervisory role. The programme has piloted and is nationally scaling up a number of novel systems (99DOTS, MERM-Medication Event Reminder Monitor System).[4] Through 99DOTS, patients give a missed call to a secret toll free number after they have consumed their daily dosage. The MERM pill box records each time the drug box is accessed for consuming medicines. A cafeteria-based approach, including the above measures, traditional DOT (Direct Observed Therapy), inpatient-based observation, or a combination of these are used, to select the most appropriate mechanism. This selection takes into consideration patient preferences, physician requirements and local contextual and health system characteristics.

Patients are also empowered with information. Prompts for critical action, such as information regarding undergoing various follow ups and examination, such as monthly clinical check-up, end IP testing, end CP testing, etc are being sent to the patients as SMSs. Depending upon the nutritional status of each TB patient, he/she has to take the appropriate intake of various food types. A freely downloadable app, N-TB, makes individualized recommendation of food intake.

In the near future, patients will be able to refer themselves to the nearest TB diagnosing or follow-up facility using geo-

location. They will be able to see all their own health records available in the system such as tests, prescriptions and adherence information through the system. With the implementation of the national call centre, follow-up calls for providing better access to services, can be made; patients can also report grievances and track its status online.

1. Opportunities for health care providers

Healthcare providers, especially those in the private sector, have experienced a number of challenges in linking up with the government health system. The primary challenge till date was to be able to notify cases and follow them up till cure. Through Nikshay's mobile app for private practitioners, they notify cases quickly and directly to Nikshay by entering a minimum number of parameters. If a health facility collects TB related data in an electronic Hospital Management Information System (HMIS), then using the HMIS cases may also be automatically notified to Nikshay by linking the HMIS to Nikshay.

The programme is now scaling up the Public Private Interface Agency (PPIA)[5] model for effective linkages with the private sector and extension of TB care to those cases seeking care from the private sector. Through Nikshay, the private health sector can coordinate with the PPIAs or directly with the public health system for notification and subsequent public health action. They may refer patients to laboratories or treatment centers in the public sector, throughout the country, for diagnosis and continued patient care free-of-cost.

In the near future, they will be able to keep a record of cases notified and details of public health action (counselling, contact tracing, treatment support, linkages to patient support etc.) initiated for them. They should also be able to monitor receipts of incentives and benefits provided to them through the programme.

2. Further challenges to system strengthening with technology

New developments occur with improved features and additional abilities all the time. The effective implementation of these new developments needs to be pushed to the periphery rapidly. It is important to the system that peripheral users have access to both, the facilities and the requisite training to use them. These facilities need to be as user-friendly as possible while being able to capture the necessary details required by the public health system. For this purpose, these technologies need to be optimized for a range of requirements by different stakeholders and devices that are in use.

Each stakeholder needs to have access to the information that is most relevant to them for the purpose of monitoring, supervision and feedback. The system should be able to identify these varying needs and provide this information upfront to them in a way that action can quickly be taken. In order to ensure consistent and complete filling of records, the burden of data entry to each stakeholder should be minimal and transaction-based. Here, data collection is minimal and is linked to its use in a particular transaction. For example, a person's test result is entered at the laboratory while treatment initiation information is entered by the physician initiating treatment. There should be mechanisms in place to identify areas with low utilisation and performance and resources to provide the necessary hand-holding in such places need to be quickly allocated and deployed. Poor connectivity is always a challenge for centralised systems. Offline data entry options and related process should mitigate this to a large extent.

Despite the above challenges, the programme has been moving ahead. The system over the past two years has been under continuous improvement and consistent efforts are being made to overcome these new challenges. These improvements will bring patients, providers and the public health system together to achieve the goal of ending TB.

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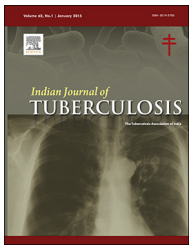

Viewpoint

Administrative challenges in the implementation of RNTCP

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TB control has a long history in India. In the good old days patients were sent to sanatoria to be treated in isolation. The National TB programme started in 1962 which led to the establishment of District TB Centres (DTC) and TB clinics across the country. It became essentially a vertical and technical programme. It was centralised in the DTC which provided diagnostic and treatment services in the district. The DTO implemented it, largely in a routine manner, with little interference or supervision. There were many technical problems and programme deficiencies. It was concerned only with patients who came to the DTC. Drug shortages were endemic. Completion of treatment was neither ensured nor monitored. Re-treatment of cases was fairly routine. The central structure was weak. For a long time, it did not provide leadership in updating policy and technical procedures and providing adequate funds. The picture was one of gross neglect. There was little epidemiological impact. The silent epidemic of TB flourished, as did the stigma associated with it.

The Revised National TB Control programme incorporating the DOTS strategy addressed these issues in the nineties. The world suddenly awoke to the grave threat posed by TB once it was realised that its spread through movement of people cannot be restricted by borders or oceans. The World Bank, WHO and some developed countries provided technical and financial support. At the turn of the century the Global Fund was set up. The approach to TB control changed and it became somewhat of a global priority.

The DOTS strategy completely changed the methodology of TB control. Realising that X-ray diagnosis was not very reliable, and often deceptive, diagnosis by sputum microscopy became the standard. This had the benefit of identifying quickly the infectious cases. Microscopy centres then required to be set up in a decentralised manner across the country. Drugs were to be provided in patient-wise boxes which contained the entire treatment requirement. DOT providers 'directly observed' the taking of these drugs by the patient who then got fully cured, and not left half way. Treatment could be taken at home and there was now no need for isolation. Detection and cure both became important with defined targets.

I was fortunate to become Joint Secretary of this programme in October 1998 when the RNTCP was just starting. Unfortunately, it had also landed into problems because of which the World Bank had suspended credit. RNTCP provided a great management challenge as also an enormous opportunity. A new programmatic and administrative approach became necessary.

This approach was first reflected in change of strategy regarding expansion of DOTS strategy. The initial plan for RNTCP coverage under the World Bank plan was to expand slowly. A population of 300 million people were to be covered in three years, a part to be covered every year. While the precautionary principle was understandable because of the enormity of the change, complete uncertainty about the future appeared unacceptable. There was no satisfactory answer to my question by when the entire country would be covered. Meanwhile, three different kinds of programme would continue to run in different parts of the country. With the evident perceived benefits of the new strategy it almost became a moral imperative to cover the entire country as soon as possible. Policy makers must be ambitious even as their feet remain firmly planted on the ground. Disruptive change has sometimes to be deliberately caused to shake people out of their lethargy or acceptance of the status quo approach. We, therefore, led the international effort to put a target date of 2006 for entire coverage of the country. There was to be a summit of leaders in Amsterdam in 2000. At a preparatory conference in Bangkok I argued for this. Coming from India at that time this surprised many. Many opposed including our own technical division. Some questioned what appeared to be misguided enthusiasm on the part of a generalist, who does not understand the technicalities involved. But we proved the naysayers wrong. In

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the next few years, with the efforts of a large number of people, we were largely able to achieve full coverage on schedule. The WHO called this the inspirational story coming out of India.[a]

Essentially, this was the outcome of a completely managerial approach and administrative measures proceeding simultaneously with all technical requirements. In many technical programmes, this is often lacking. Implementing RNTCP throughout the country in a relatively short time frame was a big challenge. The first step was a strategic change of approach which was not recommended on technical considerations. The whole planning had been to proceed sequentially, covering some districts first and then going to others. This would have led to indefinite delay. Therefore, we started work in the entire country simultaneously. Always some will go faster than others. Nobody now had to wait for anyone else. There was also a sense of competition. But this became a huge administrative task.

Microscopy laboratories had to be built in remote centres; binocular microscopes and laboratory reagents were to be procured and distributed; contractual staff had to be recruited; drug stocking, distribution and monitoring/reporting system established; all levels of persons, which became very substantial in number, had to be trained. All this involved hundreds of sites, people and management entities. Budgets had to be prepared and approved; funds transferred to societies down the line and on time; time lines for different activities had to be prepared and adhered to. When request for funds from Central TB Division[1] came we managed to release, after consultation with the Financial Adviser, in a day or two, and sometimes even the same day! Often this takes a long time, and even in the TB programme in later years, this had become a bottleneck leading even to delays in procurement of drugs. I think the importance of smooth fund flow is not adequately realised. The nuts and bolts and small things matter a great deal. Often these get neglected which impact the implementation in the field adversely. It must be mentioned that the decision to flow funds through the state budget has hurt such programmes because releases get delayed. Amalgamation with AIDS may allow funds to be routed through Societies. There is urgent need for streamlining.

We used to be in constant telephonic touch with the field. I often knew of a file going to the DM for approval before he did. Personal phone calls to them helped. Most responded positively. We monitored the preparatory activities and all aspects of performance very closely. Constant field visits were necessary and made. This included state and district level reviews. Reviews were done at micro level. Performance of each microscopy centre and each big hospital was known. Improvements could then be made from bottom up.

All this seems to have gone away. The inclusion in the National Health Mission has led to its virtual isolation within the state and certainly at the district level. I have made many field visits after my retirement. Vacancies and lack of arrangements of different kinds were routinely found. Worse, they often had remained unaddressed. Micro level reviews have been given up. We had tried to make the STO and the DTO managers rather than just being technical officers. It does not appear to be so any longer. The DTO has once again become the master of the programme at the district level and technical issues gained prominence. As a further consequence, and like the good old days, the DTC has again become the centre of TB control. I often used to say that the TB programme would really succeed if the DTC were to become redundant. In all the districts that I visited, the DTC was thriving, full of patients and the DTO busy with OPD through the day. He is no longer programme manager of the district. This requires urgently to be changed. Perhaps the recent decision of the Health Ministry to tag TB along with AIDS will provide the necessary impetus. This only goes to show that a programme cannot succeed if these administrative issues are not paid enough attention to.

This administrative approach is also necessary for the most important issue which is the detection rate of patients and ensuring their treatment and cure. This has become even more important now than before. The Government has declared that TB will end by 2025. It is not clear what the definition of this is. But as per the National Strategic Plan (2017–25),[2] it would appear that, as compared to 2015, by 2025, TB incidence rate would decline to 44 from 217; TB prevalence rate would decline to 65 from 320 and mortality rate to 3 from 32. It implies also that total notification of TB patients would rise from 1.74 million in 2015 to 3 million in the current year and 3.6 million in 2020. The entire increase is proposed to come from the private sector which will rise from 0.19 million in 2015 to 1.5 million in the current year. By any stretch of imagination this is a stupendous task. It means perhaps an annual decline in incidence rate of 15% when the best we have done is perhaps around 2%. In my non-technical view this is simply not possible. But irrespective of targets what this means is that we have to rapidly detect considerably more patients. This will require a huge administrative effort in the field.

Let me go back to the past. Under the DOTS strategy, the targets of case detection and treatment success were 70% of the estimated cases per lakh population and 85% of the cases registered for treatment respectively. Of course, that estimated number never got really defined. The programme focus initially had been on cure rate, perhaps correctly, so that systems become operationally robust. That focus, however, continued. I believed the major challenge was, and would remain, the detection rate. Unless we substantially increase detection, the epidemiological impact will not come. Besides, if the number of cases detected is low, the cure rate can be very high because we are catching the easiest patients. As detection increases the cure rate will be challenged. This required movement away from the clinical approach. It also required collaboration with and involvement of all health sectors and adopting a people centric strategy. This is what we did. Today we need this to be done in a much more intensive manner.

The first requirement is to reorient the management of the programme. I have mentioned above the kind of pro-active approach we had adopted and emphasis on micro level analysis. This must happen again. Intensive monitoring is required. The DTO must become a programme manager and visit the field intensively. Reviews have to be done diagnostically. These are not only stock taking but discussions of how to improve after finding out what is going wrong or inadequate. A district may have certain global figures but it does not mean that all microscopy centres have performed uniformly. We have to find who has done best and why and who has not done well and why. These will tell us what to do. When I visited

[a] I have described this process and performance in detail in my book, Covering a billion with DOTS, 2004, Central TB Division.

certain districts, I found simple instances where performance could be improved. In a centre there was no lab technician for months. A microscopy centre had a population of 1.6 lakhs with a large slum area included but the OPD was very poor and nobody could explain why. In other area the MC was far away and a huge population was virtually left unattended. Almost uniformly, patients notified by the private sector in many parts of a district were not tracked. These are small examples but indicative both of the problems and pointing to the remedies.

Under the NSP, 83 high TB districts have been identified where detection has been more than 180 per lakh. Perhaps there will be special attention given to them. This is also indicative of the problem of approach. High detection on the average for the district could be caused because of local factors in some areas of the district where rates may be even higher. Similarly, there could be many such localised areas within other districts. What I would have done is to identify **all MCs** where detection rates are over 200, or can potentially be, and focus on them. One would imagine that many of these will actually cover urban slum areas. In my experience of over 10 years and repeated visits to the field thereafter, the detection rates of these areas could potentially perhaps be even more than 300. This is where the maximum missing patients are, where the maximum involvement of disorganised private sector is and where mistreatment and potential MDR the greatest. Should we not give them concentrated attention? The new technologies such as Gene Xpert, Line probe Assay, MGIT are able to diagnose quickly and also determine resistance to drugs.[3] We have now sent one Gene Xpertmachine to every district. Additional machines should be immediately procured and made available to all these MC's in identified urban slum areas. In my visits to 4 cities the neglect of such areas was evident. I have recorded this in my Reports. I have urged the Central Government and technical agencies supporting the programme like WHO, USAID, Union etc to have small slum studies done across the country but none has been done. I urge this with all the emphasis at my command.

There are various sectors and segments which need to be reached and fully involved. This we had tried to do in earlier years. These are briefly enumerated below.

There is a very large non-health public sector delivering health services – Railways; Mines; ESIC; Armed Forces; Police and Paramilitary forces; jails; Ports; PSU's. All these must be fully involved. State and District level co-ordination committees need to be formed wherever required.

There are large number of Trust/NGO/non-profit hospitals, and even dispensaries, across the country. Many poor people go to them. They all need to be fully involved. I recall the very substantial contributions large NGO hospitals at Bareilly and Varanasi made to the detection rate in those districts. There is the almost miraculous case of a Muslim NGO dispensary made into a MC in Meerut which led to detection of a large number of 'missing' patients. Such instances can be replicated across the country increasing the numbers detected substantially.

The programme cannot enter into mission mode and reach the last mile without involvement of the community. We had initiated policies to involve local communities, NGO's with volunteers, and all kinds of individuals, including cured TB patients, to act as DOT providers. I personally met many of them back then, and even last year on my field visits. Such young ladies are best placed to reach out to their kind, whom others cannot. Imagine the role which can be played by thousands of such Community DOT providers! In a sense the programme would be 'communitised'. Whether we like it or not, this would involve hundreds of non MBBS medical practitioners. In my field visits last year, I saw some kiosks in slum areas under the Akshay programme which remained open from 6 am to 9 pm. Hundreds of such kiosks could help greatly. Active case detection is now part of the strategy. It will work much better when there is a huge network available. Availability of proper services and community outreach will give greater dividends.

Of course, the private sector remains the key, as also emphasised by the NSP. Over the last two decades there have been hundreds of conferences and a whole literature has developed about the involvement of the private sector. Yet it remains marginal, at best. What could be wrong? Why are we failing? We must re-strategise. I think we should be more concerned with private practitioners and small clinics, especially in urban slums and some identified hot spots. They now have to notify every TB case. As per the NSP, since 2012, private sector notifications had been about 0.7 million in 4 years.[3] 25% of these were from Surat and Maharashtra. What are the lessons? Clearly, not all are notifying, and all those notified are simply not followed up. I was told in one district that the DM has written a letter to private doctors. This is not enough. The time for come for this casual approach to end. Notification must be rigidly enforced and notifications must be rigorously followed up. This work must now be done by a Committee headed by the District Magistrate, which will include representatives of the private doctors and chemists. The NSP also says that under another programme funded from outside 144 private labs are involved. This is good but simply not enough. The time has come for all private labs and chemists in a district to be involved. Clearly it is now a social responsibility.

TB is facing a crisis. India continues to be the biggest global contributor. We may not end TB by 2025 but the missing millions must be detected. TB must become a people's programme. This will also require much more resources. There is enough evidence to show that economic and societal returns, especially for the poor, are great. A TB Board could be set up as proposed under NSP, at central and State levels. An Advisory Committee to oversee field implementation may also be required, preferable at both levels. There is now renewed political commitment right from the top. We must not miss this opportunity.

Conflicts of interest

The author has none to declare.

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Review article

Smear microscopy as a diagnostic tool of tuberculosis: Review of smear negative cases, frequency, risk factors, and prevention criteria

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ABSTRACT

Tuberculosis is one of the global health problems, the estimated deaths due to TB was around 2 million in the year 2013. Failure in early diagnosis and providing suitable treatment leads to increase the prognosis of the disease. Smear microscopy is used in many countries as a primary diagnosis of TB especially in the district poor facility laboratories, where smear negative frequency is high. This review aimed to reflects the importance of smear negative tuberculosis as a source of infection and poor prognosis of TB treatment and prevention. In addition to, discuss the possible causes and suggests solutions to improve the yields of smear microscopy.

1. Introduction

Tuberculosis (TB) is still a public health problem with estimated one third of world population have been infected. According to the global tuberculosis report issued on 13 October 2016, the WHO announced that In 2015, 10.4 million people fell ill with TB and 1.8 million died from the disease (including 0.4 million among people with HIV).[1] The causative agents of this disease is the slow grower, acid fast bacteria, *Mycobacterium tuberculosis* complex (MTBC) which comprises 7 closely related *Mycobacterium* species (*M. tuberculosis*, *M. bovis*, *M. africanum*, *M. microti*, *M. canetti*, *M. pinnipedii*, and *M. caprae*).[2,3] The gold standard method for diagnosis of pulmonary TB is mycobacterium culture but this method is very slow, expensive and requires well equipped specialized laboratory.[4,5] Acid fast staining techniques such as Ziehl Neelsen (ZN) stain or Auramine O – Rhodamine stain remain the easiest and cheapest methods, although they are less sensitive and not specific for diagnosis of MTBC.[6] Its estimated that up to 50% of Ziehl Neelsen staining smear were negative, although the samples showed the presence of MTBC by other methods including culture.[6] This review aimed to highlight the smear negative pulmonary tuberculosis (SNPT), how it occurs? What's the reasons to have SNPT?, and suggests some solutions to avoid SNPT and increase the outcome of smear microscopy. Most publication and clinical practice have not tend to distinguish between smear negative pulmonary tuberculosis and smear positive although it's obvious that patients with SNPT have poor prognosis, could be infectious and tend to spread the disease in the community.

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2. What's smear negative pulmonary tuberculosis (SNPT)?

Smear-negative pulmonary tuberculosis (SNPT) is defined, according to the WHO (2010), as a clinical suspect with at least two negative acid fast bacilli (AFB) smears and a positive culture for TB in either solid or liquid media. Another way to classify the patient as SNPT is to have two negative smears, radiographical abnormalities consistent with active pulmonary TB and No improvement with a course of broad-spectrum antibiotic (if HIV-negative), in addition to physician decision to treat the patient as TB suspects. Also, HIV-positive patients with radiological abnormalities similar to TB granuloma is treated as smear negative PTB patient.[7–9]

3. Factors influencing to have smear negative pulmonary tuberculosis?

Several factors attributed to have smear negative culture positive cases; this might be categorized into laboratory errors, patient's status or habits, and presence of other infectious diseases (mainly HIV).

3.1. *Laboratory errors*

A well-equipped tuberculosis laboratory with well-trained personnel has few frequency of SNPT.[10,11] Laboratory personnel, specimens quality, numbers of provided samples, types of the stains used and to somehow types of microscope used may considered also as a laboratory errors to have smear negative PTB.[12,13] Lack or deficiency in the training of tuberculosis laboratory technologist plays a major role in laboratory errors to have false negative staining results. Many laboratories in low-income countries could not obtained such facilities especially that located in rural areas.[14] Other mentioned factors may also linked to laboratory errors for having false negative sputum smears.

3.2. *Patient's status or habits*

Age of the patient is one of the important factors contributed to SNPT. Children who are unable to produce quality sputum samples are the main reason to have smear negative PTB.[15,16] In one study, Smear-negative tuberculosis was more common in older than younger patients in a country with low prevalence of HIV infection.[17] Diabetes and smoking habits were investigated as risk factors for smear negative but No proved correlation were founded.[18–20]

3.3. *Presence of infectious diseases*

Human immunodeficiency virus (HIV) is the main reasons to have SNPT. Many investigators correlated the HIV infection with smear negative pulmonary tuberculosis.[18,21–34] The WHO announce that any HIV with pulmonary lesion typical to TB lesion not responding to antibacterial treatment should be treated as smear negative PTB.[1]

The main reason of having smear negative among patient with AIDS is lack of immunity which leads to disappearance of cavitation and TB associated granuloma and high possibility of extra-pulmonary spreading of the disease.[21] This might be associated with normal or atypical chest radiography.

4. Frequency of smear negative tuberculosis

Smear negative account for 30–60% of tuberculosis patients[6,17,18]; Extreme studies conducted in Pakistan (4 years retrospective study) by Ahmed et al.,[35] in Guatemala by Samayoa-Peláez et al.[36] and in Ethiopian prisons by Biadglegne et al.[37] They found low frequency of smear negative pulmonary tuberculosis (SNPT), 15.63%, 14% and 8%, respectively. In western pacific region, the WHO case notification rates in the year 2012 showed an average frequency of 50.7%, the lowest frequencies were in Tonga and Papua New Guinea (9.1% for both), while the highest 59.3% was scored in China.[38]

5. Risk factors of have smear negative pulmonary tuberculosis

5.1. *Infectivity*

The first question which come to your mind when any person talk about smear negative pulmonary tuberculosis is does Smear Negative Pulmonary Tuberculosis patient able to transmit the disease? In the past, many investigators thought that SNPT patients are not infectious or weakly infectious, but recently several investigators described the possibility of TB transmission from SNPT. Tostmann et al. showed that smear negative (culture positive) pulmonary tuberculosis responsible for 13% of tuberculosis transmission in a large cohort study done in Netherlands.[39] Thapa estimated that smear negative tuberculosis responsible for 13–41% of disease transmission.[40] In San Francisco, smear negative culture positive responsible for 17% of tuberculosis transmission.[41] High risk of possibility of transmission was noted by Hernández-Garduño et al. in the Greater Vancouver regional district, they stated that 41% of pulmonary and extrapulmonary smear negative cases appear responsible for TB transmission.[42]

5.2. *Possibility to spread multidrug resistant* Mycobacterium tuberculosis *MDR – MTB*

One of the most important problem in Tuberculosis is the development of multidrug resistant strains (MDR-MTB), this might be due to delay in diagnosis and irregular uptake of antituberculosis drugs without final judgment of having TB. Liu et al. estimated the percentage of MDR – MTB strains among smear negative pulmonary tuberculosis was 26.5% in Beijing, China, which might increase the possibility of spreading MDR strains and affects the outcome of controlling these organisms.[43]

5.3. *Treatment outcome*

Treatment outcome may be affected by smear negative tuberculosis cases. In one study done by Mukherjee et al.,

they compare the treatment outcome between smear positive pulmonary TB and smear negative ones in India. They concluded that smear negative patients had a worse treatment outcome compared to smear positive patients including lower favorable outcomes and higher deaths and defaults.[44]

6. Improve smear microscopy outcome

As several factors contributed to poor outcomes of smear microscopy such as samples quality, diagnostic procedures and staff training, the following strategies which collected from various publications, might increase the outcomes of smear microscopy and reduces the frequency of smear negative:

a. Avoid false negative smear microscopy[10,13,14,45–48] by:
   - Collect adequate sputum sample.
   - Reject any saliva samples.
   - Avoid delay in sputum processing for microscopy.
   - Label the samples correctly.
   - Prepare proper smears from most purulent areas.
   - If concentration technique is available and applicable do it before smear microscopy.
   - Combine both procedures (ZN stain and Auramine O Rhodamin) for better diagnosis.
   - Joint the technique with quality control samples (known +ve and known −ve).
   - Spent enough time for smear examination.
   - Blindly recheck random samples of sputa smears.
   - Report the positive samples correctly.
   - Give regular training program for all TB laboratory technologist.
b. Use other sampling techniques such as fiber optic bronchial aspirate[49,50] and bronchial washing.[51]

Due to reduction of sensitivity of smear microscopy, negative sputa smears should be confirmed by at least one further techniques such as culture in both liquid or solid media (available in TB specialized laboratory with high facilities),[8,52,53] nucleic acid amplification techniques such as line probe assay[52,54,55] or GeneXpert[56–66] and follow assigned algorithm for diagnosis of sputum smear negative.[4,6,8,31,67–69]

7. Conclusion

Smear negative tuberculosis is one of the obstacles facing diagnosis, treatment and proper prevention of the disease. Several factors contributed to this situation such as poor microscopy yields, HIV co-infection or failure to deliver high quality samples.

8. Recommendation

Its highly recommended to improve smear microscopy yield in addition to improve the diagnosis of smear as early diagnosis will initiate early starting of treatment and thus give us good prognosis with decrease possibility of drug resistance.

Conflict of interest

The author has none to declare.

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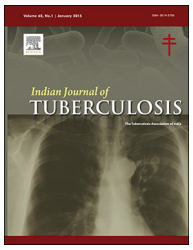

Original article

Management practices of tuberculosis in children among pediatric practitioners in Mangalore, South India

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ABSTRACT

Introduction: In spite of having BCG vaccination and tuberculosis control program for the last 50 years, prevalence of tuberculosis continues to be high in India. Inadequate diagnostic methods, suboptimal treatment and monitoring, and the lack of vigilant reporting system are some of the contributing factors for the failure of TB control.

Objectives: To know the current practices among local pediatricians regarding management of TB.

Materials and methods: Field based cross sectional study. All the registered pediatricians who were practicing in Mangalore, (list – local IAP branch) were included in the study. A structured Questionnaire on signs and symptoms of TB, diagnosis, strategies adopted in treatment, MDR tuberculosis and reporting of cases to RNTCP was asked. Management practice standards according to the Updated National Guidelines for Pediatric Tuberculosis in India, 2012, RNTCP guidelines in consensus with IAP, latest at the time of the study.

Results: 50 pediatricians participated in the study with 62% having an attachment to the teaching institution. More than 50% identified all the symptoms of TB. 64% were sending chest X-ray, Mantoux test and gastric lavage/induced sputum examination for AFB to diagnose TB. 22% were not stressing for AFB examination. Still 16% told serological tests as one of the diagnostic modality. 52% were not aware about the diagnosis of latent TB. In 16% of their cases ATT was on a trial basis. Only 52% of the clinicians are adhering to updated national (RNTCP) guidelines. 30% felt still there are drawbacks in the current RNTCP guidelines. 72% knew the correct definition of MDR tuberculosis. But only 36% of them knew the diagnostic method (gene expert/CB NAAT) of confirming the MDR TB.

Conclusion: Management practices are found to be still suboptimum. Better engagement of the private sector is urgently required to improve TB management practices and to prevent diagnostic delay and drug resistance.

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1. Introduction

Tuberculosis (TB) is the common chronic infectious disease affecting children. The burden of tuberculosis in India is highest in the world. India accounts for one fourth of the global TB burden. An estimated 28 lakh new cases occurred in India and 4.8 lakh people died due to TB according to the WHO Global Report for the year 2015. The proportion of children among new TB patients in India was reported to be 6% in 2016 as per the annual report of RNTCP 2017.[1]

In spite of having BCG vaccination and tuberculosis control program for the last 50 years, prevalence of tuberculosis continues to be high. Since it is a paucibacillary disease in children, diagnostic dilemma is more in children compared to adults. Inadequate diagnostic methods, suboptimal treatment and monitoring, and the lack of vigilant reporting system are some of the contributing factors for the failure of TB control as noted in various studies.

Although standardized tuberculosis treatment is delivered by the public sector through RNTCP, private medical sector contribute to a majority of health care provided to TB patients. Over the period of time private hospitals and clinics have seen a rise in the number of tuberculosis cases. Private sector is treating twice as many as the public sector as per the recent study published in Lancet.[2] Incorporation of the private sector is equally important to deliver uniform and standard patient care as this is a essential public health responsibility. There are many studies regarding current diagnostic and treatment practices among practicing doctors in adult population, but was lacking in pediatric population. So this study was undertaken to know the current practices in management of TB suspected children among local pediatricians.

2. Materials and methods

The present study was a field based cross sectional study. The list of all the registered pediatricians who are practicing in the city of Mangalore was procured form the local IAP branch and those who were willing to participate were included in the study. Informed consent was taken from each participant and confidentiality was maintained with data containing no personal information. Appointment was taken beforehand over the phone and Questionnaire was handed over to them which needed to be filled up without any source of information being available. Management practice standards were according to the updated national guidelines for pediatric tuberculosis in India, 2012, which is a updated RNTCP guidelines in consensus with Indian academy of pediatrics, latest at the time of study.[3]

A pre-designed structured Questionnaire on signs and symptoms of TB, diagnosis, strategies adopted in treatment and reporting of cases to RNTCP was asked. Questionnaire was validated by experts (by the pediatricians of our department without private practice/clinic who were not included in the study). Importance was given to the MDR TB as well. Their views on pitfalls/difficulties regarding following RNTCP was also noted down. Questions were multiple choices, agreement/disagreement based or one word answer. The variables were compared with the help of chi square test and p value less than 0.05 was taken as significant. Descriptive statistics was used to evaluate the other collected data. Ethical clearance was obtained from the institutional committee.

3. Results

There were approximately 70 pediatricians practicing in the city of Mangalore at the time of study period out of which 56 were contacted. Other people could not be consulted due to various circumstantial reasons. 50 of them consented to be the part of the study. 62% of the pediatricians had an attachment to the teaching institution and 38% were doing only private practice. Clinicians had varied experience ranging from 1 year to 36 years. Table 1 shows the general characteristics of the practitioners.

More than 50% of the pediatricians suspected tuberculosis with any of the five symptoms mentioned in the questionnaire. Fever and cough more than 2 weeks and contact history were the common symptoms for suspecting TB. Lymphadenopathy (96%) was the commonest finding noted during general physical examination.

64% of the clinicians were relying on the all the 3 investigations i.e. Chest X-ray, Mantoux test and gastric lavage/induced sputum examination for AFB. 22% of them were not stressing for AFB examination. Still 16% of them believed that serological tests as one of the diagnostic modality. Gastric lavage was felt as better yielding method (34%) compared to sputum induction (12.5%). Radiology was helpful in making the diagnosis in only 32% of their cases. Hilar lymphadenopathy was the commonest radiological finding noted (48%). 72% of the clinicians did not want to replace Mantoux test with Quantiferon gold test in their day to day practice. 48% of them suggested Mantoux test as a diagnostic test in latent tuberculosis but 34% of them wanted PCR test to be done. Table 2 shows the sample of the type of questions asked in the questionnaire and the response which was considered as compliant.

In 61% of cases, the physicians initiated ATT based on the combination of history, examination findings and supportive investigations. Only in 23% of cases ATT was initiated based on sputum/gastric lavage positive results. In 16% of the cases ATT was started on a trial basis.

Only 52% of the clinicians were adhering to updated national (RNTCP) guidelines for treatment. 82% of the clinicians agreed that all patients should be referred to DOTS center. 54% of the clinicians told that they are maintaining the

Table 1 – General characteristics of the practitioners.

General characteristics	No.	Percentage
Years of experience		
<10 years	23	46
>10 years	27	54
Attachment to the institution		
Yes	35	70
No	15	30
No. of TB patients visiting their clinic		
<5 per month	47	94
>5 per month	3	6

Table 2 – Decision aid for analysis.

Question	Choices given	Compliant response
1. When do you suspect tuberculosis in children?	a) Fever > 2 weeks b) Chronic cough c) H/O contact with tuberculosis d) H/O loss of weight/loss of appetite e) h/o neck swelling	To tick all the five.
2. What are the investigations that you send to confirm tuberculosis?	a) Chest X-ray b) Mantoux test c) Gastric lavage/induced sputum for AFB d) Serological tests	a, b and c are correct answers.
3. Drug resistance should be suspected for	a) All retreatment cases at diagnosis b) Any smear positive cases after 12 weeks of intensive therapy during follow up c) Contacts of confirmed MDR case d) HIV associated TB cases	To tick all the five.

Table 3 – List of problems stated with RNTCP.

1	Follow up is difficult.
2	Not suitable for pediatric patients.
3	Treatment guidelines are confusing.
4	Low quality of medicines.
5	High SES refuse to go to DOTS center.

records of the patients whom they are treating. 96% of the clinicians were aware that now TB is a notifiable disease. 58% of them were reviewing the patients after 2 weeks after the initiation of ATT. 68% of the clinicians were able to successfully follow up 50% of their patients. Only 32% were aware of the Nikshay portal, a website where doctors can notify RNTCP regarding TB cases.

30% of them felt still there are drawbacks in the current RNTCP guidelines. List of the problems mentioned by the clinicians is given below (Table 3). 46% of the clinicians opined that guidelines for the treatment of tubercular meningitis are still not very clear. 68% were aware that according to the revised RNTCP guidelines there are only two categories of treatment but only 22% of them were correct in knowing the duration of treatment of category 2 (8 months). 94% of the clinicians agreed that INH prophylaxis should be given to the breast-feeding babies whose mother had active TB.

72% knew the correct definition of MDR tuberculosis but only 36% of them knew the diagnostic method (gene expert/CB NAAT) of confirming the MDR TB. Only 32% of the clinicians knew clinical scenarios when exactly to suspect drug resistant tuberculosis. 48% of the practitioners have come across MDR TB in their practice. More than 50% of them want MDR suspected cases to be referred to the RNTCP. 36% preferred referring it to an institution. 46% of the clinicians have managed TB with HIV coinfection. 86% of them were aware that fluoroquinolones and aminoglycosides are two important groups of drugs to be reserved for MDR TB.

20% of the doctors underwent training organized by RNTCP while majority of them (80%) have not received any further training from RNTCP. More than 90% felt the need for training and continuous medical education program regarding the optimum practice and recent advances in the field of tuberculosis.

Overall the management practices were found to be better in people with an attachment to the teaching institution compared to the people restricted to private practice though none of them were statistically significant (Table 4).

4. Discussion

This study was conducted to know the diagnostic and treatment practices among pediatricians. The early diagnosis of tuberculosis is particularly difficult in pediatric age group and the higher incidence of extra pulmonary TB makes it more challenging. Around 50% of the practitioners were correct in identifying all the symptoms of tuberculosis which is similar to the finding reported by Basu et al.[4] 22% of the pediatricians were not relying on gastric lavage/induced sputum examination as essential modality for the diagnosis of tuberculosis in children. In a study done by Achanta et al., it was found that around 55% of the adult clinicians had not adopted sputum smear examination as the standard diagnostic practice.[5] Now as per the recent guidelines every attempt should be made for the bacteriological diagnosis.[6]

16% of them still believed in serological diagnosis, which is at a higher percentage compared to the study done by Srivastava et al. (9%).[7] Though 48% of the clinicians reported that they have appreciated hilar lymphadenopathy in a study done by Jain et al., it was found that the reporting of hilar lymphadenopathy was discordant in 39% of children, when the same study was read by two independent radiologists.[8,9] Only 48% of the pediatricians had an idea about latent tuberculosis, which is very important to control TB.[10]

Though in 61% of cases ATT was started based on the combination of history, examination findings and supportive investigations but in 16% of cases ATT was started as a trial basis. According to the study done by Singh et al. it was found that majority of the practitioners (91.3%) were starting the treatment after the diagnosis is established. This difference may be due to the fact later study was done in adult subjects where establishing bacteriological diagnosis is much easier.[11]

94% of our clinicians agreed with INH prophylaxis, where it was noted in a study done by Datta et al., that only 13% of the adult clinicians advised sputum positive patients to take care of children below 6 years and advised INH prophylaxis.[12]

Table 4 – The number of clinicians with correct response for selected components with or without attachment to the institution.

		Attachment to institution		
Serial no.	Components	Yes	No	*p* value
1	Symptoms	17 (54%)	9 (47%)	0.06
2	Serological tests	28 (90%)	14 (73%)	0.69
3	Sputum examination	19 (61%)	8 (42%)	0.25
4	Latent tuberculosis	14 (45%)	10 (52%)	0.06
5	Follow up	20 (64%)	9 (47%)	0.31
6	Duration of treatment	7 (22%)	4 (21%)	0.61
7	INH prophylaxis	30 (96%)	17 (89%)	0.74
8	MDR TB	23 (74%)	13 (68%)	0.54
9	Gene expert	15 (48%)	3 (15%)	0.45
10	NIKSHAY Portal	10 (32%)	6 (31%)	0.45

Only 52% of the clinicians were adhering to the revised RNTCP guidelines. In a study done by Vandan et al., 69% reported that they follow DOTS methodology for TB treatmet.[13] Higher percentage may be due to that more than 50% of the doctors were working in public sector compared to our study where majority (>90%) are from private sector. Though 96% of them knew that TB is a notifiable disease, only 32% of them were aware of the Nikshay portal which is comparable to the study done by the Thomas et al. where only 30% notified the disease.[14]

In our study 30% of the pediatricians mentioned that current RNTCP guidelines are not satisfactory. In a study done by Krishnan et al., there was a significant increase ($p < 0.001$) in the proportion of PPs adopting DOTS, after sensitization.[15] So there is a challenge for the program managers to make sustained efforts for building mutual trust, educate them about the program and clarify their doubts in order to increase their participation in the program. 22% of the clinicians knew correctly the duration of treatment in category 2. Different prescription writing was noted by Udwadia et al.[16]

Only 32% of the clinicians were sure when to suspect MDR tuberculosis and only 36% knew the correct diagnostic method of confirming the MDR. In an article published in BMJ, it is mentioned that detection and treatment of multidrug resistant TB in India remains low.[17]

It is encouraging to note that more than 90% are willing for further training under RNTCP and 82% of the clinicians are ready to send their patients to DOTS center. It is also noted by Bhatia et al. that there is willingness amongst both public and private sector to collaborate.[18] In a study done in the city of Pune, it was found that despite a decade of training activities by the RNTCP, high proportions of the doctors were not following the standardized guidelines asking for more direct involvement of the private practitioners in the program.[19] Utilization of this widespread private health care is essential to attain the optimum TB control and to curb the drug resistance.

5. Conclusion

Management practices are found to be still suboptimum. Better engagement of the private sector is urgently required to improve TB management practices and to prevent diagnostic delay and drug resistance.

Authors' contribution

KSS conceived the idea, collected the data, entered data, did analysis, wrote first draft and approved the final manuscript. PS helped in designing of the study. SK helped in the statistical analysis. AP reviewed and edited the script.

Conflicts of interest

The authors have none to declare.

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Original article

Interleukin-17 A and F gene polymorphisms affect the risk of tuberculosis: An updated meta-analysis

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ABSTRACT

Background: Cytokines are fundamental elements in mediating and stimulating the immune response against tuberculosis (TB). Growing evidence indicated that polymorphisms in the interleukin-17 (IL-17) A and F genes are implicated in TB.
Objectives: This meta-analysis was aimed to re-evaluate and update the relationship between IL-17A rs2275913 G/A and IL17F rs763780 T/C polymorphisms and TB risk.
Methods: Using inclusive searches of the PubMed, MEDLINE, EMBASE, Web of Science and Elsevier Science Direct, we identified outcome data from all articles estimating the association between IL-17 A and F polymorphisms and TB risk.
Results: A total of 15 studies comprising 7130 patients and 7540 controls were included. Our pooled analysis demonstrated that the IL-17A rs2275913 G/A SNP was not associated with the risk of TB in overall, or in Asians and Caucasians, but it conferred resistance to TB in Latin Americans using allele (OR = 0.53), codominant (OR = 0.53 and 0.38), dominant (OR = 0.49) and recessive (OR = 0.46) inheritance models. For IL-17F rs763780 T/C, the pooled evidence indicated that this variation was a risk factor for TB in allele (C vs T) and dominant (TC+CC vs TT) models in overall (OR of 1.35) and among Asians (OR = 1.40), but not in Caucasians.
Conclusion: In summary, our meta-analysis suggested that the IL-17A rs2275913 was a protective factor against TB, but −17F rs763780 T/C was a risk factor for TB.

1. Introduction

Tuberculosis (TB) is the second commonest cause of death from infectious disease after HIV/AIDS worldwide. The TB causative agent, *Mycobacterium tuberculosis* (MTB), affects roughly nine million new cases and 1.5 million deaths annually, although generally in countries with poor economies.[1,2] The features of active disease are widely different among patients from minor symptoms to severe or fatal TB,

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with the latter is defined by big cavitary lung lesions, miliary TB, or meningitis.[3,4] Despite the high prevalence of TB infection, only 5–10% of infected individuals develop active disease with clinical symptoms indicating that the interaction between host genetic susceptibility and environmental factors plays a crucial role in exploring the infection mechanism of MTB.[5–7]

The innate and adaptive immunity of the host are essential factor, which determines the elimination or suppression of TB.[8] The immune response to TB is regulated by interactions between antigen-presenting cells (APCs), lymphocytes, macrophages, monocytes, and immune mediators.[9,10] T helper (Th)-dependent immune response has been proved to be essential in protective immunity against intracellular pathogens like MTB.[11] A new subset of Th cells, Th17 cells release IL-17 cytokine, which is an alternative macrophage activation cytokine with a vital pro-inflammatory role in an organism, including recruiting of granulocytes to sites of infection.[12,13] Attention in IL-17 has been growing because of its significance as a marker of Th17. Many in vitro[14,15] and in vivo[16,17] studies supported the central role of this cytokine in protective immunity against MTB.[4]

Two important members of the IL-17 cytokine family, IL-17A and IL-17F, are preferentially produced by Th17 cells, and are responsible for the pathogenic activity of CD4+ effector cells and multiple proinflammatory mediators. IL-17A and IL-17F are encoded by the IL17A and IL17F genes, respectively, which are located close to each other on chromosome 6 (6p12). Polymorphisms in cytokine genes that could potentially affect gene expression and or biological activity are valuable to study. Many polymorphisms in cytokine genes have been shown to be associated with TB disease status in various populations.[7] The IL-17A-152G/A (rs2275913) and IL17F rs763780 T/C are two putative single nucleotide polymorphism (SNP) loci in the IL-17 genes, which affect the transcriptional regulation and gene expression of IL-17. These two SNPs have been analyzed for the association with occurrence of TB in different populations.[1,18,19] However, the results were rather inconsistent, partially due to the relative small sample size of individual studies. An inclusive retrieval of the pertinent literature will help reach a more precise estimation of the association with disease susceptibility. Therefore, in the present study we performed a meta-analysis to combine the available data and assess whether IL-17A-152G/A (rs2275913) and IL17F rs763780 T/C gene polymorphisms are associated with the susceptibility to TB.

2. Methodology

2.1. Literature search

We performed the literature search using the electronic databases PubMed, MEDLINE, EMBASE, Web of Science and Elsevier Science Direct. All languages were searched. The comprehensive search strategies included the Mesh term and Keywords: ('Interleukin-17A' or 'Interleukin17A' or Interleukin-17F' or 'Interleukin17F' or IL-17A or IL17A, or IL-17F or IL17F'), ('polymorphism' or 'variant' or 'genotype', 'SNP' or 'mutations'), (tuberculosis or TB or MTB) through March 06, 2017. Eligible studies were retrieved and examined carefully. Review articles and bibliographies of other relevant studies identified were hand-searched to find additional eligible studies.

2.2. Data collection

The articles were screened by two independent reviewers (E.EN, M.M) to evaluate the suitability of the articles selected by using a standardized protocol and data collection form. Studies were included if they met all of the following criteria: (a) original data, (b) study which assessed the association of IL-17A rs2275913 or IL-17F rs763780 and the susceptibility to TB(c) comparison between patients with TB and controls. Exclusion criteria were (a) non-human studies, abstracts only, comments, reviews, editorials or letters, mechanism studies and studies that lacked controls, (b) family-based design or sibling pair studies, (c) studies with insufficient information for data extraction and (d) unpublished data. We followed the PRISMA guidelines.

The following data information was collected from each study: authors, year of publication, country, ethnicity, sample size, allele and genotype frequency distribution and Hardy Weinberg equilibrium (HWE). Inconsistencies about inclusion of studies and interpretation of data were solved with discussion.

2.3. Statistical analyses

Quantitative meta-analysis was utilized by RevMan version.5.3.[9,20] Crude ORs with 95% CIs were used to compute the strength of association between the IL-17A rs2275913 or IL-17F rs763780 and TB risk. The significance of the pooled OR was determined by the Z-test, and $P < 0.05$ was considered as statistically significant.

The pooled ORs for the IL-17A rs2275913 G/A polymorphism and TB risk were performed for the codominant model (GA vs GG and AA vs GG), dominant model (GA+AA vs GG), the recessive models (AA vs GA+GG), and for the allelic comparison (A vs G). The pooled ORs for the IL-17F rs763780 T/C polymorphism and TB risk were performed using the same models. Forest-plots graphs were produced in order to estimate the pooled association between the IL-17A rs2275913 or IL-17F rs763780 and TB risk. Heterogeneity among studies was assessed by Cochrane's Q-test and I^2 measurement, which was interpreted as the proportion of total variation contributed among study variants. A P-value ≤0.10 and an I^2 value ≥50% shown significant heterogeneity. A random-effect model was used in the incidence of significant heterogeneity; if not, a fixed-effect model was executed. Stratified analyses were completed by racial descent to evaluate the difference in odds ratio between studies of Caucasians and those of Asians. Sensitivity analysis was conducted to evaluate the validity and reliability of the primary meta-analysis, to ascertain the effects attributed to any individual study.

3. Results

3.1. Study characteristics

In this meta-analysis, a total of 15 studies fulfilled the inclusion criteria for both IL-17A and IL-17F SNPs in TB

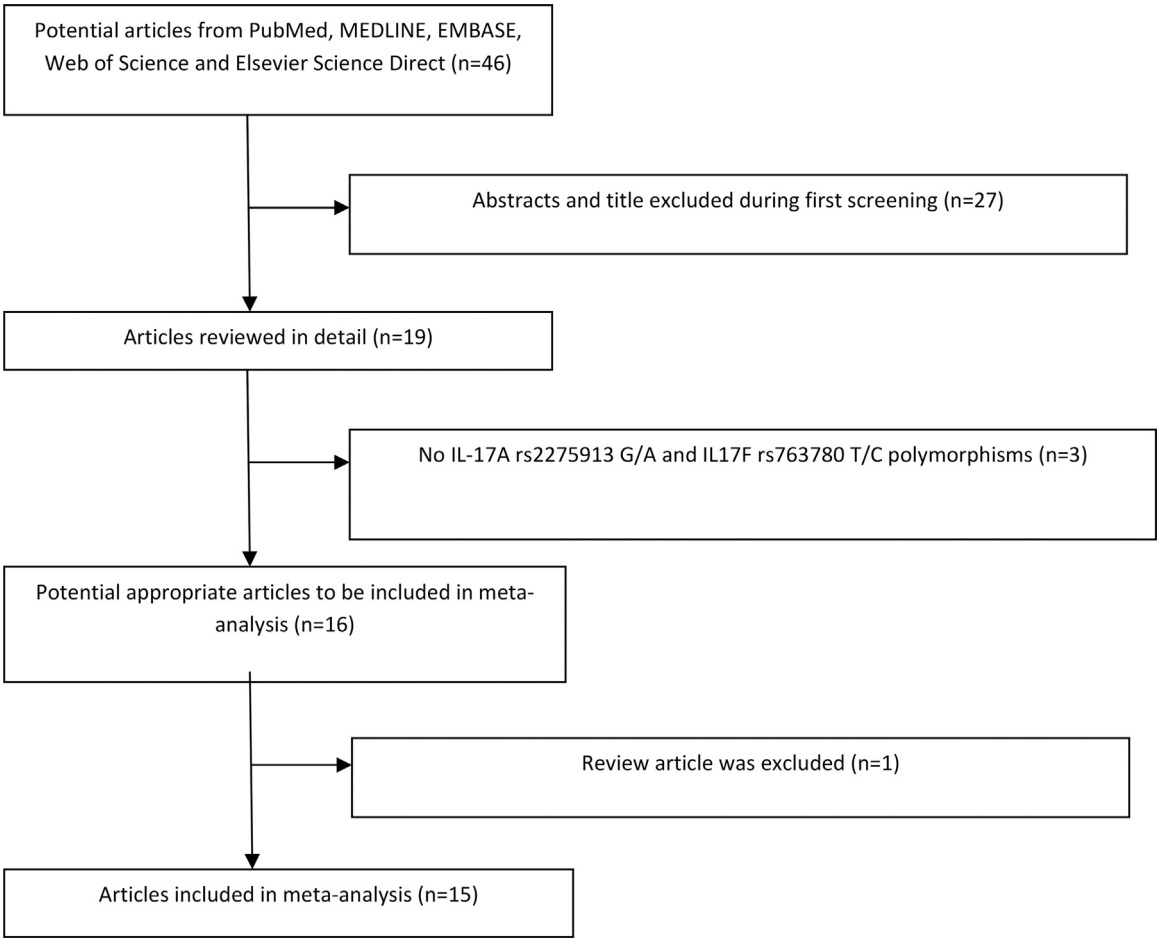

Fig. 1 – The flow chart of study selection.

(Fig. 1). Nine studies assessed the association between IL-17A rs2275913 G/A polymorphism and the risk of TB. Six studies examined the association between IL-17F rs763780 T/C variation and the risk for TB. Baseline characteristics of the included studies on IL-17A and IL-17F SNPs on TB are shown in Tables 1 and 2, respectively.

3.2. *IL-17A rs2275913 G/A polymorphism and susceptibility to TB*

Nine studies including 3805 patients and 4055 controls evaluated the association between IL-17A rs2275913 G/A polymorphism and susceptibility to TB. The distributions of genotypes in control subjects among all included studies were in HWE (Table 1). The pooled results showed that the A vs G allele was not associated with the risk of TB with the overall OR of 0.90 (95% CI = 0.75–1.07). In the codominant model, the pooled evidence suggested that GA vs GG genotype distribution between groups was not statistically significant (OR = 0.95, 95% CI = 0.87–1.04). Likewise, the general difference between groups for the AA genotype compared to GG did not reach the statistical significance using the codominant model with the overall OR of 0.91 (95% CI = 0.67–1.23), as it happened in the dominant model for the GA+AA vs GG genotype (OR = 0.87; 95% CI = 0.69–1.08), as well as in the recessive model for AA vs GA +GG genotype (OR = 0.96; 95% CI = 0.76–1.20). Fig. 2 represents the forest plot of the risk of TB associated with IL-17A rs2275913 G/A polymorphism using allele, codominant, dominant and recessive models.

3.3. *IL-17F rs763780 T/C variation and the risk for TB*

Six studies including 3325 patients and 3485 controls assessed the association between IL-17F rs763780 T/C variation and the risk for TB. The pooled evidence suggested that the C allele compared to T allele was significantly differed between the groups (95% CI = 1.01–1.80), and it was a risk factor for TB with the overall OR of 1.35. Similarly, TC+CC vs TT in dominant model increased the risk of TB with the OR of 1.35 (95% CI = 1.01–1.82). However, TC vs TT genotype (OR = 1.30; 95% CI = 0.96–1.76) and the CC vs TT in the codominant model (OR = 1.38; 95% CI = 0.71–2.68), as well as the CC vs TC+TT in the recessive model (OR = 1.31; 95% CI = 0.67–2.55) were not associated with overall risk of TB. Fig. 3 demonstrates the forest plot of the risk of TB associated with IL-17A rs763780 T/C polymorphism.

3.4. *Subgroup meta-analysis of IL-17A rs2275913 G/A polymorphism and TB by ethnicity*

In subgroup analysis of IL-17A rs2275913 G/A polymorphism, the nine studies were partitioned into Asian (five), Caucasian

Table 1 – Major characteristics of included studies in a meta-analysis of Interleukin-17A gene rs2275913 G/A polymorphism and tuberculosis.

Author	Year	Country	Ethnicity	Sample size	Allele frequency		Genotype frequency			HWE
					G	A	GG	GA	AA	P-value
Ocejo-Vinyals	2013	Spain	Caucasian	P 192	P 270	P 114	P 97	P 76	P 19	P 0.47
				C 266	C 334	C 198	C 104	C 126	C 36	C 0.82
Peng	2013	China	Asian	P 596	P 688	P 504	P 196	P 296	P 104	P 0.66
				C 622	C 684	C 560	C 176	C 332	C 114	C 0.05
Abhimanyu	2013	India	Asian	P 146	P 120	P 172	P 17	P 86	P 43	P 0.001
				C 119	C 91	C 147	C 14	C 63	C 42	C 0.18
Shi	2015	China	Asian	P 336	P 401	P 271	P 129	P 143	P 64	P 0.03
				C 351	C 484	C 218	C 171	C 142	C 38	C 0.30
Du	2015	China	Asian	P 428	P 556	P 300	P 184	P 188	P 56	P 0.46
				C 428	C 592	C 264	C 210	C 172	C 46	C 0.23
Bulat-Kardum	2015	Croatia	Caucasian	P 244	P 328	P 160	P 113	P 102	P 29	P 0.42
				C 407	C 552	C 262	C 190	C 172	C 45	C 0.51
Milano	2016	Brazil	Latin American	P 171	P 307	P 35	P 141	P 25	P 5	P 0.02
				C 133	C 214	C 52	C 89	C 36	C 8	C 0.10
Wang	2016	China	Asian	P 1507	P 1683	P 1331	P 477	P 729	P 301	P 0.45
				C 1522	C 1641	C 1403	C 450	C 741	C 331	C 0.42
Rolandelli	2017	Argentina	Latin American	P 185	P 299	P 71	P 124	P 51	P 10	P 0.13
				C 207	C 292	C 122	C 108	C 76	C 23	C 0.09

(two) and Latin American (two) subgroups. The analysis indicated that the A allele compared to G allele was not associated the risk of TB in Asians (OR = 1.06, 95% CI = 0.88–1.28), Caucasians (OR = 0.86, 95% CI = 0.60–1.23). However, in Latin Americans the A vs G allele reduced the risk of TB (OR = 0.53, 95% CI = 0.43–0.70).

In codominant heterozygote model, and in the subgroup of Latin Americans the GA vs GG genotype was a protective factor for TB (OR = 0.53, 95% CI = 0.37–0.75). However, no association between GA vs GG and the TB risk was found in Asians (OR = 1.03, 95% CI = 0.85–1.26) and Caucasians (OR = 0.81, 95% CI = 0.53–1.24).

In the codominant homozygote model, no association between AA vs GG and the TB risk was observed among Asians (OR = 1.12, 95% CI = 0.78–1.62) and Caucasians (OR = 0.80, 95% CI = 0.42–1.51). In contrast, in the subgroup of Latin Americans the AA vs GG genotype reduced the risk of TB (OR = 0.38, 95% CI = 0.20–0.73).

In the dominant model, the GA+AA vs GG genotype did not affect the risk of TB in both Asians (OR = 1.07, 95% CI = 0.84–1.36) and Caucasians (OR = 0.81, 95% CI = 0.51–1.29), but GA+AA genotype in Latin Americans was a protective factor against TB (OR = 0.49, 95% CI = 0.36–0.68).

The AA vs GA+GG genotype in the recessive model was not associated with the TB risk in Asians (OR = 1.07; 95% CI = 0.82–1.41) and Caucasians (OR = 0.90, 95% CI = 0.62–1.32), except for Latin Americans which decreased the TB risk (OR = 0.46, 95% CI = 0.24–0.87).

3.5. *Subgroup meta-analysis of IL-17F rs763780 T/C polymorphism and TB by ethnicity*

In subgroup analysis of IL-17F rs763780 T/C, the six studies were divided to Asian (five) and Caucasian (one) subgroups. In Asian subgroup, and in allele comparison, the C vs T was a risk factor for TB (OR = 1.40; 95% CI = 1.03–1.92). Likewise, in

Table 2 – Major characteristics of included studies in a meta-analysis of Interleukin-17F gene polymorphism (rs763780 T/C) and tuberculosis.

Author	Year	Country	Ethnicity	Sample size	Allele frequency		Genotype frequency			HWE
					T	C	TT	TC	CC	P-value
Peng	2013	China	Asian	P 596	P 1021	P 171	P 435	P 151	P 10	P 0.45
				C 622	C 1114	C 130	C 511	C 92	C 19	C 0.00
Abhimanyu	2013	India	Asian	P 165	P 324	P 6	P 159	P 6	P 0	P 0.81
				C 130	C 256	C 4	C 126	C 4	C 0	C 0.85
Shi	2015	China	Asian	P 335	P 554	P 116	P 250	P 54	P 31	P 0.00
				C 351	C 622	C 80	C 289	C 44	C 18	C 0.00
Du	2015	China	Asian	P 428	P 707	P 149	P 319	P 69	P 40	P 0.00
				C 428	C 770	C 86	C 357	C 56	C 15	C 0.00
Bulat-Kardum	2015	Croatia	Caucasian	P 222	P 433	P 11	P 211	P 11	P 0	P 0.70
				C 429	C 835	C 23	C 406	C 23	C 0	C 0.56
Wang	2016	China	Asian	P 1579	P 2773	P 385	P 1225	P 323	P 31	P 0.07
				C 1525	C 2668	C 382	C 1175	C 318	C 32	C 0.06

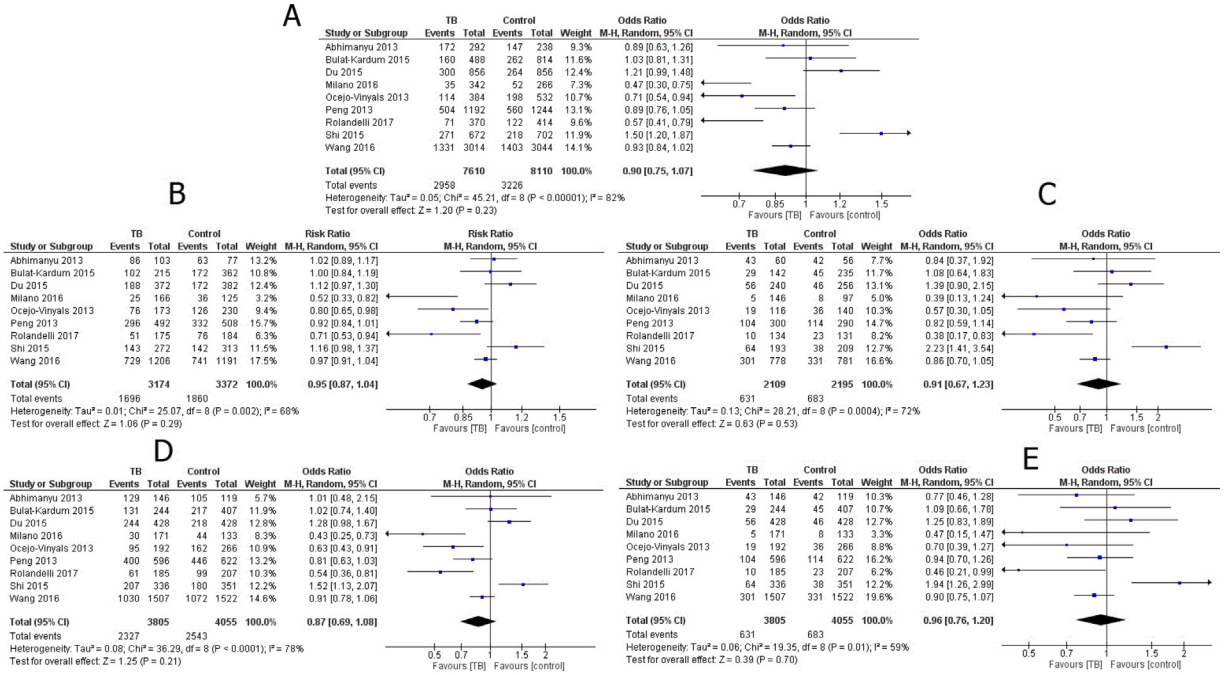

Fig. 2 – Forest plot of the risk of tuberculosis associated with IL-17A rs2275913 G/A polymorphism (A: A vs G, B: GA vs GG, C: AA vs GG, D: GA+AA vs GG, E: AA vs GA+GG).

dominant model the CC+CT vs TT elevated the TB risk (OR = 1.42; 95% CI = 1.03–1.95). However, we found no significant difference among groups in the codominant heterozygote ($P = 0.07$) and homozygote ($P = 0.34$), and recessive ($P = 0.43$) models. In the Caucasian subgroup there was only one study, so no pooled result was generated.

3.6. *Heterogeneity and sensitivity analyses and publication bias*

Significant heterogeneities in the data for IL-17A rs2275913 and IL-17F rs763780 polymorphisms were observed ($I^2 > 50\%$) and we used Random-Effect model; otherwise the Fixed-effect

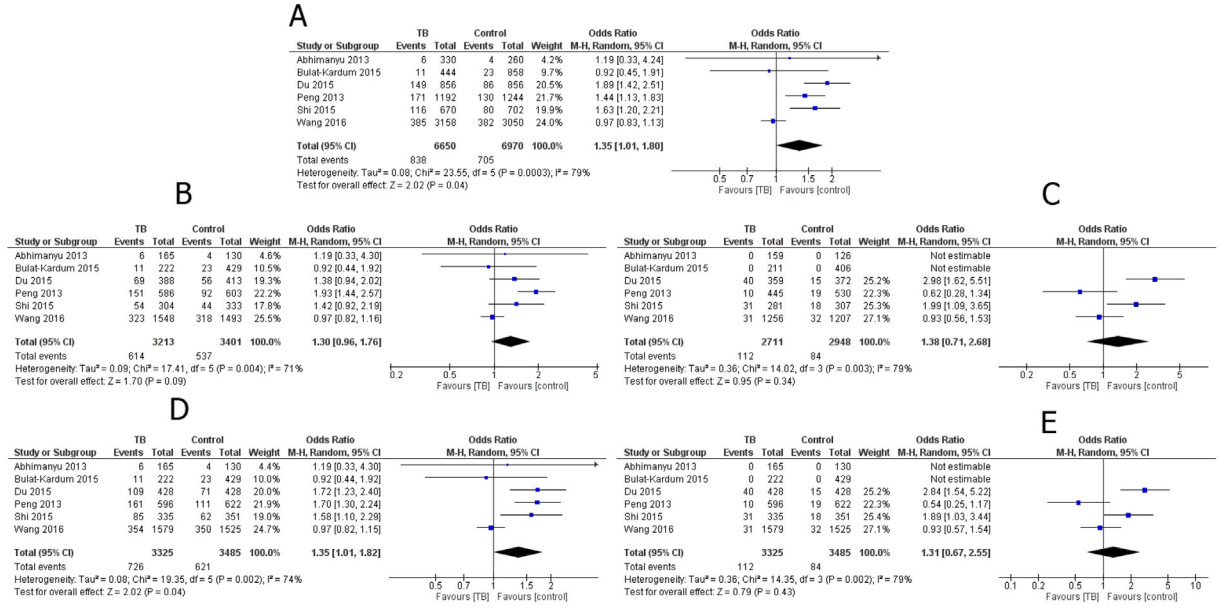

Fig. 3 – Forest plot of the risk of tuberculosis associated with IL-17F rs763780 T/C polymorphism (A: C vs T, B: TC vs TT, C: CC vs TT, D: CT+CC vs TT, E: TT vs TC+CC).

model was applied. For sensitivity analysis, individual studies used in the meta-analysis were omitted in order to identify the source. The results showed that no individual study influenced the pooled OR values for studied IL-17A and F SNPs. We did not measure the publication bias because it is inapplicable once the number of included studies is less than ten.

4. Discussion

Meta-analysis is an increasingly popular tool for combining multiple genetic association studies in a single analysis to determine more precise estimation of the association with disease susceptibility. Nine studies were processed in the current meta-analysis of the association between IL-17A rs2275913 G/A and TB. Our pooled evidence suggested that the rs2275913 G/A SNP was not associated with the risk of TB in overall, as well as in Asian or Caucasian subgroups. However, rs2275913 significantly reduced the risk of TB in Latin Americans using allele (A vs G; OR = 0.53), codominant heterozygote (GA vs GG; OR = 0.53), codominant homozygote (AA vs GG; OR = 0.38), dominant (GA+AA vs GG; OR = 0.49) and recessive (AA vs GG+GA; OR = 0.46) inheritance models. A number of studies have examined the IL-17A rs2275913 SNP in ethnically dissimilar populations, in order to identify a relationship with predisposition/resistance to TB.[1,4,19,21–26] In a population from North Spain, Ocejo-Vinyals et al.[26] indicated that the rs2275913 A allele and the AA genotype were less common among TB patients compared to controls and conferred resistance to TB. Similarly, Milano et al.[23] indicated that A allele, GA (heterozygote) and GA+AA (in dominant model) were associated with reduced TB risk in a Brazilian population, supporting the findings of Rolandelli et al.[21] from Argentina who found the protective effects of rs2275913 in allele, codominant, dominant and recessive models. Conversely, Shi et al.[24] indicated IL-17A rs2275913 was associated with increased risk of TB in Chinese using allele, codominant homozygote, dominant, and recessive models. A possible explanation of the differences among these studies could be related to ethnic differences (Asians vs Latin Americans).

It has been shown that the rs2275913 SNP is a functional polymorphism that alters the attachment of the transcriptional factor NFAT to the IL-17A promoter. Espinoza et al.[27] indicated that the A variant promotes the stronger binding of NFAT, resulting in increased transcription and production of the IL-17A protein.[27] Likewise, Rolandelli et al.[21] detected up-regulation of IL-17A in individuals with AA genotype compared to those who carry the GG genotype, both in plasma and in supernatants of in vitro stimulated PBMC. Interestingly, in inflammatory diseases[28,29] the rs2275913 A has been found as a risk factor supporting the hypothesis that IL-17A overexpression might be destructive resulting in pathological conditions. So it is highly probable that in MTB infection, the rs2275913 G/A SNP (associated with IL-17A up-regulation) may be beneficial for the formation of mature granulomas, hence restraining mycobacteria spread.[30] This explains why rs2275913 G/A provides resistance to TB infection among Latin Americans.

With respect to IL-17F rs763780 T/C variation, the pooled analysis of six studies indicated that this variation was a risk factor for TB both in allele (C vs T) and dominant (TC+CC vs TT) model with the same OR of 1.35. The subgroup analysis confirmed the association of rs763780 T/C with increased TB risk among Asians using allele (OR = 1.40) and dominant (OR = 1.42) comparisons but not in the Caucasians. Our data supports the findings of Peng et al.,[4] Shi et al.[24] and Du et al.[25] who reported that the this polymorphism was associated with an increased risk of TB. Peng et al.[4] found that rs763780 was a risk factor for TB using allele (OR = 1.44), heterozygote (OR = 1.93) and dominant models (OR = 1.70). Additionally, Shi et al.[24] reported that this SNP elevated the TB risk using allele (OR = 1.63), homozygote (OR = 1.99) and dominant (OR = 1.58) models supporting the findings of Du et al.[25] who observed a significant association of rs763780 and TB risk in allele (OR = 1.89), homozygote (OR = 2.98), dominant (OR = 1.72) and recessive (OR = 2.84) models. However, other studies found no association between the IL-17F variation and TB risk.

IL-17F rs763780 T/C variant is positioned in the coding region of IL-17 F gene and results in alteration of His-to-Arg at amino acid position 161. In vitro functional analysis also proved that IL-17F function may be inhibited in the rare C allele carriers compared to those with wild-type T allele.[31] The association of IL-17F rs763780 T/C with its down-regulation supports our pooled evidence that this genetic variation is a risk factor for TB.

A recent meta-analysis by Zhao et al.[32] showed lack of any association between IL-17A rs22275913 polymorphism and TB in Asians or Caucasians. For IL-17F rs763780, they reported the significant associations under allele, heterozygote, dominant and recessive models in overall as well as in Asians. In contrast, our study is an update which included three new studies for IL-17A, and one for IL-17F. Although both meta-analyses failed to show a relationship between IL-17A rs22275913 and TB in overall and among Asians and Caucasians, our pooled evidence revealed the presence of an association between IL-17A rs22275913 with reduced TB risk among Latin Americans. Concerning IL-17F rs763780, our results supports the findings of Zhao et al.[32] but only in allele (C vs T) and dominant models, not for heterozygote, and recessive models.

Moreover, our pooled analysis showed the presence of a significant heterogeneity in overall and in the subgroups. Of six studies assessing IL-17F on TB, three deviated from HWE; thus we hypothesized that they might be the source of heterogeneity. Therefore, we performed the sensitivity analysis to assess this idea. One of the three studies was removed each time to reflect the influence of the individual data set to the overall association, but we found that none of these studies were the source of heterogeneity.

In spite of the scientific and rational design and strict implementation, several limitations should be addressed for this meta-analysis: (1) our meta-analysis only included the published articles, and there might be relevant unpublished studies we missed. (2) In subgroup analysis of IL-17F rs763780 T/C our study included only one study from Caucasians. (3) Since HIV infection is a risk factor for susceptibility to TB infection,[33] the HIV status of study population in the included studies should be known. Among all included studies in this meta-analysis, only four studies[4,21,22,26] confirmed that their study population were negative for

HIV infection, while the rest of studies[1,19,23–25,32] failed to provide the accurate status of HIV, which may weaken the strength of the pooled analyses.

In summary, our meta-analysis demonstrated that the IL-17A rs2275913 G/A polymorphism reduced the risk of TB in Latin Americans using allele, codominant (heterozygote and homozygote), dominant and recessive inheritance models. In contrast, the IL-17F rs763780 T/C variation was a risk factor for TB in overall and Asians in allele and dominant models.

Authors' contribution

MM and AAS extracted the data; EEN and AT contributed to data analysis; MM and EEN wrote and revised the manuscript.

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Ethical approval

This is a meta-analysis and for this type of study, ethical approval is not required.

Conflicts of interest

The authors have none to declare.

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Original article

Cost effectiveness of decentralised care model for managing MDR-TB in India

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ABSTRACT

Background: In India, multidrug-resistant tuberculosis (MDR-TB) patients are usually treated in hospitals. Decentralised care model, however, has been suggested as a possible alternative by the World Health Organization (WHO). In the ''End TB Strategy'', the WHO highlights, as one of the key targets for 2035, that 'no TB-affected families should face catastrophic hardship due to the tuberculosis'. Removal of financial barriers to health-care access and mitigation of catastrophic expenditures are therefore considered vital to achieve the universal health coverage (UHC) goal. Since forgoing healthcare due to the financial constraints is a known fact in India, decentralised care as an intervention choice (as against hospital-based care) might enhance equity provided it is an affordable choice. Thus, an economic evaluation was conducted, from the perspective of the national health system in India, to assess the cost-effectiveness of decentralised care compared to centralised care for MDR-TB.

Methods: This study uses a decision-analytic model with a follow-up of two years to assess the expected costs of the decentralised versus the centralised approaches for MDR-TB treatment. A published systematic review of observational studies yielded the MDR-TB treatment outcomes, which included treatment success, treatment default, treatment failure, and mortality parameters. It was observed that these parameters did not vary significantly between the two alternatives. Treatment costs included the following costs: hospital admission costs, clinic costs, visits to laboratory and MDR-TB centre, drug therapy, injections and food. Costs data of drugs, diagnosis, hospital stay and travel to public facilities, based on a simple market survey, were taken from a recently published study on MDR-TB expenditures in the Chhattisgarh state of India. Potential cost savings related to

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the implementation of decentralised MDR-TB care for all patients who initiated MDR-TB treatment in India were additionally estimated.

Results: Estimated average expected total treatment cost was US$ 3390.56 for the hospital-based model and US$ 1724.1 for the decentralised model for a patient treated for MDR-TB in India, generating potential savings of US$1666.50 per case, with ICER US$ 2382.68 per QALY gained. One of the primary drivers of this difference was the significantly more intensive (thus expensive) stay charges in the hospital. If the costs and treatment probabilities are extrapolated to the whole country, with 48114 MDR-TB patients initiated on treatment in 2017, decentralised care would have additional 1058 patients cured, gain additional 3824 QALYs, and avert 2165 deaths, as compared to centralised care, in India. At various scenarios of coverage rates of decentralised and centralised care the cost difference would range between 23% and 94% for the country.

Conclusion: Our study provides evidence of cost savings for MDR-TB patients if patients choose decentralised treatment in comparison to suggested hospitalisation of these patients for centralised treatment with similar outcomes. The economic evaluation presented in this study expected significant efficiency gains in choice of two treatment options and the cost savings may improve equity. In India, treatment of MDR-TB using decentralised care is expected to result in similar patient outcomes at markedly reduced public health costs compared with centralised care.

1. Introduction

India has around 2.8 million new tuberculosis (TB) cases each year, and accounts for the highest burden of TB, including multidrug-resistant tuberculosis (MDR-TB) in the world.[1] Mortality due to the TB in the country is the ''third leading cause of years-of-life-lost (YLL)''.[1] MDR-TB is defined as ''TB resistant to isoniazid and rifampicin, irrespective of its resistance to other drugs (DOTS-PLUS)''. In 2016, there were an estimated 79,000 and 24,000 MDR-TB cases respectively, among notified and new pulmonary TB patients in the country.[2]

Under the Revised National Tuberculosis Control Programme (RNTCP), Government of India, MDR-TB cases must undergo 24–27 months of anti-TB therapy.[3] Patients are required to undergo hospitalisation for about a week to ensure the pre-treatment evaluations, treatment initiation, to go through the counselling, and understanding of treatment adherence protocols and the monitoring of early adverse events. Efforts are made to convince the patient to undergo hospitalisation for these activities.[4] However, despite these efforts, it has been observed that the MDR-TB treatment has persistently been afflicted by the low retention and adherence to treatment.[2] Evidence from high MDR-TB burden countries like India[5] and Africa[6–8] has shown that comprehensive decentralised care, particularly for MDR-TB, is effective while meeting patient and health system needs. Some systematic reviews have suggested that decentralised care has similar patient outcomes and is as effective as centralised MDR-TB care.[9–12] Additionally, decentralised treatment approach has been recommended by the World Health Organization (WHO) as a sustainable alternative.[13] Centralised care represents care by ''specialist centres'', either by way of inpatient or outpatient services.[9] On the other hand, decentralised care include home-based and ambulatory MDR-TB care, and defined by the 'decentralization' of the MDR-TB care provided by grassroots/community workers either in peripheral facilities (health facility or workplace) close to or at the patient's residence for majority of the treatment's duration.[9,14] This is true especially in poor-resource settings having high MDR-TB burden, where this approach has been subsequently adopted by many countries.[12,13]

The ''End TB Strategy'' by WHO highlights, as one of core targets to be achieved by 2035, that none of the TB-affected families should face catastrophic hardship due to the tuberculosis.[15] Elimination of financial barriers to healthcare access and mitigation of catastrophic expenditures are therefore considered vital to achieve the universal health coverage (UHC) goal.[16] Additionally, in resource-constrained settings, the centralised care model could result in waiting for hospital beds thus leading to infection spread in the community, the nosocomial spread of MDR *Mycobacterium tuberculosis*, and questionable affordability due to its high costs.[17]

Despite these problems, the emphasis continues to be on centralised care for the MDR-TB patients in India. While decentralised care can provide significant efficiencies and appropriate ''support structures'' to battle the MDR-TB epidemic[5] particularly in countries having serious shortage of the human resource,[6] there is a lack of published evidence on its costs compared to that of centralised care. This study aims to conduct an economic evaluation to compare the cost of the two MDR-TB treatments – the centralised and the decentralised – approaches from the Indian national health-care system perspective.

2. Methods

The study population consisted of Multi-Drug Resistant Tuberculosis (MDR-TB) patients defined as a ''MDR-TB suspect

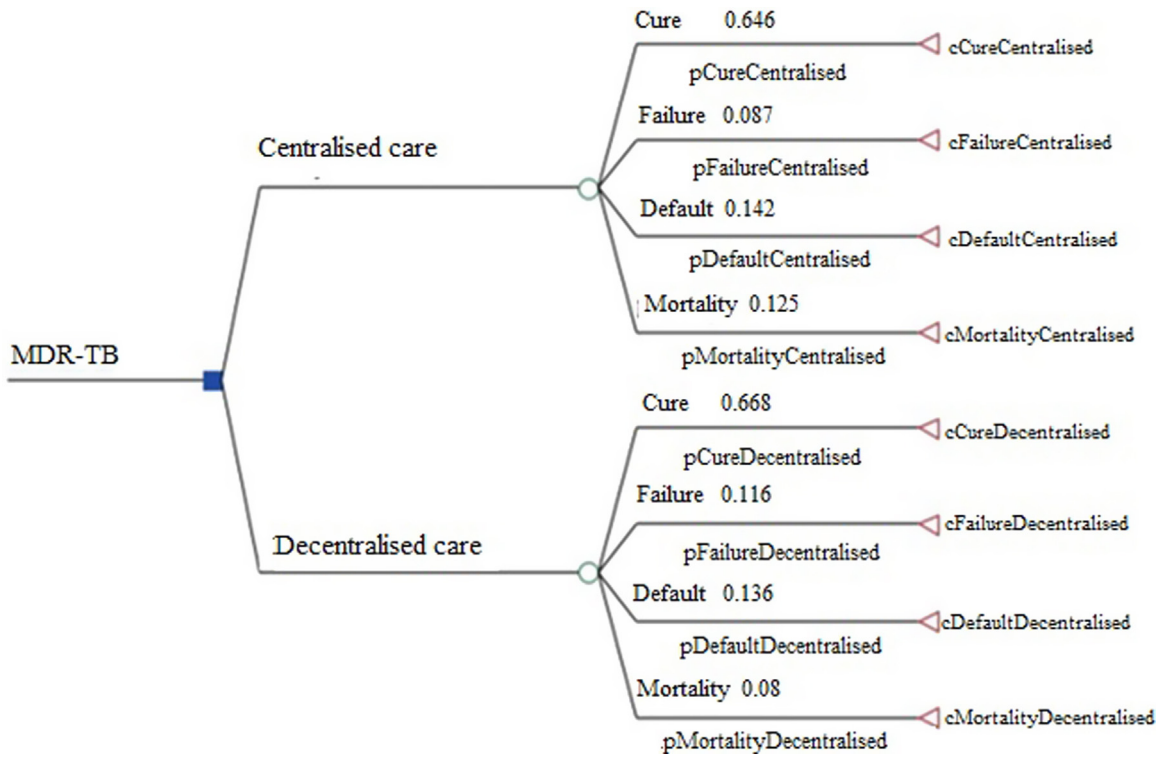

Fig. 1 – Decision tree for MDR-TB care.

who is sputum culture positive, whose TB is due to Mycobacterium tuberculosis resistant in vitro to isoniazid and rifampicin with or without other anti-tubercular drugs''.[18] MDR-TB cases were those who received six to nine months of intensive phase therapy of kanamycin, ofloxacin (levofloxacin), ethionamide, pyrazinamide, ethambutol, cycloserine and eighteen months of continuation phase ((levofloxacin), ethionamide, ethambutol, cycloserine).[3]

The intervention for the economic evaluation was the decentralised MDR-TB treatment with the centralised treatment for MDR-TB being the comparator. This study incorporates a decision-analytic model using a follow-up of two years to assess the expected costs of centralised and decentralised MDR-TB care. A published systematic review and meta-analysis of randomised clinical trials (RCT) yielded the outcomes of MDR-TB treatment.[10] These included parameters of ''treatment success, treatment failure, treatment default, and mortality''. It was observed that these parameters, between the two approaches, did not differ significantly. The primary outcome was 'estimated average cost per MDR-TB patient treated'. Additionally, potential cost savings associated with the implementation of decentralised treatment model across various scenarios for patients who initiated MDR-TB treatment in India, were also estimated.

2.1. *Decision analytic model*

The study employs a cost-minimisation approach as it was found that the outcome parameters, as outlined above, based on the systematic reviews.[19] Decentralised treatment was taken as the base case, and centralised treatment was the alternative case. Similar to an early study, a decision-analytic model using up to two years of follow up period was used to examine and analyse the estimated cost of the centralised and decentralised MDR-TB treatment approaches.[16] A published systematic review and meta-analysis of observational studies yielded the outcomes of MDR-TB treatment, including their probabilities.[10] Patients were considered to incur the full cost of the MDR-TB treatment if they completed the treatment, irrespective of the outcomes i.e. favourable (cure after treatment completion) or unfavourable (failure after treatment completion). For those who did not complete the treatment, designated as the defaulters, the study apportioned 50% of the full treatment costs for these cases. A 'dominant' treatment strategy was one that was associated with lower costs. The calculations were performed on a spreadsheet on Microsoft Excel 2007. The model was constructed using Treeplan (Treeplan Software Inc, San Francisco, USA) (Fig. 1).

2.2. *Cost inputs*

The study collated the cost data of drugs, diagnosis, hospital stay and travel for public health facilities from recently published study on MDR-TB expenditure in Chhattisgarh.[20] Costs of sputum drug sensitivity were not included in computations as they were equal for both the arms. Similarly, cost imputation was limited to six months of intensive treatment phase, since the costs incurred during the 18 months in the continuation phase were equal in both the arms. Costs collected from various sources were adjusted for the inflation for the reference year 2016 and later converted to US$ (INR 65.48 equivalent to one US$, reference date: 18 March 2017).

The treatment costs included the following costs in both the arms of centralised care (F) and ambulatory care (A):

Table 1 – Treatment outcomes across various studies.

Study ID	Location	Study design	Number of patients (decentralised/ centralised)	Treatment outcomes					
				Model of care	Treatment success rate%, 95% CI	Cure (%)	Failure (%)	Default (%)	Mortality (%)
Bassili 2013[10]	NA	Systematic Review & Meta-Analysis		Home-based	65.5 (55.1–74.6)	64.6	8.7	14.2	12.5
				Facility-based	66.7 (61–72)	66.8	11.6	13.6	8.0
Weiss 2014[12]	NA	Systematic Review & Meta-Analysis		Home-based	64 (45–79)				
				Facility-based	63 (45–79)				
Yin 2016[11]	NA	Systematic Review & Meta-Analysis		Home-based	68.4 (51.5–81.5)				
				Facility-based	70.5 (61.5–78.1)				
Ho 2017[9]	NA	Systematic Review & Meta-Analysis	2126/1862	Decentralised care	67.3 (53.8–78.5)	67.3	4.2		17.8
				Centralised care	61.0 (49–71.7)	61.0	4.3		18.6
Kabongo 2010[6]	Kweneng West subdistrict, Botswana	Observational	95/279	Home-based	84	20	2	1	16
				Facility-based	82	25	1	3	12
Loveday 2015[7]	KwaZulu-Natal, South Africa	Non-randomised observational prospective cohort	736/813	Home-based	58	50.7	6.7	14.5	18.1
				Facility-based	54	34.4	3.6	28.3	13.9
Joseph 2011[35]	Tamil Nadu, India	Prospective observational	138	Home-based		66	13	13	8
Thomas 2007[36]	Tamil Nadu, India	Prospective observational	68	Home-based		48	0	37	3
Udwadia 2014[37]	Mumbai, India	Prospective	78	Facility-based		68	15	13	0

- drug therapy (for both F and A)
- clinic visits (for only A)
- hospital admission (for only F)
- injections (for only F)
- food (for both F and A)
- visits to laboratory and MDR centre (for only A) and
- travel (for only A).

The sources of data on costs and methodology are detailed in Tables 1 and 2. Based on this data, potential cost savings and efficiency gains associated with the implementation of the decentralised treatment were estimated for all MDR-TB patients initiating MDR-TB treatment in India.

2.3. *Treatment efficacy*

The probabilities for the treatment outcomes for decentralised and centralised care were obtained from a systematic-review and meta-analysis which included a total of 14,478 patients from 35 studies.[10] To obtain a total of 100% in the decentralised and centralised care arms, the estimates of these parameters were adjusted proportionately for the sum of all the outcomes. Patients in both the arms were provided ambulatory care during the continuation treatment phase of the MDR-TB treatment, thus experiencing same exposure and outcomes. For centralised MDR-TB care, the probabilities were as follows: 64.6% for Cure, 14.2% for Default, 12.5% for Mortality, and 9% for Failure. Corresponding estimates for decentralised treatment were: 66.8% for Cure, 13.6% for Default, 8% for Mortality, and 11.6% for Failure (Table 3). It is noteworthy that adherence to treatment in the continuation phase was not significantly different in the two models of care.

2.4. *Subgroup analysis*

A subgroup analysis was additionally performed using results of a meta-analysis conducted to obtain pooled estimates for treatment outcomes including treatment success, cure, failure, mortality and default. In order to conduct the meta-analysis, studies conducted after year 2000 were selected from five published systematic reviews on centralised and decentralised care for MDR-TB.[9–12,21] The studies selected had centralised and/or decentralised care for adult non-HIV MDR-TB patients, or reported treatment outcomes on a subgroup of non-HIV MDR-TB patients. A total of 22 studies with a sample size of 5894 were included and a meta-analysis was conducted using a random-effects model. The pooled treatment outcomes were found similar for both treatment models (centralised: 60.4%; 95% CI: 54.6–65.8%; decentralised: 64.3%; 95% CI: 54.1–75.4%). For centralised MDR-TB care, the probabilities were as follows: 64% for Cure, 17% for Default, 9% for Mortality, and 10.2% for Failure. The corresponding estimates for decentralised treatment were: 60% for Cure, 18% for Default, 14% for Mortality, and 8% for Failure.

Table 2 – Cost inputs used in computation of cost of MDR-TB treatment.

Cost indices	Centralised care [RNTCP medicines] US$	Decentralised care [RNTCP medicines] US$	Source of data	Cost difference US$
Total therapy drug cost	1663.13	1663.13	Kundu et al., 2015 (India)[19]	–
Cost at Clinic US$64.95 for pre-Rx testing US$51.88 for post-Rx testing	116.83	116.83		–
7-day admission for all	89.63	89.63		–
Bed charges, doctors' consultation fees and ancillary drugs for 6 months (hospital)	2143.27	–		2143.7
HW cost for injections	57.61	57.61	₹26.20 (US$0.40) × 6 months × 6 days × 4 weeks for injections = ₹3772 (US$57.61)	−657.61
Food in Town	14.42	19.21	12 visits @ ₹104.79 (US$ = 1.60) = ₹1257.48 (US$19.20) for Home and 9 visits post-Hospital = ₹943.11 (US$14.40)	−4.80
Visits to Laboratory and MDR Centre	24.01	28.82	12 visits to a diagnostic laboratory @ ₹104.79 (US$1.60) during follow-up visits and 3 visits with an attendant to the DR-TB centres @ ₹209.59 (US$3.20) = ₹1800 (US$27.49) and home = ₹1500 (US$22.91)	−4.81
Overall total with 2014–15 figures	4108.88	1975.23		2133.66

2.5. *Health utilities for QALYs and disability weights*

Utility weights for assessing QALYs across various outcome categories were used from previous studies.[22–24] The quality of life of MDR-TB patients who had passed the intensive phase but finally failed therapy was assumed with a utility of 0.68. No disutility was provided for patients cured after 2 years, thus a utility of 1 was used.

2.6. *Cost-effectiveness analysis*

Since the cost imputation was considered only for the first six months, costs and health outcomes were not discounted. Strategies are ranked in order of increasing costs, and any strategy that is costlier and less beneficial than another strategy is considered dominated. The incremental cost-effectiveness ratio of each remaining strategy was calculated by dividing the additional benefit (QALYs gained or TB deaths averted). The WHO suggests that interventions costing less than three times the gross domestic product (GDP) per disability-adjusted life year (DALY) averted may be considered good value.[25] (One DALY averted is analogous to one QALY gained.) In our evaluation, we considered an incremental cost per QALY that was less than the per capita GDP to be highly cost-effective, 2–3 times per capita GDP to be cost-effective, and three times per capita GDP to be a threshold beyond which an intervention would be considered too expensive. The per capita GDP for India for year 2017 is US$ 1861.50.[26]

2.7. *Sensitivity analysis*

The robustness of the results was assessed using a one-way sensitivity analysis by evaluating the effect of changes in key parameters in the model. The lower and higher ranges of ''a fifty percent decrease and increase in the baseline costs associated with every MDR-TB treatment outcome'' was used. The probability of the four treatment outcomes was informed by the upper and lower limits of 95% Confidence Intervals (CI). In addition to this, the impacts of setting the cost of defaulting treatment equal to the cost of cure, and the cost of mortality equal to that of cure were tested.[17,18] Additionally, results were also calculated based on the observational studies that have compared decentralised care and centralised care (Table 4).

2.8. *Scenario analysis*

A scenario analysis was performed using 10 scenarios by varying the ration of proportion of patients in centralised to decentralised care, to report the range of costs that would be saved proportionate to the varying ratio in both care models.

3. Results

3.1. *Base-case analysis*

The estimates of the expected average total MDR-TB treatment cost were US$ 3390.56 for the centralised treatment and US

Table 3 – Input variables for cost effectiveness analysis.

Variable category	Distribution	Value	Reference
Probability of cure (Decentralised)[a]	Fixed	0.668	Bassili 2013[e]
Probability of cure (Centralised)[a]	Fixed	0.646	Bassili 2013[e]
Probability of failure (Decentralised)[b]	Fixed	0.116	Bassili 2013[e]
Probability of failure (Centralised)[b]	Fixed	0.087	Bassili 2013[e]
Probability of default (Decentralised)[c]	Fixed	0.136	Bassili 2013[e]
Probability of default (Centralised)[c]	Fixed	0.142	Bassili 2013[e]
Probability of mortality (Decentralised)[d]	Fixed	0.08	Bassili 2013[e]
Probability of mortality (Centralised)[d]	Fixed	0.125	Bassili 2013[e]
Cost of treatment (Decentralised)	Fixed	1724.10	Calculated
Cost of treatment (Centralised)	Fixed	3390.56	Calculated
Utility following treatment completed or cure	Fixed	1	Assumption
Utility following treatment failure	Beta	0.68	Guo 2009
Utility following default	Beta	0.58	Salomon 2010
Utility following mortality	Fixed	0	Assumption

[a] Defined as "5 consistently negative cultures for the final 12 months of treatment".
[b] Defined as "≥2 positive sputum cultures towards the end of treatment (or a case that defaulted after 12 months of treatment with persistently positive sputum cultures) in accordance to WHO guidelines."
[c] Defined as "a patient who had interrupted treatment of ≥2 consecutive months and never returned for treatment (in line with WHO guidelines).
[d] Defined as "death from any cause (TB or non-TB) during the course of chemotherapy (in line with WHO guidelines)".
[e] Adjusted values.

$ 1724.10 for the decentralised treatment, for a patient on MDR-TB treatment in India; the potential cost savings being US $ 1666.46 (Table 4). Accordingly, in the base case analysis, decentralised treatment provided to be dominant over centralised treatment with an ICER US$ 2382.68 per QALY gained. The cost of stay in the hospital, which was significantly more intensive and thus more expensive, was one of the most important drivers of this difference. Using the WHO

Table 4 – Results of base case and univariate sensitivity analysis.

Base case analysis	Intervention	Cost per patient (US$)	Effectiveness gained	Incremental cost per incremental effectiveness unit
QALY gained	Decentralised	1724.10	0.826	Dominant (US$2382.67)
	Centralised	3390.56	0.787	Reference

Parameter varied	Variation	Intervention	Cost per patient	QALYs gained	Incremental cost per incremental QALY
Efficacy lower-range	Lower range probability	Decentralised	1666.12	0.787	Dominant (US$2543.63)
		Centralised	3310.87	0.763	Reference
Efficacy higher-range	Higher range probability	Decentralised	1774.22	0.859	Dominant (US$2261.91)
		Centralised	3467.15	0.810	Reference
Cost lower range	−50% base cost	Decentralised	740.26	0.826	Dominant (US$1051.14)
		Centralised	1478.21	0.787	Reference
Cost higher range	+50% base cost	Decentralised	2219.85	0.826	Dominant (US$3151.03)
		Centralised	4435.70	0.787	Reference
Cost	Cost (Default) = Cost(Cure)	Decentralised	1858.40	0.826	Dominant (US$2596.77)
		Centralised	3678.25	0.787	Reference
Cost	Cost (Mortality) = Cost(Cure)	Decentralised	1840.70	0.826	Dominant (US$2718.68)
		Centralised	3764.31	0.787	Reference
Loveday 2015[7]	Treatment outcomes	Decentralised	1370.50	0.637	Dominant (US$2180.96)
		Centralised	2260.74	0.532	Reference
Kabongo 2010[6]	Treatment outcomes	Decentralised	527.17	0.219	US$681.04/QALY gained
		Centralised	1241.74	0.274	Reference
Joseph 2011[35]	Treatment outcomes	Decentralised	1797.25	0.824	US$2746.84.61/QALY gained
Thomas 2007[36]		Decentralised	1523.59	0.679	US$3906.19/QALY gained
Udwadia 2014[37]		Centralised	3687.32	0.874	Reference
Sub-group analysis	Treatment outcomes	Decentralised	1720.14	0.803	US$2726/QALY gained
		Centralised	3572.78	0.807	Reference

willingness-to-pay thresholds at 2–3 times per capita GDP, decentralised care is shown to be cost-effective in comparison with centralised care for India (Table 4).

3.2. *Sensitivity analysis*

The one-way sensitivity analysis showed that the results were robust to different variations in parameters of the model (Table 4) and were highly sensitive to costs. Depending on the scenario, the estimated potential of cost savings with the decentralised model was consistently less costly and dominant when compared to the centralised model except when calculated using the treatment outcomes of Kabongo (2010),[6] studies from India and revised sub-group analysis (Table 4).[20] The Tornado Analysis showed that cost and efficacy of the care models were sensitive (Fig. 2). Using the additional meta-analysis results on studies conducted after the year 2000 and non-HIV patients, showed potential cost savings of decentralised care at US$ 1842.14, however with negative QALYs in comparison with centralised care. Fig. 3 shows the cost-effectiveness plane of the base-case and values used in the sensitivity analyses. All parameters fall in North East (NE) quadrant hence can be considered as non-dominant, i.e. these parameters where less expensive and had higher effectiveness in comparison with centralised care. Kabongo (2010),[6] Joseph (2011),[35] and Thomas (2007)[36] fall in the North West (NW), i.e. these parameters are less expensive but less effective as well when compared to centralised care.

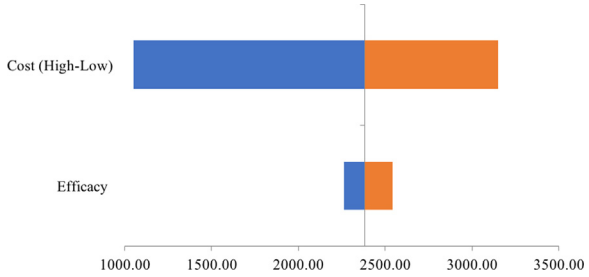

Fig. 2 – Tornado Analysis (ICER) of the one-way sensitivity analysis. The middle line denotes the Expected Value (EV) at US$2382.67.

3.3. *Scenario analysis*

If the costs and treatment probabilities are extrapolated to the whole country, with 48114 MDR-TB patients initiated on treatment in 2017,[1] decentralised care would have additional 1058 patients cured, gain additional 3824 QALYs, and avert 2165 deaths, as compared to centralised care, in India. At various scenarios of coverage rates of decentralised and

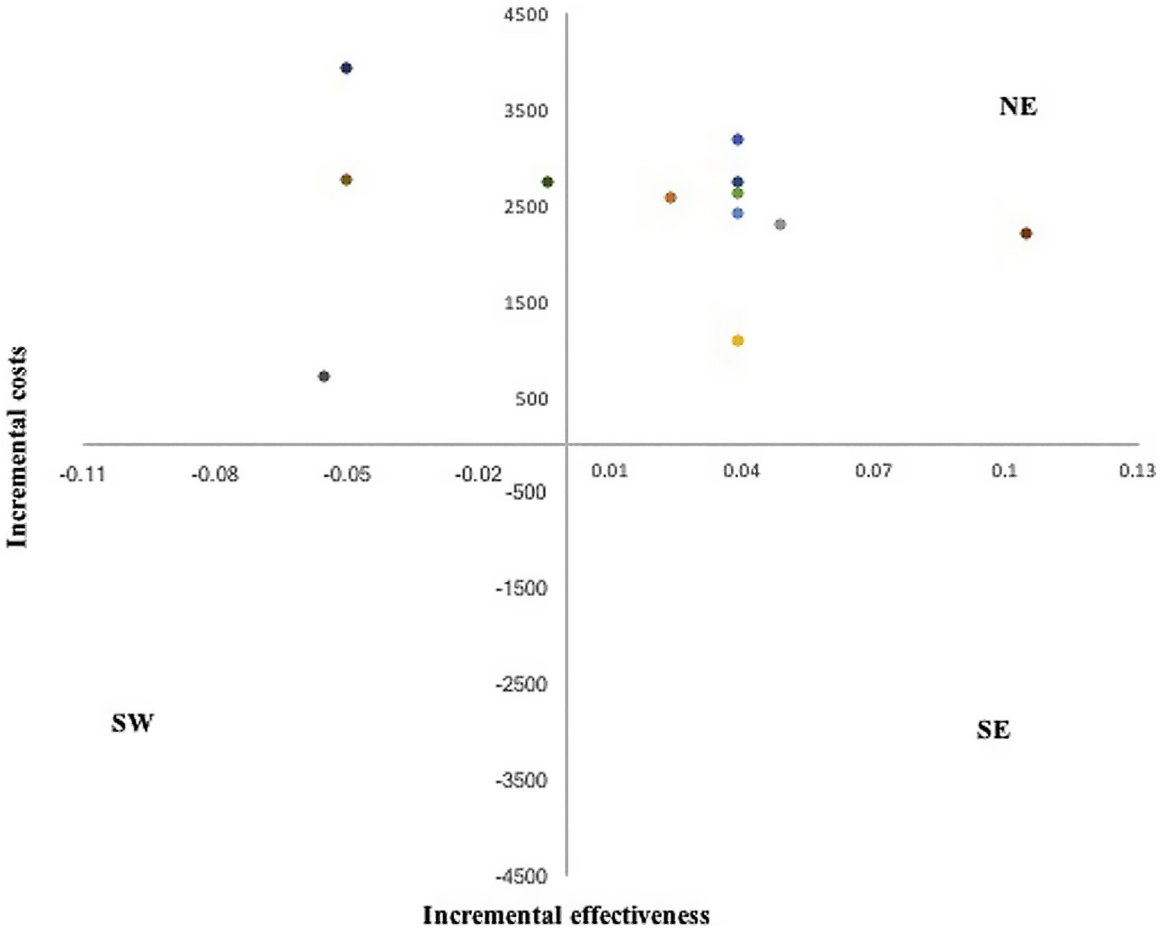

Fig. 3 – Cost-effectiveness plane showing the ICER for each parameter of base-case and sensitivity analysis.

Table 5 – Scenario analysis.

	Centralised care (US$)	Decentralised care (US$)	Cost difference (US$)	% Cost difference
Total programme cost	163,133,404	82,954,791	80,178,613	49.15
Programme cost per patient cured	105,384,179	55,413,800	49,970,379	47.42
Programme cost per death averted	20,391,675	6,636,383	13,755,292	67.46
Coverage rates (centralised:decentralised)				
90%:10%	146,820,063	8,295,479	138,524,584	94.35
80%:20%	130,506,723	16,590,958	113,915,765	87.29
70%:30%	114,193,383	24,886,437	89,306,945	78.21
60%:40%	97,880,042	33,181,916	64,698,126	66.10
50%:50%	81,566,702	41,477,395	40,089,307	49.15
40%:60%	65,253,362	49,772,874	15,480,487	23.72
30%:70%	48,940,021	58,068,354	−9,128,332	−18.65
20%:80%	32,626,681	66,363,833	−33,737,152	−103.40
10%:90%	16,313,340	74,659,312	−58,345,971	−357.66

centralised care the cost difference would range between 23% and 94% (Table 5).

4. Discussion

Decentralised care for TB, especially MDR-TB, has proven to produce similar patient outcomes as that of the centralised care model in constrained and poor-resource settings.[9] Community-based targeted intervention models, successfully implemented for patients infected with HIV, has a lot of promise and pertinent for the control of MDR-TB when combined with strategies like counselling and ongoing training and support for health workers.[27–30]

Attempts to implement decentralised care treatment models for MDR-TB has been found to be encouraging across Uzbekistan, Ethiopia and India. Among 129 MDR-TB patients in Uzbekistan, treatment outcomes were found to be similar between patients treated in decentralised and centralised groups (treatment success: 63%, decentralised care; 53%, centralised care, Cured: 46%, decentralised care; 49%, centralised care). A pilot-study done among 101 patients with MDR-TB in two government hospitals in New Delhi, had treatment success rate of 71.3%, and concluded that the low default rate of 6.9% seemed to be due to decentralised care.[5] Between 2012 and 2015, a nationally approved ambulatory service delivery model for MDR-TB treatment in two regions of Ethiopia, has seen the cumulative number of MDR-TB initiating centres and MDR-TB patients increasing from 1 to 23, and from 56 to 790 respectively, with treatment success rates of 75%.[31] Along with the feasibility of scaling-up of an ambulatory model of MDR-TB, it should be noted that these studies report higher treatment success rates than the recently reported global average of 52%.

From our decision-analytic model, which compares centralised treatment with the decentralised treatment model for MDR-TB in India, it is evident that implementation of the decentralised MDR-TB care is likely to be associated with a markedly lower cost and substantial efficiency gains. Our base-case analysis and across a range of scenario assumptions of decentralised care for MDR-TB when compared to centralised care was found to be cost-effective in India against WHO thresholds. The findings from our study are consistent with the other cost effectiveness studies reported from Nigeria and South Africa comparing these two models of care for MDR-TB.[17,32] Owing to lower economic costs, decentralised care has been recommended except in instances with strong evidence warranting hospitalisation in order to attain high levels of adherence.[33] Owing to the benefits achieved due to the improved cost-effectiveness, WHO guidelines for MDR-TB treatment, in 2011, highlights the use of ambulatory care chiefly when compared to hospitalisation-based models for treating MDR-TB cases.[34]

Stay charges in the hospital were costlier and the primary drivers of the costs incurred in centralised care in our study. Similarly, it was observed that the hospitalisation contributed to a major share in the average treatment cost incurred per patient ($17,164) in a study conducted in South Africa.[27] Such high costs of care pose a challenge to resource-limited settings. In constrained-resource contexts having similar socio-economic profile to India, the findings from our study are of particular importance and relevance.[27,29,30] Findings from this study suggest that for India, the implementation of various coverage rates of decentralised care could achieve cost differences between 23.72% and 94% in comparison with centralised care on an annual basis. Alternatively, more number of MDR-cases can be treated effectively with the same amount of resources in that year without any added cost to the national healthcare budget.

In early 2012, the Chhattisgarh State government included packages of hospitalisation services suggested under various national health programmes including RNTCP in the ''Rashtriya Swasthya Bima Yojana (RSBY)'' and ''Mukhyamantri Swasthya Bima Yojana (MSBY)''.[20] The State Tuberculosis Control Programme in Chhattisgarh, subsequently, enabled the partnership of RNTCP with RSBY and MSBY by creation of ''innovative MDR-TB packages'' under the Universal Health Insurance Scheme (UHIS) in December 2012, integrating it with various disease packages.[20] Our study provides evidence of cost efficiencies for MDR-TB patients requiring hospitalisation for decentralised care patients compared to centralised treatment with similar outcomes. These substantial cost efficiencies may improve equity and access to care particularly where patients are spending various costs on travel and other indirect services. However, covering indirect costs such as travel as part of the current government initiative in which

MDR-TB associated costs are covered under the state health insurance schemes could mitigate the hardships of low-income families.

There were some potential limitations in our study. One, our model was informed by the data on outcomes derived from a systematic review of studies outside India.[10] This systematic review focused on observational studies, and had high heterogeneity in its study characteristics. Second, the cost data has been derived from one state, i.e. Chhattisgarh, hence caution should be exercised before generalisation across the entire country.[20] Further, sourcing of data provided by government agencies was performed for loco-regional cost inputs that were unavailable in the public domain. The model assumes that for the outcome parameters, i.e. QALYs and DALYs, the patients who achieved treatment success did not experience any lasting disutility (in terms of quality of life) or disability (in terms of DALYs). In the sensitivity analysis, negative QALYs were found when we compared the three studies from India.[35–37] However, the sample sizes across these studies were quite low.

In the wake of continuing challenges to increase the number of patients initiating and additionally, adhering to the MDR-TB treatment regimen, the burden will continue to persist in near future. A recent modelling study has shown that if the current practices of managing MDR-TB in the country continue, the incidence of MDR-TB could increase substantially over the next 25 years.[38] In this context, and given the objective of scaling-up of the number of patients in need of MDR-TB therapy, the strategy of switching over to the decentralised care model can be considered to be appropriate for India. The aim of economic evaluations in general, and our cost-effectiveness analysis in particular, is to optimise healthcare delivery.

5. Conclusion

In India, the decentralised MDR-TB treatment model, in comparison to the centralised MDR-TB treatment model, is expected to result in similar treatment outcomes at strikingly lower public health costs. Considering the recommendations made by the WHO, and an urgent need to improve treatment initiation and adherence rate, decision-makers are thus urged to consider the implementation of the decentralised MDR-TB care model where feasible.

Conflicts of interest

The authors have none to declare.

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Original article

Active case finding of rifampicin sensitive and resistant TB among household contacts of drug resistant TB patients in Andhra Pradesh and Telangana states of India – A systematic screening intervention

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Background: India has the world's highest estimated burden of multi-drug-resistant tuberculosis (MDR-TB). While prevalence of MDR-TB is known to be 2–3% among new TB patients and 12–17% in previously treated patients, programmatic information on the extent of transmission of TB and MDR-TB among household contacts of known MDR-TB patients is scarce. Systematic screening of household contacts of all MDR-TB patients on treatment was implemented as an intervention in the states of Andhra Pradesh and Telangana states of India. We undertook this prospective interventional study to measure the extent of TB symptoms developed among the household contacts of the known MDR-TB patients treated under Revised National TB Control Programme (RNTCP). The extent of rifampicin sensitive or resistance TB, bacteriologically confirmed using Xpert MTB-RIF, was examined among the symptomatic household contacts.

Methods: All MDR-TB patients registered and on treatment under RNTCP between July 2011 and Sep 2013 in Andhra Pradesh and Telangana States were selected for the study. They were contacted through home visit by the trained RNTCP teams during 11th Dec 2013 and 7th Jan 2014. All household contacts of MDR-TB patients were screened once for TB symptoms such as cough, fever, weight loss, night sweats, and haemoptysis and extra pulmonary site specific symptoms if any. If found symptomatic, two sputum specimen were collected (spot-morning) from each of the contact and transported for testing on Xpert MTB-RIF for detection of pulmonary TB with or without RR-TB.

Results: A total of 1750 MDR-TB patients were registered between July 2011 and Sep 2013. Of these, 1602 (91.5%) MDR-TB patients were included in the study. A total of 4858 household contacts of these 1602 patients were identified with an average of 3 contacts per MDR-TB patient. Of these, after excluding 87 (1.8%) contacts with past history of diagnosis and/or

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treatment for TB, 4771 (98.2%) contacts were screened for current signs and symptoms suggestive of TB. Their mean age was 28.5 years and 2151 (45%) were females.

Of the 4771 contacts screened, 793 (16.6%) had at least one of the symptoms suggestive of TB of whom 781 (98.5%) had two sputum specimen transported and tested on Xpert MTB-Rif. Specimen could not be collected during the study period in 12 symptomatic patients including 4 with symptoms of extra pulmonary TB. Among 781 symptomatic contacts examined, 34 (4.4%) were bacteriologically confirmed with TB and 15 (44%) also had Rif resistance (RR).

Conclusions: High extent of TB, particularly RR-TB was observed among household contacts of known MDR-TB patients with symptom screening and early diagnosis using Xpert-MTB-Rif. Regular systematic active screening for TB and MDR-TB among this highly vulnerable group using Xpert-MTB-Rif is useful in India for early diagnosis among close contacts of known MDR-TB patients.

1. Introduction

Tuberculosis (TB) is caused by infection with *Mycobacterium tuberculosis*, which spreads from person to person through inhalation of droplets nuclei containing the bacteria. TB is one of the leading causes of morbidity, mortality and financial catastrophe in the world. Globally, 10.4 million incident TB patients and 580,000 incident MDR-TB patients (including rifampicin-resistant TB) are estimated to have emerged in 2015. Similarly 2.84 million incident TB patients and 130,000 incident MDR/RR-TB patients are estimated to have emerged in India.[1] India, China and the Russian Federation accounted for 45% of these patients.[1]

Delayed diagnosis, treatment initiation and lack of adherence to treatment further results in increased transmission of infection, increases the incidence rates of the disease and in turn increase the cost of TB control programme implementation.[2–5] Home visits and counselling of patients at regular intervals are good opportunities to remind the patients about modes of transmission of TB, the care to be taken while at homes or work places to prevent transmission to household contacts as well as active case finding to enable early diagnosis and prompt initiation of treatment reducing transmission opportunities.

Under India's Revised National Tuberculosis Control Programme (RNTCP), sputum smear microscopy has been the main method of TB diagnosis and culture and phenotypic drug susceptibility testing (DST) for diagnosis of MDR-TB. Over the recent years the WHO endorsed rapid diagnostics (WRD) such as Xpert MTB-Rif and LPA (Line Probe Assay)[6,7] are being utilized as primary methods for diagnosing drug resistant TB among presumptive MDR-TB patients. Xpert MTB-Rif is also used as a diagnostic tool among presumptive TB patients in key populations like people living with HIV (PLHIV), children, extra-pulmonary and smear negative patients with chest X-Ray suggestive of TB to enhance TB case finding through systematic active screening programmes.[8]

Active Case Finding (ACF) or Intensified Case Finding (ICF) activities are some of the methods followed in TB control programmes for detecting the TB patients early among the household contacts of known TB patients. These activities include patients' home visits made by the health care providers, educating the family about the disease, the services available as well as symptom screening and testing of household contacts to detect TB. As part of PMDT (Programmatic Management of Drug Resistant TB) services under RNTCP, a symptomatic contact of a known MDR-TB patient is considered as a presumptive patient for MDR-TB. Thus the programme recommends testing of presumptive MDR-TB patients with the available C&DST (Culture and Drug Sensitivity Testing) facilities, preferably a WHO endorsed rapid molecular test like Xpert MTB-Rif or LPA and provide treatment with the regimen as per the RNTCP PMDT guidelines.[9]

Some studies tried to estimate the incidence of secondary cases of tuberculosis among contacts of patients with MDR-TB and among the contacts of patients with drug-susceptible tuberculosis (DS-TB). Studies that have measured the incidence of secondary cases in households with MDR-TB have lacked statistical power[10] or have not included drug-susceptible controls for comparison.[11]

While prevalence of MDR-TB is known to be 2–3% among new TB patients and 12–17% in previously treated patients, programmatic information on the extent of transmission of TB/MDR-TB among contacts of known MDR-TB patients is scarce. Systematic screening of household contacts of all MDR-TB patients on treatment was implemented intensively through active case finding approach as an intervention in the states of Andhra Pradesh and Telangana states of India. We undertook this study to measure the extent of TB symptoms developed among the household contact of the known MDR-TB patients treated under RNTCP and examine the symptomatic patients to measure the extent of Rifampicin sensitive TB (RS-TB) or Rifampicin resistance TB (RR-TB) among them, bacteriologically confirmed using Xpert MTB-Rif.

2. Methods

This prospective interventional study was conducted in Andhra Pradesh and Telangana states of India simultaneously

during the period between 11th Dec 2013 and 7th Jan 2014 when the systematic screening was implemented. Andhra Pradesh and Telangana states are in southern part of India with a population of nearly 8.65 crores. These states have well established general health system and a well-structured RNTCP programme with nearly 1000 designated microscopy centres (DMCs) and 10 Drug Resistant TB (DR-TB) treatment centres. Approximately 1 lakh TB patients were diagnosed per year in this region and more than 89% treatment success rate was achieved among the new smear positive pulmonary TB patients. MDR-TB diagnosis started in December 2008 in the states and annually approximately 85% of the >3000 diagnosed patients were initiated on treatment at 10 DR-TB centres. All MDR-TB patients registered for treatment in RNTCP from 1st July 2011 to 30th September 2013 who were on active care at the time of the intervention were line listed from all districts. All household contacts of such MDR-TB patients on active care were identified and included in the study.

MDR-TB patients whose treatment outcomes were already declared by the programme officially were excluded. Thus, household contacts of only the patients who were currently on treatment or who have not interrupted more than 2 months were considered for the study.

As part of the systematic screening intervention, home visits were made to the households of every MDR-TB patient selected for the study by RNTCP programme staff across the two states. Information of all the household contacts was collected with the specially designed pre-piloted and pre-structured questionnaire. Detailed history was taken for each of the household contact met to elicit the signs and symptoms of TB, past history of TB screening, diagnosis and treatment if any.

Contacts with past history of diagnosis and treatment of TB were excluded from the study analysis. Symptom screening for TB was performed to all the remaining contacts of the index MDR-TB cases and the symptoms noted. The symptoms elicited were current cough, current fever, night sweats, haemoptysis and significant weight loss. In case of paediatric contacts, 'child not gaining weight' was considered in place of 'significant weight loss'. Information on duration of any existing symptom was also collected. In addition, symptoms related to extra pulmonary TB and HIV testing and result status were also explored.

If any one of the symptoms screened for was present in any contact, the contact was denoted eligible for being subjected to diagnosis through Xpert MTB-Rif. Two sputum specimen (at least one specimen preferably an early morning specimen where two specimen collection was not possible) were collected from all the eligible contacts and transported through courier in properly packed cold chain containers to the Xpert MTB-Rif facility. The results of the test were transmitted via e-mail to respective District TB Control Officers (DTCO) of the two states. The contacts with confirmed RS-TB or RR-TB were traced back to provide necessary treatment based on the results of the testing.

Before actual field level implementation of the data collection tools, an orientation training of DTCOs was conducted. This was followed by orientation training of DR-TB supervisors of RNTCP who are programme staff primarily responsible for monitoring the drug resistant TB patients in the respective districts before the systematic screening intervention was initiated.

Specimen collection, transportation and documentation were as per the National PMDT Guidelines and in line with the established programme at the time of study. All the specimen were transported to the C&DST lab equipped with Xpert MTB-Rif facility under cold chain and with triple layer packing so as to reach the destination within 72 h from the time of specimen collection.

Local administrative approvals were also taken to conduct the study. No informed consent was required as the intervention offers minimal risk to the participants, and protocol activities were considered part of routine programmatic functions of TB treatment and care.

Data entry was done initially at the C&DST lab equipped with Xpert MTB-Rif by the data entry operators. Once the hard copies of the data collection formats were received by the investigators double entry was done. After data validation, data discrepancies were resolved by referring to the hard copies. IBM SPSS Statistics v 21.0 was used to analyze the data. Simple frequencies and percentages described the number and proportion of household contacts identified, screened, evaluated, bacteriologically confirmed as TB and Rifampicin resistant (RR-TB).

3. Results

Of the 1602 MDR-TB patients who were visited at their homes, 36 (2.24%) did not have any contact at home. There were 490 (30.6%) female and 1112 (69.4%) male Index TB cases whose homes were visited. Mean age of index cases was 36.82 years with median 35 and mode 45 years, range of 2–75 years. A total of 4858 household contacts were identified and interviewed among the house holds of 1602 Index MDR-TB cases. The mean number of contacts per index case was 3 as was also the median (range 0–23).

More than 95% of the index MDR-TB cases knew their HIV status and approximately 5% of them were positive for HIV.

Of the 4858 household contacts interviewed for past history of symptoms of TB, diagnosis of or treatment for TB, 733 (15%) contacts informed that the screening of symptoms for TB was done by the health visitors in the past and 387 (8%) contacts informed that they were subjected to TB diagnosis in the past of which 79 (20.5%) were diagnosed with drug sensitive TB of which 8 (2%) were also diagnosed with MDR-TB (Fig. 1). After excluding the contacts with known diagnosis of drug sensitive or MDR-TB (79 and 8), a total of 4771 contacts were considered as eligible for eliciting current symptoms and signs for tuberculosis and thus interviewed as part of the intervention.

Of the 4771 contacts screened, 793 (16.6%) contacts had one or more symptoms of TB as shown in Fig. 1. Among the symptomatic contacts, 75% (n = 594) had cough as one of the symptoms, 35% (n = 275) had fever, 8% (n = 60) had weight loss, 4.2% (n = 33) night sweats and 1.5% (n = 12) haemoptysis. Four (0.5%) of them had symptoms related to extra pulmonary site for TB as shown in Fig. 2. Of the 793, sputum specimen of 781 (98.5%) symptomatic contacts could be sent to the Xpert MTB-Rif laboratory and tested further. Specimen could not be

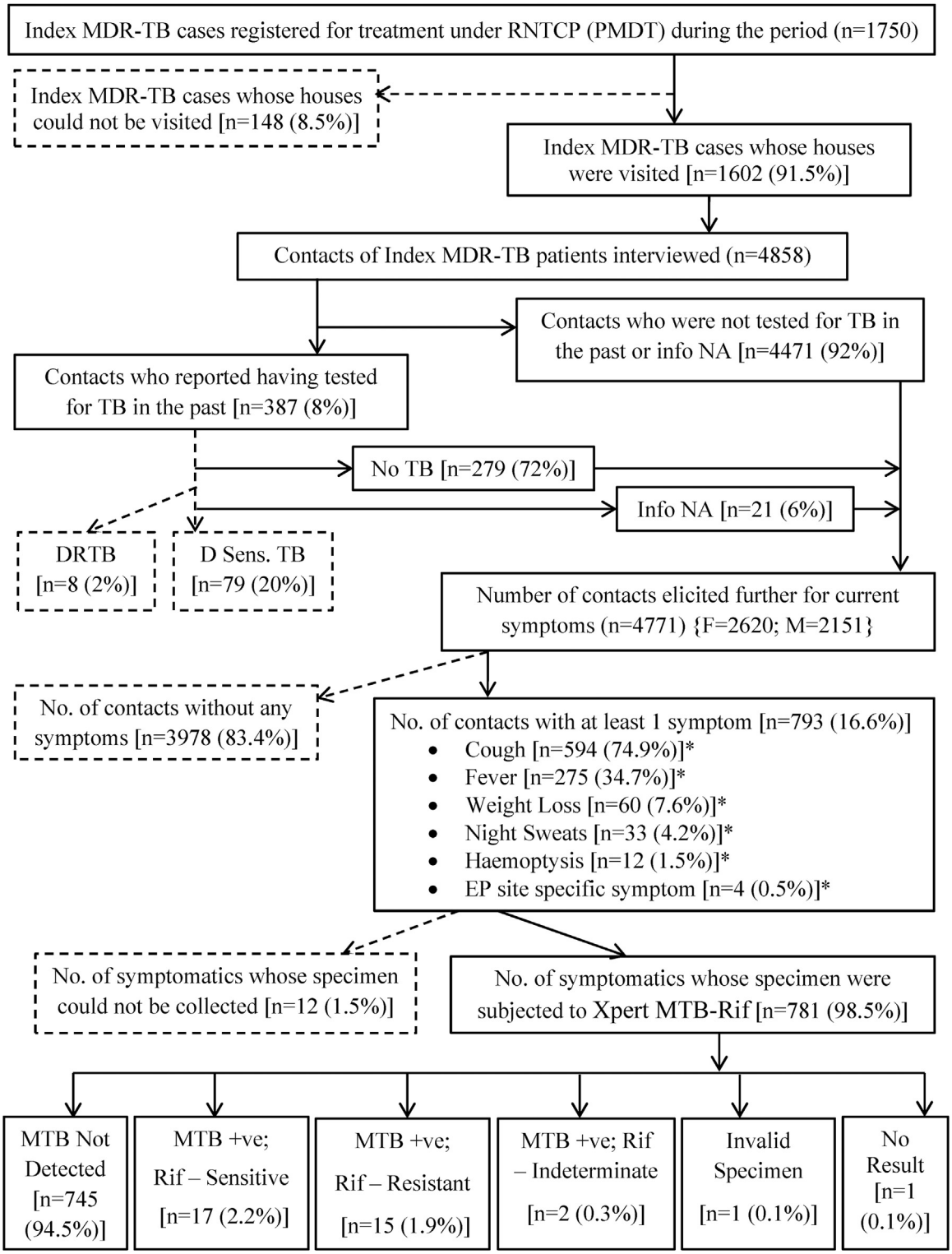

Fig. 1 – Flow diagram depicting the results of systematic screening of household contacts. * Not mutually exclusive. Dotted boxes indicate subjects censored from the analysis.

collected for 12 (1.5%) patients due to non-availability of the contacts later on.

The mean age of the contacts screened for current symptoms of TB was 28.46 years (SD 18.23 years), median age of 25 years and ranging from 1 month child to 95 years old person. There were 45% (n = 2151) females and 55% (n = 2620) males in the contacts screened for current symptoms (Fig. 2).

Of the 781 symptomatic contacts whose sputum specimen were subjected to Xpert MTB-Rif, 34 (4.4%) were positive for TB of which 17 (50%) were rifampicin sensitive TB, 15 (44%) were

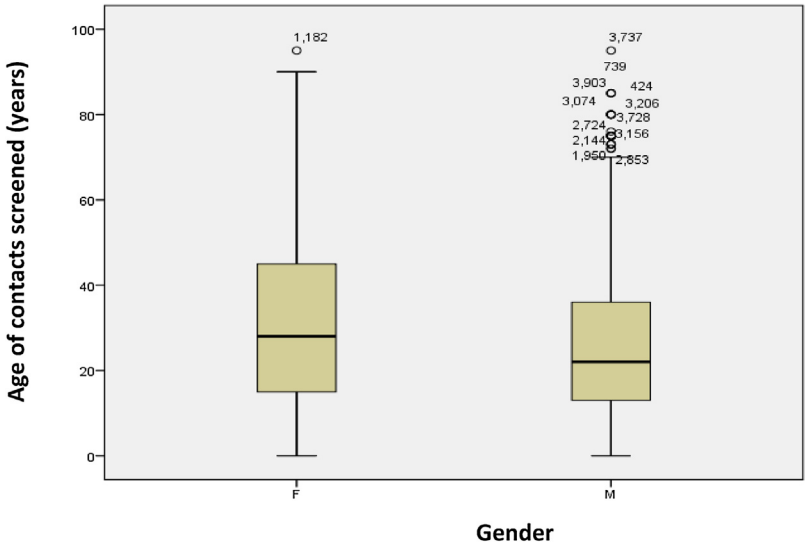

Fig. 2 – Gender wise age distribution of contacts screened for current TB symptoms.

RR-TB and 2 (6%) were indeterminate for rifampicin resistance. The diagnosed patients were provided with appropriate treatment as per RNTCP guidelines.

4. Discussion

Tuberculosis (TB) being an airborne disease, the household contacts of a TB patient are more vulnerable for acquiring the infection compared to general population. RNTCP emphasises on periodic visits by the health workers in the programme to the home of TB patient and trace contacts of known TB patients with signs and symptoms of TB as part of the treatment support services and counselling. PMDT guidelines of RNTCP also urge all the health workers in the field to visit the homes of TB patients on treatment and document the observations on progress in treatment, screen the contacts for signs and symptoms of TB and provide prophylactic isoniazid as needed. However; based on the feedback from various review meetings or supervisory visits by state or national level officials or based on the performance indicators of the programme, it is felt that there is lot of scope for improving the regular home visits and screening of the contacts towards early diagnosis and comprehensive adherence to the PMDT guidelines. The need for strengthening the home based care and demonstration of linking the symptomatic contacts to the rapid diagnostic facilities such as Xpert MTB-Rif was becoming more evident from the review of performance. Our study revealed that the system of screening household contacts was poorly established in the two states with only 15% contacts revealed that they were screened by the health visitors in the past of whom only half were subjected to TB diagnostic test. Thus the study made an impact in the field workers of RNTCP of the two states in strengthening their understanding in contact screening and linkages to early diagnosis thus paving way for reduction in transmission of TB among the contacts of DR-TB patients on treatment.

There were nearly 3 household contacts per Index MDR-TB case. On an average every sixth contact (16.6%) of known MDR-TB patient had one or more symptoms of TB. Upon further investigation, there was one TB patient among 140 household contacts (34 in 4771) and one Rifampicin resistant patient among 318 household contacts (15 in 4771) which amounts to 1.9% (15 in 781) among those subjected to Xpert MTB-Rif.

Early identification of symptomatic household contacts of known TB/RR-TB cases, rapid accurate diagnosis and prompt treatment of confirmed TB/RR-TB patients is the key for effective prevention of transmission of TB. Hence, having a diagnostic tool with high sensitivity and specificity is all the more important in these efforts. World Health Organization (WHO) in its 2013 policy statement, recommends using Xpert MTB-Rif for the diagnosis of pulmonary TB and Rifampicin Resistance in adults and children and for the diagnosis of Extra Pulmonary TB and Rifampicin resistance in adults and children.[12,13] In our study, all the specimen were processed through Xpert MTB-Rif according to the guidelines of WHO and RNTCP.

The intervention study also facilitated the programme by providing first hand learning by the field staff that the early detection of more MDR-TB patients can be made possible by stringent implementation of the contact tracing for TB symptoms among the known MDR-TB patients under treatment in RNTCP. The staff could see the advantages and the simplicity of contact tracing during the exercise which resulted in sustained incremental contact screening and yielded early diagnosis of more MDRTB patients which might have been diagnosed late if not for the contact screening by field worker.

Finally, the observation that systematic screening of TB among household contacts of known MDR-TB patients yielded 5% bacteriologically confirmed TB with 50% probability of transmission directly of rifampicin resistant TB is alarming. This emphasizes the need for integrating such systematic screening programmes into the general health system as a periodic phenomenon. The ANMs (auxillary nurse midwives)/ MPWs (multi-purpose worker) or ASHA (Accredited Social

Health Activist) from the general health system visit all households in the community periodically to deliver services under public health programmes like RCH (Reproductive and Child Health)/Malaria screening etc. Opportunities exist here to tag the household contact screening activity with these home visits. These primary health care staff could be trained in administering the pre-structured questionnaire and in specimen collection and transportation from every DMC in the state.

4.1. *Limitations*

Since the time taken for implementation was less than a month, not all potential Index MDR TB Cases could be visited with in the short period and some of the contacts were missed from the interview process due to non-availability during home visits. The intervention was limited to less than a month, however; the appearance of signs and symptoms of TB or activation of latent TB can happen anytime ranging from months to years in a household contact of known TB/MDR-TB patient if the transmission of infection occurred. Thus this small window of study period could have detected lesser than all such potential TB patients among the contacts. Thus continuous surveillance on TB symptoms among the contacts of known MDR-TB patients is needed to identify all potential secondary TB cases. Due to short time period of study, we could not gather information on duration of each contact with the index MDR-TB patient.

Eliciting history from the household members is subjective and depends on the skill of the health staff; observational errors may have occurred in patients where the history was not elicited directly from the contact. Considering the emphasis on contact screening for symptoms and no additional funding was involved, chest X-ray was not included as a screening tool in the study. This was an opportunity to augment the yield of TB/RR-TB patients through the active case finding intervention. Another limitation could be the quality and type of specimen that were collected and transported for testing to the Xpert MTB/RIF Facility. Only pulmonary specimen were tested with emphasis on good quality. Specimen especially in case of children e.g. bronchial wash or gastric lavage etc., if collected, could have improved the detection of TB patients. Also, since genotyping of TB bacilli infecting the contacts is not done, it is not possible to ascertain whether the index case is indeed the source of infection. Since, ours is an interventional study within the guidelines of RNTCP programme, we did not achieve a sample size to have good statistical power.

5. Conclusions

Active case finding efforts among the house hold contacts of known MDR-TB patients yielded equal proportion of rifampicin sensitive and rifampicin resistant TB patients in the two states. All of them might have gone undetected for longer periods without this active systematic screening intervention. Hence, it is clearly understood that active case finding among contacts of all known MDR-TB patients is very much essential to enable early detection and early initiation of appropriate treatment for TB or MDR-TB in order to cut the chain of transmission. Meticulous implementation and monitoring of systematic active case finding among household contacts through screening programmes periodically as per the existing national guidelines utilizing the huge work force present in both public such as ANMs/ASHAs/MPWs etc. and private sectors in the country is possible and a necessary intervention to achieve long term goals of ending TB in India.

Disclaimer

The findings and conclusions in this paper are those of the authors and do not necessarily reflect the official position of the Revised National Tuberculosis Control Program or the World Health Organization.

Conflicts of interest

The authors have none to declare.

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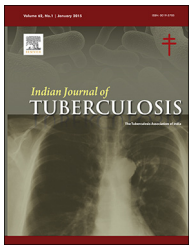

Original Article

Tuberculosis at Raffic Hariri University Hospital (RHUH) during 10 years period 2005–2015, cross sectional, observational study

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ABSTRACT

Aim: Tuberculosis is a contagious disease caused by *Mycobacterium tuberculosis*. It represents, according to WHO, one of the most leading causes of death worldwide.[1]

Background: Based on our regional conditions, such as Syrian immigration, poor nutritional status, are contributors for the development of the disease.

Methods: This was a retrospective analytical cross sectional study done to review all cases of tuberculosis newly diagnosed at RHUH during 10 years period (2005–2015). 128 TB labeled patients were retrieved. A standardized checklist was used to collect data. Patients were then classified as TB diseased and TB infected.

Results: The total number of TB suspected patients was 128 over 10 years which represents 1.77% of all patients admitted to the medical floor. Among these, the total number of PPD positive patients was 40.6% from our study population (2005–2015), 48% were TB infected and 52% had positive CXR. Among those with positive CXR, 41% were confirmed TB disease and 59% not confirmed TB disease. There was significant variation in evolution through years (2005–2015). By comparing the socio-demographic findings between TB disease, TB infection and non-TB group no statistical significance was found. Same analysis were repeated between TB infection and TB disease groups showed one significant association between age and TB disease vs. TB infection ($p = 0.034$), where the younger population belongs to TB infected group (42%), while 50% of TB diseased group were older. As for scoring severity index, ANOVA in the three groups showed a significant association with a p value of 0.046. The TB diseased patients have the highest severity score index.

Conclusion: TB disease is still present in Lebanon with fluctuating level with the highest peak found in 2013 explained by the influx of Syrian refugee population. Followed by a gradual drop in the following years. The younger population belongs to TB infected group, while TB disease patients had the most severe clinical course compared to TB infected and non TB patients.

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1. Introduction

Tuberculosis is a contagious disease caused by *Mycobacterium tuberculosis*. It represents, according to WHO, one of the most leading causes of death worldwide, with nearly 8 million new cases each year, tuberculosis is still a public health problem. Despite the decrease in incidence, morbidity and mortality remain important partially due to co-infection with HIV and emergence of resistant bacilli.[1]

The epidemiology of tuberculosis varies across the world. More than 5.8 million new cases of TB (all forms, both pulmonary and extra pulmonary) were reported to the WHO in 2009; 95% of cases were reported from developing countries. The WHO estimated that 9.4 million (range, 8.9–9.9 million) new cases of TB occurred worldwide in 2009, 95% of them in developing countries of Asia (5.2 million), Africa (2.8 million), the Middle East (0.7 million), and Latin America (0.3 million).[2]

The rate of TB is higher among men than women, beginning in the young adult years and persisting throughout life.[3] In the developing world, TB rates are highest among young adults, reflecting primary transmission in this age group. In the United States and other developed countries, the rate of TB among older adults is higher than among younger adults and children, reflecting reactivation disease, possibly attributable to impaired immunity with aging.[4] TB has traditionally been associated with low socioeconomic status, which also may be associated with crowding, poor nutrition, and poor access to medical care, public assistance, unemployment and low education.[5]

Based on our regional conditions, factors such as Syrian immigration, population inflation, poor nutritional status, poverty, smoking, lack of awareness and poor access to health facilities are substantial contributors for the development of the disease. In this context, study is conducted to assess the epidemiological burden of tuberculosis between 2005 and 2015 in order to plan control and prevention strategies.

The primary objective is to determine the incidence rate of TB cases diagnosed at RHUH during 10 years period (2005–2015) as well as the annual rate of percent change in tuberculosis incidence during this 10 years period.

The secondary objective consists of assessing the risk factors or change of incidence rate according to socio demographic data (age, gender, nationality) socio-economic status (educational status, occupational status) and evaluating the prognosis (access by phone number the ''living status'' of the patients, still alive or not).

2. Methodology

Our study is a cross sectional observational study, which recruited all TB suspected patients during 10 years period 2005–2015, at ''Raffic Hariri University Hospital (RHUH)''.

Our target population included all patients labeled as having suspected TB according to the medical diagnosis on admission. The total number of these patients was 128 over 10 years.

The inclusion criteria include all patients diagnosed as having suspected tuberculosis during their hospital stay at RHUH during 10 years period 2005–2015 while the exclusion criteria was patients already diagnosed as having tuberculosis outside RHUH and admitted for other causes. The study population was further classified as TB diseased patient, TB infected patients and non TB patients based on their history, physical exam and a set of tests that allows us to classify them as such.

All information were retrieved from the patients charts based on a standardized check list which included[6,7]:

Socio demographic variables: Age, gender, marital status, educational status, occupational status, geographical location, nationality.
Life style factors: Smoking status and alcohol status.

Comorbidities: old TB, HTN, diabetes, COPD, CAD, HIV, etc.
Tuberculosis information: Symptoms like cough, fever, sputum, weight loss, and diagnostic method like PPD, Sputum analysis, Bronchoscopy analysis, chest X-ray, pleural tap, lymph node biopsy, peritoneal tap, lumbar puncture, open surgical biopsy.

The data was collected over a one week period. All available information mentioned in the check list was collected.

The data analysis was divided into two main chapters:

- Descriptive results:

The analysis of different questions was conducted by calculating the frequency and percentage of each answer in relation to the total for each question. These information included general points mentioned in the check list listed above. Data analysis was done using SPSS 20 and Excel 2013.

- Analytical results:

The study population was divided into 3 groups: TB disease, TB infection and non TB. All the data collected in the descriptive part was resumed in a table including the percentage of each criteria in each group. Cross table Test for testing association between qualitative variables: Chi-square for $n > 30$: age, gender and geographical location, and Fisher for $n < 30$: marital status, educational status and occupational status. Finally, ANOVA for testing statistically significant differences between quantitative variables and qualitative variables (score severity).

2.1. Score severity index

The score severity index included all the following signs and symptoms (Table 1):

According to the presence of these symptoms and radiological signs we calculated a score severity index for each patient. A coefficient was assigned for each variable based on its contribution to the severity of the TB disease. The total score was equal to 26. Patients were classified as having mild score severity index if they scored less than 4, moderate if the score was 4 or 8 and severe if they score more than 8.

Table 1 – Score severity index.

Symptoms	Score
Lymphadenopathy	2
Appetite or weight loss	2
Hemoptysis	2
Confusion/DLOC	2
Fever	1
Headache	1
Sweat	1
Vomiting	1
Cough	1
Sputum	1
Pain	1
Dyspnea	1
Radiological signs	**Score**
Miliary	3
Cavity	2
Consolidation	1
Effusion	1
Hiliary mass	1
Nodularity	1
Infiltrates	1

3. Results

3.1. *Descriptive results*

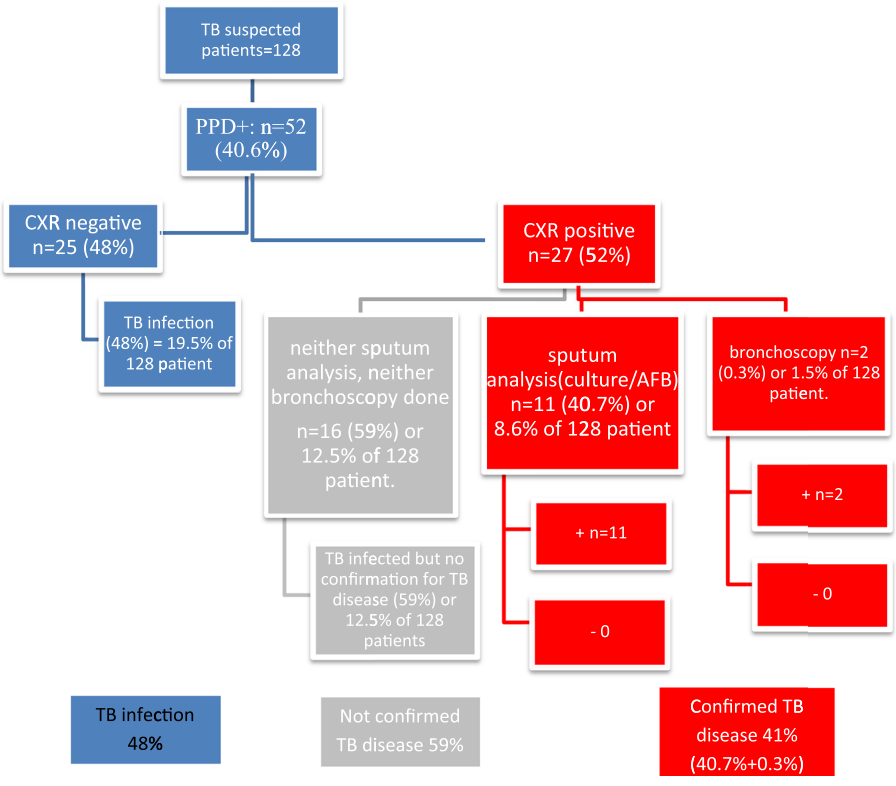
The total number of "TB suspected patients" according to patient files was 128 (from 2005 to 2015). More than half of these patients were men, almost 2/3 were married and almost half were are aged more than 25 years. The majority, as 43%, reported an educational level less than grade 8, while a quarter (25%) were illiterate, and only a minority reported a high grade education. The majority (57%) were unemployed and 75% living in urban areas and 90% were Lebanese. According to the patient files, the majority were nonsmoker (59%) and non-alcoholic (94%). From 128 patients, 20% had old TB, 15% HTN, and 14% diabetes. Among our population, the most common comorbidity was an old TB (20%).

Most of the TB suspected patients presented with cough (76%), fever (63%), while 49% reported having sputum production, 39% reported weight loss and dyspnea, and 30% reported hemoptysis. The majority of our suspected TB patients were PPD positive (43%), while 1/3 (34%) did not have mentioned PPD in their corresponding files.

The majority of our study population, as 54%, did not report neither sputum culture for TB nor AFB in the corresponding patient files. Among the reported one, the minority as 5.4% and 7% was either sputum culture positive for TB or positive AFB respectively. The majority of our study population, as 60%, did not undergo a bronchoscopy for sputum culture or AFB. While among those who had bronchoscopy, a minority as 7–8% was positive for either culture of AFB respectively.

A minority as 10 patients did not have a reported chest X-ray in their files. Among those who had it (n = 118) the majority as 34% of these patients presented with infiltrates, followed by cavities in 19%, consolidations in 18%, and pleural effusion in 16%. Moreover, among those patients (n = 118), the majority as 40% had only one radiological sign on chest X-ray, while a minority as 7% had more than 2 signs. We have to notice that a third (31%) had a normal chest X-ray.

According to the previous information mentioned above, the following algorithm assigns a different TB status based on the results of the clinical tests performed on our study population during their hospital stay.



3.1.1. TB status

In conclusion, 19.5% of 128 patients were *TB infected*, 10.1% of 128 patients were *confirmed TB disease* and 12.5% of 128 patients were *non-confirmed TB disease*.

3.2. Analytical results

More than half of our study population with suspected TB (57%) were classified as having moderate score severity index.

3.2.1. Comparison of sociodemographic and TB data between TB infection, TB disease, and non TB patients

Summary of the distribution of the socio demographic variables, life style factors, comorbidities, symptoms, radiological signs and score severity in the three groups (TB infection, TB disease and non TB):

The majority of **TB infected** patients were women (60%)*aged less than 25* (40%) having and education *less than grade 8* (56%) and *unemployed* (64%). However, in **TB diseased** patients, the majority were *men* (67%), *older* aged more than 50 (47%), *more educated* between grades 8–12 (41%) and *employed* (52%). In the non TB group, 41% were between 25 and 50 years old, 55% men, 42% less than grade 8 and the majority as of 68.5% unemployed. In the three groups, the majority were married, Lebanese, living in rural areas, non-alcoholic and non-smoker, except for **TB disease** where 52% of this group population were *smoker*. As for the comorbidities, *old TB* was the **predominant** one in the three groups. **Most** of the patients, presented with *cough* in the three groups. As well, on the chest X-ray, the most common sign was *infiltrates* with 38% in non-TB, followed by 37% in **TB disease** and as expected 8% in TB infection. Finally, the score severity, had almost a normal distribution, with the majority of patients in **TB disease** and non TB group falling in the *moderate* category while in **TB infection** equal distribution of patients was seen in *mild* as well as *moderate* score severity.

3.2.2. Association between socio demographic data and 3 TB status (TB infection, TB disease and non TB)

In **TB infection** group, the majority were aged *less than 25 years* while in **TB disease** the majority were *more than 50 years old*. The remaining non TB were between 25 and 50 years old. However no significant association was found, between the three groups according to Chi square test with a p value of 0.102. The majority were woman in **TB infection** group, while in **TB disease** group the majority was men, as well as for **non TB group**. However, no significant association was found according to Chi square test with p value of 0.187. In the **three groups**, TB infection, TB disease and non TB the majority were *married* with 53.8%, 70.8% and 63.2% respectively. Consequently, no association was found between the three groups according to Fisher exact test. The majority of the *employed* population belongs to **TB diseased** patients as of 46.2%, while the majority among **TB infected** patient 64% were *unemployed*. However, no significant association was found between the three groups according to Fisher exact test. The majority of *illiterate* belongs to **TB disease** group as of 29.2%, while *less than grade 8* were **TB infected** in 57.5%. Finally, the majority of **TB diseased** were *between grades 8 and 12*. However, no significant association was found between the three groups according to Fisher exact test. No ANOVA test was done for differences in comorbidities, since one comorbidity was equal between the three groups with Old TB being the predominant one. The **TB diseased** patients have the highest severity score index followed by **non TB** than **TB infection**. The difference was statistically significant according to ANOVA test.

Table 2 – Association between TB infection and TB disease group.

	TB infection	TB disease	p value
Severity score[b]			
Mild	46.2	15.4	0.010*
Moderate	50	69.2	
Severe	3.8	15.4	
Age[a]			
<25 years	42.3	23.1	0.034*
25–50 years	34.6	26.9	
>50 years	23.1	50	
Gender[a]			
Male	42.3	65.4	0.082
Female	57.7	34.6	
Marital status[b]			
Single	46.2	29.2	0.173
Married	53.8	70.8	
Education status[b]			
Illiterate	19.2	29.2	0.436
<Grade 8	57.7	37.5	
Grades 8–12	23.1	33.3	
Occupational status[b]			
Employed	36	46.2	0.326
Unemployed	64	53.8	

The qualitative variables are expressed as percentages and the quantitative variables as mean ± standard deviation.
* Significant difference between the two groups with a value of $p < 0.05$.
Chi square test was used:
[a] Pearson chi square.
[b] Fisher exact test.

3.2.3. Association between socio demographic and 2 TB status (TB infection and TB disease)

Since no significant association was found between the sociodemographic data and the three TB groups, the same analysis was repeated between these data and 2 TB groups, TB infection and TB disease groups only. The results are shown in Table 2.

4. Discussion

4.1. Descriptive results

The total number of TB suspected patients was 128 patients over 10 years at RHUH. Accordingly, 1.77% of all patients admitted to the medical floors from 2005 to 2015 were labeled as TB suspected by the admitting physician.

The majority of **TB infected** patients were *women* (60%), while **TB diseased** patients were *men* (67%), almost half of **TB infected** patients were aged *less than* 25 while the majority of **TB diseased** patients were *older than* 50. Almost 2/3 were *married* in the three group. For the educational status, **TB infected** patients were more predominant in *less than grade*

8 group (56%) while 41% of **TB diseased** population were *between grade 8 and 12*. Furthermore, the majority 64% of **TB infected** patients were *unemployed* and 52% of **TB diseased** patients were *employed*. The majority of **TB diseased** and **TB infected** group were living in *urban areas* (76% and 81% respectively), were Lebanese representing 96% and 85% in TB infection and TB disease patient respectively.

These findings could be explained by several factors:

- TB rates (infection and disease) are highest among young adults in developing country reflecting primary transmission.[8] In addition TB rate is higher among men in a study done in Poland 2013 showing that the incidence among men (26.8) was more than two times higher than among women (11.4).[9]
- Concerning the low educational level and occupational status of our study population, we have to stress on the fact that RHUH is a main tertiary care governmental hospital serving low and very low socioeconomic class patients, knowing that these findings cannot be generalized to the socioeconomic distribution of the Lebanese society.
- The majority of our study population were living in urban areas. It is well known that the major contributing factor for TB transmission is crowding, poor sanitation which are more present in urban areas vs. rural areas.[9] Indeed, this finding was similar to Poland tuberculosis study done in 2013, showing that the incidence rate in rural population was lower than in urban areas; 17.1 vs. 20.[9]
- Syrians and Palestinians were the dominant nationalities after the Lebanese, this finding is easily explained by the influx of refugees from both nationalities that started since 1948 till 2015.

Concerning life style factors, the majority of our **TB infected** population as 64% were *nonsmoker* while 52% of **TB diseased** population were *smoker*. The majority of the three groups (TB infection, TB diseased and non TB group) were *non-alcoholic*. These results could suffer a detection bias since it was based on the information retrieved from the patients' charts (retrospective data). Furthermore, RHUH is located in an Islamic neighborhood which may explains the high percentage of non-alcoholic patients.

However, almost 16% of **TB infection**, **TB disease** and **non TB** population reported having *old TB*. This finding is less than the results found in USA in 2010 where more than half of active TB cases currently occurring in foreign born individuals result from reactivation of latent TB infection (LTBI).[10] This discrepancy between our study and USA study findings could be explained by the facts that the vast majority of our study population are Lebanese patients and not a foreign population.

The majority of our 3 groups population reported *cough* (56% for TB infection group, 67% for TB disease) as initial complaint, followed by *fever* (56% for TB infection, 41% for TB disease), *sputum production* (24% for TB infection, 44% for TB disease), weight loss (36% for TB infection, 37% for TB disease) and *hemoptysis* (16% for TB infection 30% for TB disease). These findings are similar to the classic TB symptoms: chronic cough with blood tinged sputum, late day fever, night sweats, weight loss, lymph node enlargement, chest pain, and spread to other organs with or without the development of cold abscess and other symptoms.[11] Like many diseases, TB is diagnosed according to a comprehensive approach including clinical examinations followed by Para clinical tests. Clinical examination involves collecting information on the patient's history which includes whether the person has been in a country with a high TB incidence rate or in contact with a patient having TB. In addition to clinical examinations, several tests should be done in order to confirm TB diagnosis such as, tuberculin test, radiological examination, bacteriological diagnosis and others. In the management of a TB patient, the first recommended test is PPD, followed by other diagnostic tests according to the complaints.[12] Any patient is usually labeled as having TB infection if he is PPD positive with negative CXR while TB disease is confirmed if he has PPD positive with either sputum analysis positive (AFB positive or sputum culture positive) or other diagnostic test positive according to the involved organ (LP positive, pleural tap positive, lymph node biopsy positive, OSB positive or peritoneal tap positive).[6] In our study, the total number of PPD positive patients was 40.62%, very similar result to other studies findings: 49.2% in a retrospective study[13] done in China from 2007 until 2015, and 50.7% in a study done in Iran.[14] According to the results of CXR and other diagnostic tests, almost half of our study population (52%) were labeled as TB diseased (PPD positive + one of the diagnostic test positive) and the other half (48%) just TB infected (PPD positive only). By comparing our results to the study done in Iran, among those with positive PPD, 60% had positive sputum smear (culture/AFB) compared to 41% in our study.[15] Therefore, we can conclude that we found lower TB prevalence (TB infection and TB disease) in one tertiary care center in Beirut comparing to other study results in the region.[2]

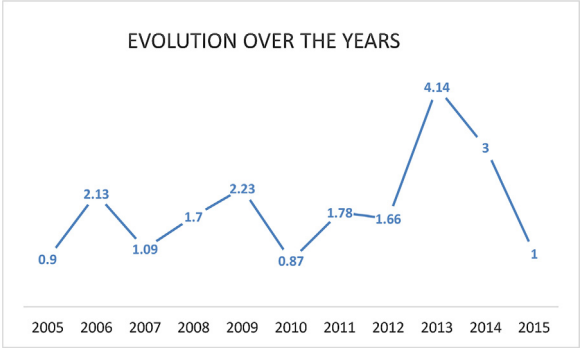


Fig. 1 – Ratio of number of suspected TB to number of admissions to medical floor.

Between 2005 and 2010, the ratio fluctuates between a nadir of 0.87 and a maximum of 2.23. However, a highest peak was noticed from 1.66 to 4.14 in 2013, which could be explained by the influx of Syrians refugee population.[15] Following 2013, there was a gradual drop from 4.14 to 1 in the two following years that could result from awareness campaign and drastic measurements to control TB, done by the Ministry of Public Health with the Official TB office (Fig. 1).

4.1.1. *Case fatality rate CFR*

Among the 128 patients "TB suspected" 17 deaths were registered, so CFR = 13.2% of suspected TB. From the 17 dead

patients, 2 had TB infection (12%), 4 had TB disease (23%) and the 11 remaining were from the TB suspected group (65%). Among TB infected patients ($n = 25$), 2 deaths were registered, so CFR = 7.5% of infected TB. Among TB diseased patients ($n = 13$), 4 deaths were registered, so CFR = 16% of diseased TB.

Worldwide, the case-fatality rate of smear positive pulmonary tuberculosis among persons on treatment is 3.8%.[16] Compared to a population-based descriptive epidemiological study of all notified cases of TB in Brazil, during the period from 01/01/2008 to 31/12/2011 showing that the CFR varies between 2.8% and 3.8%,while the CFR in our study was higher than in Brazil[14] (7.5% and 16% compared to 2.8% and 3.8%). In another retrospective cohort study of all pulmonary TB patients registered in four districts in Shanghai from 2004 to 2008, TB was responsible for 7.2 potential years of life lost (PYLL) almost equal to CFR registered among TB infected patients in our study.[17] This high case fatality rate could be explained by lower socio economic status, associated comorbidities and poor access to hospitalization delaying the appropriate therapy and worsening the outcomes.

4.1.2. *Comparison between our results and WHO reported data in Lebanon generated in 2015-10-30*

The incidence of TB disease in Lebanon was 0.92/1000/year according to WHO,[16] while in our study (27/128 = 0.21% equal to 0.21/1000/year) the incidence was lower. As for bacteriologically confirmed TB cases, the results were almost similar with 40.7% in our study confirmed by sputum analysis and 44.8% in the data reported by WHO for Lebanon. By comparing the socio demographic variables, M/F ratio was 0.7 in Lebanon, compared to 0.66 (40/60) for TB infection and 2 (67/33) for TB disease in our study. Concerning the age, 8% of TB cases were under 15 years old in Lebanon, while in our study 40% of TB infected group were less than 25 and 23% of TB disease group were less than 25.[18] Finally, the mortality from TB in Lebanon was 0.089. In our study population, both TB infected and TB diseased group the mortality was 0.04 (2 + 6/128) inferior to WHO results.[18]

This difference could be explained by the fact that our study included one tertiary care center that's why the results differ from the WHO statistics that includes the whole country.

4.2. *Analytical results*

A comparison concerning sociodemographic variables: age, gender, marital status, occupational status and educational status done between TB infection, TB disease and non TB group showed that for each criteria, no significant level was reached despite the difference found between the three groups, with all p values greater than 0.05. This could be explained by the low number of patients in TB diseased group ($n = 27$).

Since no significant association was found between the sociodemographic variables and the three TB groups, the same analysis was repeated between these variables and 2 TB groups only: TB infection and TB disease.

A significant association was found as well between age and the 2 TB groups with a p of 0.034. The younger population was more frequent in TB infected group (42.3%) while 50% of TB diseased group were older. As a result, as the patient increases with age he tends to have a TB disease rather than TB infection. This result is also expected since the risk of switching to TB disease from TB infection increases with age.[7]

As for gender, marital status and occupational status, no significant association was found with the 2 TB group with a p value more than 0.05 for each group. In both groups, the majority were married (53.8% for TB infection vs. 70.8% for TB disease). In both groups, the majority had an educational level less than grade 8 (57.7% and 37.5% in TB infection and disease respectively).

The absence of significant association in the preceding criteria for both groups could be explained by the demographic homogeneity in our study population across the 2 TB groups. Finally, for the occupational status, the majority were unemployed with 64% and 53.8% in both groups.

However, the majority in TB infection group were woman (57.7%) while in TB disease group the majority were men (65.4%), but no statistical significant association was found due to the small number of patients in TB disease (<30).

As for scoring severity index, ANOVA showed a significant difference with a p value of 0.046. The TB diseased patients have the highest severity score index followed by non TB than TB infection. This finding was expected due to the natural history of the disease where TB infected people do not feel sick and rarely have symptoms.[7] This difference was also found between the 2 TB groups: TB infection and TB disease: with a p value of 0.034. More TB infected patients tend to fall in the mild to moderate group (46%) while more TB diseased patients tend to fall in moderate to severe group (69.2%). This finding is expected since the symptoms are more severe in TB disease than in TB infection.[7]

Finally, by comparing TB incidence (0.21) and mortality rates (0.04) results in our study to 2014 WHO (38) results found in Mexico (incidence: 0.02/mortality: 1.7), China (incidence: 0.9/mortality: 2.8) and South Africa (incidence: 0.45/mortality: 44), we can conclude that TB incidence and mortality in our study were lower than those found in South of Africa and China, where TB is considered endemic. However, in Mexico the incidence was lower but the mortality was higher than the results found in our studies.[17]

5. Conclusion

Our cross sectional observational study was performed according to data retrieved from patients' files during 2005–2015 at Raffic Hariri University Hospital. Our study demonstrated the primary objectives, computing the incidence rate of TB cases diagnosed at RHUH during 10 years period (2005–2015), determining the annual rate of percent change in tuberculosis incidence during this 10 years period, assessing the risk factors or change of incidence rate according to socio demographic data (age, gender, nationality) socio economic status (educational status, occupational status) and finally evaluating prognosis by calculating severity score, case fatality rate and mortality rate. Accordingly, we had 52 patients with positive PPD out of 128 TB suspected patients, reading an incidence rate of 0.21/100/10 years. Between 2005 and 2015, the

ratio of number of suspected TB to number of admissions to medical floors fluctuated between a nadir of 0.87 and a maximum of 2.23. Noting that the highest peak was in 2013 explained by the influx of Syrian refugee followed by a gradual drop in the years that followed. By dividing the data into 3 groups, TB disease, TB infection and non TB group, and by analyzing the association with the socio demographic data as potential risk factors, a significant level was found between TB disease and TB group with the age variable. TB disease was associated with older age than TB infection. Furthermore, ANOVA analysis showed that the highest severity score was found with TB disease group at a significant level. Finally, crude fatality rates were higher in our study (7.5% among TB infected and 16% among TB diseased patients) than in others such one study done in Brazil: between 2008 and 2011 2.8% and 3.8% respectively (TB infection and TB disease). However, by comparing our study results done in one tertiary care center in Beirut with WHO results for Lebanon, the crude fatality rate was lower in our study (0.04) compared to WHO results (0.089). Thus, the role of the Lebanese Ministry of Public Health is very essential to enhance knowledge and develop awareness campaign about TB and other highly contagious diseases, including sign and symptoms, mode of transmission, precautions, treatment, post exposure prophylaxis and isolation practice.

Finally, it is essential to enhance knowledge and develop awareness campaign regarding TB and other highly contagious diseases, including sign and symptoms, treatment, precaution, isolation practices, post exposure prophylaxis. Further improvements in the control and prevention of TB will require a continued strong public health infrastructure and involvement of a range of health professionals outside the public health sector. The success in controlling TB and progressing toward its elimination will depend on the integrated activities of professionals from different fields in the health sciences.

6. Limitations of the study

The study is an observational cross sectional study; we tried to eliminate any selection bias. For this reason we included all TB labeled patients upon admission to the medical floor through the 10 years periods.

Our survey has two limitations. Since RHUH is a governmental tertiary care hospital, our study results may not be fully representative of the Lebanese population, knowing that we never aimed to generalize the results of our study.

Our result is underestimated because of the limitations in data collection and patients files.

Secondly, there is no questionnaire bias in our study since we used a standardized check list.

Finally, this survey represents a snapshot of the suburb of Beirut before an outbreak became apparent to the world and three years after TB had been emerged in Lebanon due to influx of Syrian refugees. Since then, preparedness activities of hospitals including formation, training and well structuring, should have been intensified. These results, including identified gaps or concerns, help to provide direction toward further preparedness activities.

Conflicts of interest

The authors have none to declare.

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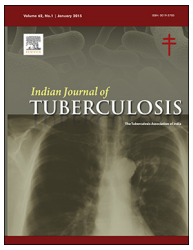

Original article

A study on pattern of resistance to second line anti tubercular drugs among multi drug resistant tuberculosis patients

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ABSTRACT

Aims and objectives: To determine the prevalence and pattern of resistance to second line drugs among multi drug resistant (MDR) tuberculosis patients being treated on category IV regimen.

Methodology: This study was conducted at Department of Respiratory Medicine, J.L.N. Medical College, Ajmer in collaboration with IRL, STDC, Ajmer. Second line anti tubercular drug sensitivity for 398 multi drug resistant tuberculosis patients (between June-2015 and June-2016) was done to find out prevalence and pattern of resistance to second line drugs. Second line drug sensitivity was performed at accredited laboratory, Microbiology department, S.M.S. Medical College, Jaipur.

Results: Among these 398 patients, 136 (34.17%) were resistant to fluoroquinolones (Ofloxacin) (Pre XDR); 18 (4.52%) were resistant to one of the aminoglycosides (Inj. Kanamycin, Capreomycin, Amikacin) (Pre XDR); while 22 (5.53%) patients were resistant to fluoroquinolones as well as aminoglycosides (XDR). 148 (37.18%) patients were found sensitive to both the drugs. Samples of 41 (10.3%) patients were contaminated and no growth was seen in 33 (8.29%) patients.

Conclusion: Nearly half of the multi drug resistant (MDR) tuberculosis patients (44.22%) being treated on category IV regimen also have resistance to either fluoroquinolones or aminoglycosides or both i.e. Pre XDR or XDR. This may result in poor outcome of category IV regimen under RNTCP. There is a strong need for provision of culture sensitivity for all first line drugs and at least two second line drugs viz. Fluoroquinolones and aminoglycosides for all the patients registered as smear positive under RNTCP. There is also a need for development of rapid culture technique for sensitivity to second line drugs.

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1. Introduction

Tuberculosis, despite the availability of effective diagnostic, preventive and curative strategies, ranks alongside HIV as a leading cause of death.[1] The emergence of resistance to drugs used to treat tuberculosis (TB), and particularly multi drug-resistant TB [MDR-TB, defined as resistance to both Isoniazid (INH) and Rifampicin with or without resistance to other first-line drugs] has become a significant public health problem in a number of countries and an obstacle to effective TB control. By 2014, data on drug resistance were available for 144 countries, which collect population and TB cases.[2]

Globally, an estimated 3.3% of new TB cases and 20% of previously treated cases have MDR-TB, a level that has changed little in recent years.[1] In 2013 in India, 248,000 cases of TB were tested for drug resistance and 35,400 (14.27%) were found to have either MDR or Rifampicin resistant TB.[3] Although the proportion is small, the number of persons with MDR TB is sizeable.

Extensively drug-resistant TB, or XDR-TB is a subset of MDR-TB where the bacilli in addition to being resistant to Isoniazid (H) and Rifampicin (R) are also resistant to fluoroquinolones (FQ) and any one of the second line injectable drugs (Kanamycin, Capreomycin or Amikacin). It had been reported by 105 countries by 2015. An estimated 9.7% of people with MDR-TB have XDR-TB.[1] Pre-extensively drug resistant (Pre-XDR) is defined as disease caused by a TB strain resistant to Isoniazid and Rifampicin and either a fluoroquinolone or a second-line injectable drug, but not both (World Health Organization 2008).

Overall, the proportion of MDR/RR-TB patients in the 2013 cohort who successfully completed treatment (i.e. cured or treatment completed) was 52%. Conversely, treatment success was <50% in countries with the largest cohorts: India, the Philippines, the Russian Federation, South Africa and Ukraine.[4]

Fluoroquinolones (FQ) and injectable aminoglycosides play an essential role in the treatment and control of multidrug-resistant tuberculosis (MDR-TB). The prevalence of XDR among MDR tuberculosis patients was estimated 3.2% in results of second line drug sensitivity testing (DST) on MDR isolates from Gujarat DRS survey.[5] An incidence of FQ resistant MDR-TB is increasing globally but unfortunately, limited data are available on prevalence of pre-XDR-TB worldwide and in India.[6] Use of Fluoroquinolones (FQ)[7] and injectable amino-glycosides[8] by clinicians for bacterial infection other than TB has been the reason for increased resistance to these drugs. Therefore this study was done to find out pattern of resistance to these second line anti tubercular drugs (FQ) and injectable aminoglycosides among multi drug resistant tuberculosis patients in Ajmer region.

2. Material and methods

This study was conducted at PMDT Site, Department of Respiratory Medicine, J.L.N. Medical College, Ajmer in collaboration with IRL, STDC, Ajmer between June-2015 and June-2016. A total 398 multi drug resistant and R-resistant patients who were registered for category IV regimen, their sputum samples were sent to accredited laboratory of Department of Microbiology, S.M.S. Medical College, Jaipur for second line drug sensitivity (Ofloxacin and injectables Kanamycin, Capreomycin, Amikacin).

3. Results

Among these 398 patients, 136 (34.17%) (FQ resistant) and 18 (4.52%) (aminoglycosides resistant) were Pre XDR; 22 (5.53%) were FQ + aminoglycosides resistant (XDR). 148 (37.18%) patients samples were sensitive, 41 (10.3%) samples were contaminated, while no growth was found in 33 (8.29%) samples (Fig. 1).

Table 1 and Fig. 2 depict that among total 398 patients, 165 (41.46%) were R-resistant; out of these 59/165 (35.75%) were FQ resistant (Pre XDR), 7/165 (4.24%) were aminoglycosides resistant (Pre XDR) while 5/165 (3.03%) were XDR. 67 (40.6%) patients were sensitive to FQ and aminoglycosides. Remaining 233 (58.54%) patients were HR-resistant and out of these 77/233 (33%) were FQ resistant (Pre XDR), 11/233 (4.72%) were Aminoglycosides resistant (Pre XDR) while 17/233 (7.29%) were XDR and 81/233 (34.76%) were sensitive to second line drugs.

4. Discussion

In our study we found that 34.17% MDR patients were additionally resistant to fluoroquinolones (Pre XDR). Singhal et al.,[9] (Uttar Pradesh) also reported 34% MDR patients resistant to fluoroquinolones in their series of patients of MDR TB. A study in Mumbai conducted by Udwadia et al.,[10] high level of FQ resistance i.e. 56.3% was found but it can be well explained by Mumbai being densely populated city (population density > 20,000 persons/km^2). Also proportion of MDR-TB cases in new as well as previously treated cases is much higher compared to national estimates in Mumbai[11] and this study was performed at a referral institute. FQ resistance in various Indian studies e.g. 16.4%,[16] 22%,[12] 24%[14] were reported. 8.7% FQ resistance by Yanlin Zhao et al.,[15] (China) and 13.3% by Olusoji Daniel et al.,[13] (Nigeria) were reported. 4.52% of MDR TB patients were found aminoglycosides resistant (Pre XDR) in our study which is similar to observation made in a study in China by Yanlin Zhao et al.,[15] (4.8%). 3.2–3.3% aminoglycosides resistance were found in MDR patients in studies by Olusoji Daniel et al.,[13] (Nigeria) and Ramachandran et al.,[14] (Gujarat). Although few other Indian studies reported a little higher aminoglycosides resistance between 10 and 15%.[9,10,12,16]

Patients resistant to FQ as well as aminoglycosides were 5.53% in our study (XDR). A similar XDR resistance level among MDR patients was found by Paramasivan et al.,[16] (4.6%) at Chennai. XDR resistance level ranging from 7 to 12% in MDR patients was reported in various other Indian studies.[9,10,14] In a study at China 2.1% XDR resistance level among MDR patients was reported by Yanlin Zhao et al.[15]

37.18% MDR patients were sensitive to both second line drugs tested (Ofloxacin and injectables Kanamycin, Capreo-

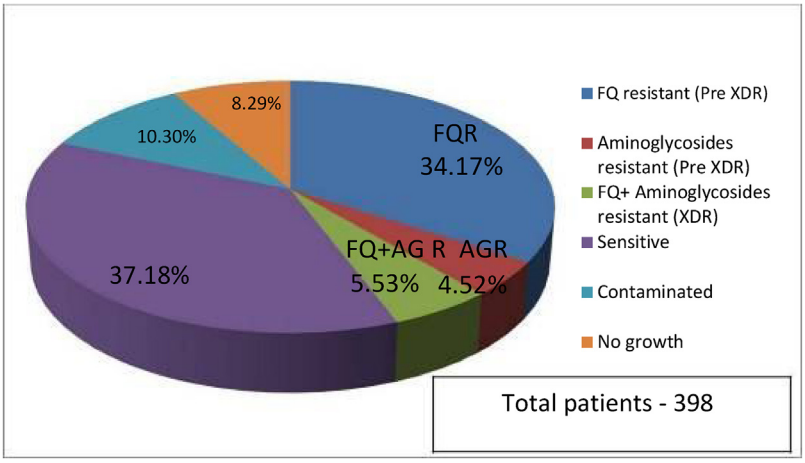

Fig. 1 – Second line drug sensitivity results in all R-resistant and MDR Tuberculosis patients.

Table 1 – Second line drug sensitivity results in R-resistant and HR-resistant Tuberculosis patients respectively.

	FQ resistant (Pre XDR)	Aminoglycosides resistant (Pre XDR)	FQ + aminoglycosides resistant (XDR)	Sensitive	Contaminated	No growth	Total
R-resistant	59	7	5	67	16	11	165
HR-resistant	77	11	17	81	25	22	233
Total	136 (34.17%)	18 (4.52%)	22 (5.53%)	148 (37.18%)	41 (10.3%)	33 (8.29%)	398

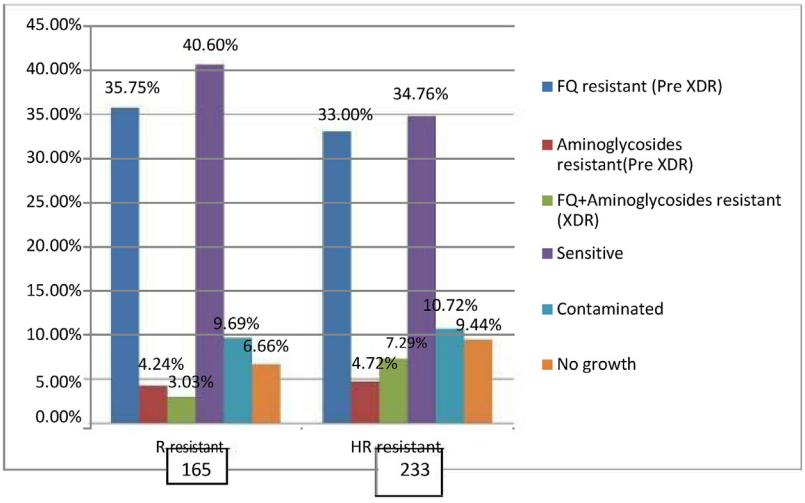

Fig. 2 – Second line drug sensitivity results in R-resistant and HR-resistant Tuberculosis patients respectively.

mycin, Amikacin) in our study. Similarly 34% MDR patients were found sensitive to second line drugs in a study by Singhal et al.,[9] in Uttar Pradesh. Udwadia et al.,[10] reported a little lower second line sensitivity level (30.14%) in Mumbai. 54% and 83% sensitivity to second line drugs in MDR patients were reported in other studies by Yanlin Zhao et al.,[15] (China) and Olusoji Daniel et al.,[13] (Nigeria) respectively.

Samples from 10.3% patients were contaminated in our study while no growth was seen in 8.29% samples which could be due to non representative samples.

Thus in our study 44.22% patients among MDR patients were resistant to one or more second line drugs. Similarly 44–60% MDR patients were found resistant to one or more second line drugs in other Indian studies by Paramasivan et al.,[16] Patel et al.,[12] and Singhal et al.[9]

For management of multi drug resistant tuberculosis patients, to make effective regimen at least four sensitive second line drugs during the intensive phase is required in category IV.[18] This much level of resistance certainly renders the regimen less effective. This may eventually result in poor

outcome of category IV regimen under RNTCP due to suboptimal treatment. In a study Falzon Dennis et al.,[19] assessed the impact of additional resistance to fluoroquinolones and/or secondline injectable drugs on treatment outcome. Compared to treatment failure, relapse and death, treatment success was B higher patients infected in with strains MDR without-T additional resistance ($N = 4763$, 64% [95% confidence interval: 57–72%]) or with resist only ($N = 1130$, 56% [45–66%]), than fluoroquinolones alone ($N = 426$, 48% [36–60%]) or to fluoroquinolones plus second-line injectable drug (XDR-TB) ($N = 405$, 40% [27–53%]).[20] Sim reported that patients with either form of pre-XDR-TB showed poorer cumulative survival than those with ofloxacin-susceptible/secondline injectable-susceptible MDR-TB ($p < 0.05$ for each comparison).

In our study we found higher level of resistance to fluoroquinolones which is certainly due to their wider availability, ease of prescription and often irrational use in the private and public sectors outside of the Revised National Tuberculosis Control Programme (RNTCP). The fact that, under poor management practices, TB isolates can develop Ofloxacin resistance within one week, makes misuse of fluoroquinolones a matter of great concern.[17] Low level of resistance to aminoglycosides found in our study could be because of their limited use. Regardless of the reason for resistance fluoroquinolones and aminoglycosides both play an essential role in the treatment and control of multidrug-resistant tuberculosis (MDR-TB).

5. Conclusion

Pre XDR TB patients should be identified earlier among MDR TB patients and these patients should be monitored closely to stop their progression to XDR. There is a strong need for provision of culture sensitivity for all first line drugs and at least two second line drugs viz. Fluoroquinolones and aminoglycosides for all the patients registered as smear positive under RNTCP. There is also a need for development of rapid culture technique for sensitivity to second line drugs.

Clinicians need to be sensitized on the rational use of fluoroquinolones and aminoglycosides in patients suspected of having TB or in patients who have failed conventional first line anti-TB medications. There is also a need for immediate modification in regimen for those who have been diagnosed as Pre XDR for better outcome.

Conflicts of interest

The authors have none to declare.

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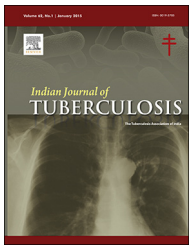

Original Article

Health benefits of Practical Approach to Lung health (PAL) experienced by patients with chronic respiratory diseases – Results from PAL pilot project in primary health care setting in Kerala, India

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ABSTRACT

Government of Kerala state had implemented a pilot project of the World Health Organisation recommended Practical Approach to Lung health (PAL) strategy, with an intention to improve the quality of diagnosis, treatment and management of common chronic respiratory diseases (CRD) in primary health care settings. The current study was done as a part of implementation of PAL pilot project and was intended to assess the benefits of PAL for the individual patients with CRDs accessing services from primary health institutions. Exit interviews were conducted at the baseline and for impact assessment after six months of pilot project by interviewing patients with CRD attending primary health institutions implementing PAL and control institutions. A total of 94 and 100 CRD patients were interviewed at baseline and after six months in the PAL implementing institutions, and 88 and 96 CRD patients were interviewed at the control institutions. Reduction in number of medical consultation, hospital admissions and exacerbations among CRD patients were 5.03, 3.20 and 2.24 times higher in PAL implementing institutions as compared to the control institutions. PAL pilot project in India implemented in an area with a reasonably sound primary health care system has proved that it might be beneficial for the patients with CRD as it reduces frequency of exacerbations, hospital visits and frequency of medical consultations.

1. Introduction

Lung diseases are one of the leading causes of death in developing countries.[1] Around 15% of all disability adjusted life years lost in South East Asia were due to lower respiratory infection, TB, chronic obstructive pulmonary disease (COPD) and asthma.[2] Chronic respiratory disorders (CRD), if not diagnosed, treated and managed correctly can adversely affect individuals and health systems. But CRD, particularly asthma

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and COPD, have attracted very little special attention in low- and middle-income countries.

Though reliable estimates are not available, studies have suggested that the prevalence of COPD in India may be around 5% in the adult population and general prevalence of chronic bronchitis in rural areas to lie between 6.5% and 7.7%.[3] In India, no definite protocol for diagnosis and management of CRDs is being practiced at primary health care levels except for Tuberculosis.

Kerala, the southern State in India, has a reasonably strong primary health care system with a good infrastructure of primary health centres.[4] Government of Kerala state had implemented a pilot project of the World Health Organisation (WHO) recommended Practical Approach to Lung health (PAL) strategy, with an intention to further strengthen the health system and to improve the quality of diagnosis, treatment and management of common chronic respiratory illnesses in primary health care settings.[5,6]

PAL is a patient-centred approach to improve the quality of diagnosis and treatment of common respiratory illnesses in primary health care (PHC) setting. It seeks to standardise service delivery through development and implementation of clinical guidelines and managerial support within the general health system.

PAL has been piloted in Kerala in12 Primary Health Centres (PHC) and four Community Health Centres (CHC), covering a population of 550,000 in Kollam district. The steps in PAL implementation included estimating the burden of respiratory diseases, assessing the capabilities of the health infrastructure in implementing the PAL strategy, developing clinical guidelines by experts, designing communication messages, formulating an information system to monitor and evaluate the implementation, developing training materials, training of staff and testing the implementation of the clinical guidelines and the information system in the pilot area.[5] Since all PHCs in the state are manned by qualified modern medicine practitioners, the PAL Treatment and Operational Guidelines (TOG) had more clinical component than that was done elsewhere. Customised and locally appropriate algorithms were prepared for managing acute breathlessness, acute respiratory illnesses and CRD at PHCs, based on International guidelines. Differentiating COPD and bronchial asthma by history, recording Peak Expiratory Flow Rate, inhaled medications, patient education, behaviour change communication for risk reduction and health system initiated retrieval for loss to follow-up were the main components of PAL strategy in the State. The service delivery for the pilot phase was from May 12, 2015 to November 30, 2015.

The current study was done as a part of implementation of PAL pilot project and was intended to assess the benefits of PAL for the individual patients with CRDs accessing services from primary health institutions.

2. Methods

Exit interviews were conducted at the baseline and for impact assessment after six months of pilot project by interviewing patients with CRD attending OPD of primary health institutions implementing PAL. In the same district, 15 other primary health institutions were randomly selected as control institutions and exit interviews were conducted with patients with CRD attending OPD of those institutions also, concurrently with baseline survey and after six months.

CRD patients less than 15 years were excluded, as the PAL TOG for pilot project addressed only patients above 15 years. Those who were beneficiaries of PAL for a minimum of three months were included during the impact assessment. Five consecutive chronic respiratory disease patients in a day from a PHC and 10 from a CHC were included. A differentiation of probable COPD or Bronchial Asthma was made based on history and prior medical records.

Patients were asked about details of visits to a doctor for their respiratory illness and exacerbations during last month. Details of hospital admissions were also collected with a time frame of three months. Each interview lasted for about 10 min.

In-depth interview was conducted by an investigator experienced in qualitative methods, with 15 randomly selected beneficiaries of PAL (registered for a minimum of three months) to explore their perceptions regarding PAL services. The questionnaire included four open-ended questions regarding their personal experiences with respiratory diseases, benefits and demerits of PAL and suggestions for improvement. Each interview lasted for about 25–30 min. The proceedings were audiotaped and two researchers recorded the proceedings, noting key themes.

Double data entry was done using Microsoft Excel and analysis was done using Statistical Package for Social Sciences version 15 (SPSS Inc., Chicago, IL, USA), for Microsoft Windows. Independent sample t test was used to compare difference between means and a p value of less than 0.05 was considered as statistically significant. Regarding qualitative study, audiotapes were transcribed verbatim. These were in Malayalam and were translated into English before coding. Sections with similar coding were grouped according to the pre-determined themes. Repeated themes were marked as important in red font colour. All the flagged statements were put together and synthesised.

3. Results

A total of 94 and 100 CRD patients were interviewed at baseline and after six months in the PAL implementing institutions and 88 and 96 CRD patients were interviewed at the control institutions. The characteristics of the study subjects are shown in Table 1. There was no significant difference between the characteristics of participants in the baseline and impact assessment surveys in pilot area and control area.

It was seen that the total visits to a doctor in a month for people with CRD at PAL implementing institutions was 5.93 (SD 7.63) at baseline and 2.56 (SD 1.33) during the impact assessment survey with a mean reduction of 3.37 (95% CI: 1.84–4.90) visits ($p < 0.001$) while at the same time the mean reduction in number of visits among the patients at control institutions was 0.67 (95% CI: 0.31–1.66). The reduction in the mean number of hospital admissions among the people with CRD attending PAL implementing institutions was 0.77 (95% CI: 0.48–1.07) ($p < 0.001$) while the figure was 0.24 (95% CI: 0.02–0.51) in the control group. The mean number of exacerbations

Table 1 – Characteristics of subjects with chronic respiratory diseases included in the exit interviews for baseline and impact assessment survey.

Characteristics	Categories	PAL implementing institutions			Control institutions		
		Baseline survey ($n = 94$)	Impact survey ($n = 100$)	p value	Baseline survey ($n = 88$)	Impact survey ($n = 96$)	p value
Age	Mean (SD)	59.31 (16.70)	62.26 (12.94)	0.171	58.9 (15.69)	58.7 (18.02)	0.922
Gender	Male	42 (44.7%)	52 (52%)	0.191	44 (50%)	58 (60.4%)	0.102
	Female	52 (55.3%)	48 (48%)		44 (50%)	38 (39.6%)	
Socio-economic status	APL	32 (34%)	39 (39%)	0.285	28 (31.8%)	40 (41.7%)	0.109
	BPL	62 (66%)	61 (61%)		60 (68.2%)	56 (58.3%)	
Probable diagnosis	COPD	60 (63.8%)	66 (66%)	0.620	54 (61.3%)	59 (61.4%)	0.984
	Bronchial asthma	29 (30.9%)	26 (26%)		30 (34.1%)	33 (34.4%)	
	Others	5 (5.3%)	8 (8%)		4 (4.5%)	4 (4.2%)	

Table 2 – Impact of PAL on patient visits, hospital admissions and exacerbations based on exit interviews of subjects with chronic respiratory disease baseline.

Characteristics	PAL implementing institutions				Control institutions			
	Baseline survey ($n = 94$)	Impact survey ($n = 100$)	p value	Difference	Baseline survey ($n = 88$)	Impact survey ($n = 96$)	p value	Difference
Total visits to a doctor in last month	5.93 (7.63)	2.56 (1.33)	<0.001	−3.37	4.11 (4.69)	3.43 (1.44)	0.181	−0.67
Number of hospital admissions in last three months	0.81 (1.48)	0.04 (0.19)	<0.001	−0.77	0.72 (1.03)	0.46 (0.79)	0.070	−0.24
Number of exacerbations in last month	2.05 (4.37)	0.57 (1.11)	<0.001	−1.48	1.86 (2.21)	1.19 (1.59)	0.020	−0.66

at baseline in PAL implementing institutions was 2.05 (SD 4.37) while the figure was 0.57 (SD 1.11) after six months of PAL implementation ($p < 0.001$) with a mean reduction in 1.48 (95% CI: 0.59–2.37) episodes per patient per month. The mean number of exacerbations per patient at control institutions was 1.86 (SD 2.21) and 1.19 (SD 1.59) with a mean reduction of 0.66 (95% CI: 0.11–1.22). The details of the analysis have been shown in Table 2.

Among the participants interviewed for qualitative study, 10 had COPD and five had bronchial asthma. Seven were females. Mean age was 57.12 (SD 19.45). PAL was perceived as beneficial by the participants. They were satisfied with the PAL services. Majority of the participants reported major health benefits after registering in PAL in terms of reduced exacerbations and decreased hospital visits. Some of the comments by the participants are given in Box 1.

Benefits were much evident for bronchial asthma patients as compared to COPD patients. Four major factors that influenced patient satisfaction in ascending order were experienced health benefits, measurement of PEFR, concern for them by the health system and reduced out-of-pocket expenditure for treatment. Three of them were motivated by their peer beneficiaries of the PAL services to attend PHCs and avail services. One participant raised concern about reluctance from the side of doctors in prescribing injections after PAL implementation, as he found more satisfaction with injections. He had visited private sector two times in last three months to get an injection. Another male patient also had difficulty initially in abruptly stopping injections, but now he found it comfortable.

4. Discussion

PAL intended to improve the quality of care in patients who seek assistance for respiratory symptoms in PHC settings and the efficiency of respiratory service delivery within health systems. Though health system strengthening is the important agenda of PAL, it also aims to reduce the patient costs by decreasing the number of visits and referrals.[7]

Our experience has shown that there was a significant decline in the number of visits to a doctor, exacerbations and hospital admissions for patients who received services from PAL implementing institutions as compared to baseline and also as compared to control institutions. The finding that PAL reduces exacerbations and emergency room visits have been documented in other country experiences also.[6–10] We also have noticed that the inpatient admission rates of PAL implementing centres had shown a decline in the number of patients getting admitted there for managing exacerbations of respiratory illness.

Prior to PAL implementation, differentiating to COPD or bronchial asthma was not prevalent at PHC setting in Kollam. Many CRD patients used to receive tablets of beta 2 agonist and bronchodilators with or without injections and antibiotics. Inhalational agents were not in the essential drug list. PAL has

Box 1. Translated verbatim statements of study participants.

"I have visited many doctors and hospitals before. I had no relief. Now I am very happy. There is no need to go and get injections during evenings now." – a 30 year old woman

"I used to come almost every day to get injections for my disease. The doctor convinced me and motivated me to use the inhalers. Now that I have not taken any injection for past two months" – a 47 year old male patient

"I used to have at least one hospital admissions every month previously. Now for last three months, I had no admissions" – a 61 year old male.

"The sisters (staff nurses) here convinced me and helped me in stopping smoking. I have stopped it" – a 54 year old male

"For each visit, we have to spend Rs 30–40. I used to come once in three days. Now since I am getting medicines for two weeks, that amount is saved" – a 67 year old male.

"Doctors should be generous to give injections also, as I may need it at times. Now a days they are reluctant to give it" – 70 year old male

"I will come and first do my measurement (PEFR) with sister (staff nurse). By doing that, I myself will get an idea about my condition. Previously I could not blow much, but now it has improved" – a 42 year old female

"I had apprehension in using inhaler devices. The staff nurses here have educated me and taught me how to use the device. Now I am telling everybody to use it." – 45 year old female

built in the capacity of staff nurses and pharmacists for educating about inhalational devices and behaviour change communication for risk reduction including smoking cessation and environmental modifications using pre-tested modules. The time saved by staff nurses by reduction in injections was being used by them for patient education. After PAL implementation, in many places, health system used to make phone calls or send field workers to trace back any loss to follow-up of CRD patients. All these factors might have led to a better control of CRD which might have resulted in reduced number of visits, reduced number of exacerbations and decrease in number of hospital admissions.

PAL is not a novel strategy. However, it is for the first time piloted in India. Significant politico-administrative commitment was required to ensure resources including inhalational drugs that were never used in program setting ever. Intense trainings, based on locally appropriate protocols and continuous supervision and monitoring were the other keys to the successful implementation of PAL in Kerala. Strict adherence to diagnostic and management algorithms rationalised the prescriptions, with far reaching benefits beyond CRD patients. Various country experiences suggest that the development of a systematic and standardised management of respiratory conditions within PHC services is likely to contribute to integrating TB control into respiratory care at PHC level, provide an integrated care to a substantial proportion of patients attending PHC facilities, reduce drug prescription in general and antibiotics in particular and improve the management of the health resources.[6]

The study was done as part of an implementation of a public health pilot project in a program setting and not planned as pure research. Many high-quality randomised controlled trials are often based on highly selected patients, but this study includes subjects who represent the population of patients seen in day-to-day practice at PHC setting of Kerala. We have taken possible steps to ensure the internal validity of the study and avoiding biases that would prevent comparability between the data sets of the baseline and impact surveys. However, factors like season of study, differences in demographic characteristics, co-morbidity and severity of disease conditions would have confounded the results. There could be a selection bias, if the pattern of patients with CRD attending the institutions has changed after PAL implementation. The effects studied were of a six months period only. Despite these limitations, the findings have many public health and policy implications.

To summarise, PAL pilot project in India implemented in an area with a reasonably sound primary health care system has proved that it is beneficial for the CRD patients as it reduces frequency of exacerbations, hospital visits and frequency of medical consultations.

Conflicts of interest

The authors have none to declare.

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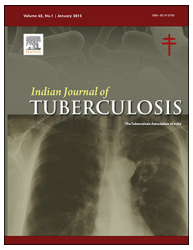

Original article

Study of adrenal function in patients with tuberculosis

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Extra pulmonary tuberculosis

SUMMARY

Background: Although subclinical adrenal insufficiency has been documented in tuberculosis but it has been neglected in mainstream management of TB due to inconclusive data on its prevalence in TB. The fact that adrenal insufficiency may result not only in poor general condition of the patient but also sudden death due to adrenal crisis, makes it all the more important to address this issue seriously. In this non-randomized interventional study comprising of 100 cases of TB, our aim was to assess the adreno-cortical functions in patients with pulmonary TB (50 cases) and extra-pulmonary TB (50 cases) in an attempt to determine if there is any compromise of adrenal function.

Methods: In this study, 100 cases of active TB were investigated for adrenal insufficiency by measuring morning fasting basal serum cortisol levels, followed by low dose ACTH stimulation test using 1 μg synacthen (synthetic ACTH analog). The post-stimulation serum cortisol levels were estimated. Basal serum cortisol levels < 220 nmol/L or post-stimulation test serum cortisol level increment < 200 nmol/L or post-stimulation serum cortisol levels < 500 nmol/L were suggestive of adrenal insufficiency.

Results: Basal serum cortisol level was low in 16% cases and after low dose ACTH stimulation test, cortisol response was subnormal in 76% cases. Incidence of adrenal insufficiency in pulmonary TB (74%) and extra-pulmonary TB (78%) were comparable. The number of females having adrenal insufficiency in both the groups was higher than the males (67.3% males and 83.3% females) but the difference was statistically significant only in extra-pulmonary TB group ($p = 0.011$). On analysing the data, the sensitivity of basal serum cortisol level estimation in diagnosing adrenal insufficiency was observed to be 21.05% and its specificity was 100%. Positive predictive value was 100% and negative predictive value was 28.57%. Diagnostic accuracy of basal serum cortisol level estimation was observed to be 40%.

Conclusion: The incidence of subclinical adrenal insufficiency in TB cases attending chest department at a tertiary care hospital was significantly high but comparable in both pulmonary and extra-pulmonary type of TB. Females in general and particularly those with

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extra-pulmonary TB were observed to be at increased risk of adrenal insufficiency. The low dose ACTH stimulation test was able to identify cases with adrenal insufficiency which had normal basal serum cortisol levels. Screening all TB cases for adrenal insufficiency by measuring both morning basal serum cortisol levels and low dose ACTH stimulation test can help identify cases at risk of fatal adrenal crisis and institute timely management, thus improving disease prognosis.

1. Introduction

The incidence of tuberculous Addison's disease is on the decrease in first world countries but still remains a problem in developing countries. Majority cases of adrenal insufficiency in the developed countries are attributed to autoimmune adrenalitis in contrast to the developing countries where tuberculosis is implicated to be the most common cause of adrenal insufficiency.[1]

However, the divergent reports on adreno-cortical status of patients with tuberculosis and paucity of conclusive consensus on the issue has lead to the neglect of this manageable condition. The fact that adrenal insufficiency may result in not only poor general condition but also sudden death due to adrenal crisis, underscores the importance of addressing this issue seriously.

The primary objective of this clinical study was to assess adreno-cortical function in patients with active pulmonary and extra-pulmonary tuberculosis in an attempt to determine if there was any compromise of adrenal function.

2. Material and methods

In this non-randomized interventional study, a total of 100 cases of active TB were enrolled from the OPD & indoor of the Department of TB and Respiratory diseases of Sri Guru Ram Das Institute of Medical Sciences and Research, Amritsar after clearance from the ethical committee of the institute. The purpose of the study was explained to them and an informed consent was obtained. Subsequently all the patients were put on DOTS as per the RNTCP guidelines. The 100 cases were divided into two groups, group A comprised of 50 cases of pulmonary TB diagnosed with sputum positive for acid fast bacilli or positive for *Mycobacterium tuberculosis* on CBNAAT. Group B comprised 50 cases of extra-pulmonary TB diagnosed on the basis of cytological or histo-pathological evidence of TB.

In order to eliminate the bias of other associated etiologies of adrenal insufficiency, cases were subjected to a set of exclusion criterias. Patients with history of anti-tuberculosis treatment (ATT), steroid therapy, estrogen therapy, diabetes, HIV seropositivity, current pregnancy or lactation or history of any other endocrine disorder were excluded from the study. Patients with history suggestive of any immunosuppressive disease, recent vaccination with any live vaccine or history of atopy or allergy were also excluded from the study.

Patients taking drugs that could have interfered with adrenal function or cortisol metabolism, e.g. oral contraceptive pills etc. were excluded from the study. Since ATT like rifampicin is implicated in enhancing cytochrome enzyme induction and accelerating cortisol metabolism, all cases were subjected to testing for hypoadrenalism before ATT was started.[2–7] After overnight fasting, they were subjected to morning basal serum cortisol level estimation and Low dose ACTH stimulation test.

A total of 3 venous blood samples were taken from each case timed according to the procedure and each time 2 mL of venous blood sample was drawn for serum cortisol level estimation. First sample was taken at 8:00 AM for the basal serum cortisol level estimation followed by intravenous injection of 1 μg of Synacthen (synthetic ACTH analog [1–24 ACTH]).

Following this, two serial samples for estimation of cortisol concentration were collected at half hour intervals. The samples were processed on the same day without delay and analyzed by chemiluminescence. The patients were started on ATT on the same day without any delay.

Basal serum cortisol level less than 220 nmol/L was taken as insufficient.

In response to the low dose ACTH stimulation test, an increment of less than 200 nmol/L or a post stimulation cortisol level of less than 500 nmol/L was taken as adrenal insufficiency.[1]

The data was statistically analyzed. Chi-square test was used for comparing proportions among groups and Student's *T*-test was used for comparing means.

3. Results

Among the 100 cases enrolled in the study 46% were males and 54% were females. There were 44% males and 56% females in group A, and 48% males and 52% females in group B. Their ages ranged between 14 and 80 years. Out of 50 cases of extra-pulmonary TB, maximum cases were of tubercular pleural effusion 24 (48%) followed by tubercular lymphadenitis 17 (34%). There were 3 (6%) cases of abdominal TB and 6 (12%) cases of other types of extra-pulmonary TB. The 6 other types of extra-pulmonary TB cases comprised of 1 case each of tubercular abscess, tubercular empyema, tubercular mastitis, tubercular anterior chest wall mass, tubercular ascitis and TB thyroid.

In our study basal serum cortisol levels were observed to be low in 16 (16%) cases and amongst these cases, 6 (12%) were pulmonary TB cases and 10 (20%) were extra-pulmonary TB cases. Out of the 6 cases having low basal serum cortisol level in group A, 2 were males and 4 were females. In group B, out of

Table 1 – Comparing gender distribution of adrenal insufficiency in Group A and Group B.

	Group A ($n = 50$)		Group B ($n = 50$)	
Gender	Male	Female	Male	Female
Number of cases with adrenal insufficiency	16	21	15	24
Percentage	72.7%	75.0%	62.5%	92.3%
p value	0.856		0.011	
Degree of freedom	1		1	
Pearson chi-square	0.033		6.462	

"$p < 0.05$ = significant."

the 10 cases having low basal serum cortisol level, 2 were males and 8 were females. In our study basal serum cortisol levels were low in 16 (16%) cases and after low dose ACTH stimulation, cortisol levels were observed to be abnormal in 76 (76%) cases with 37 (74%) cases in group A and 39 (78%) cases in group B.

Overall out of the 100 cases of tuberculosis included in this study, adrenal insufficiency (i.e. low basal serum cortisol level or abnormal ACTH stimulation test) was found in 76% cases. In group A, incidence of adrenal insufficiency was 74% and in group B, incidence of adrenal insufficiency was 78%.

Overall in the study of 100 cases, 31 (67.3%) males and 45 (83.3%) females had adrenal insufficiency. A higher percentage of adrenal insufficiency was seen in females. The incidence of adrenal insufficiency in both the groups (74% in group A and 78% in group B) was high but the difference was not statistically significant (p value < 0.5). The number of female cases with adrenal insufficiency in both the groups was higher than the male cases (67.3% males and 83.3% females) but the difference was statistically significant only in group B ($p = 0.011$) (Table 1).

Out of the 50 cases of extra-pulmonary TB in group B, adrenal insufficiency was observed in 16 (94.1%) cases of tubercular lymphadenitis and 16 (66.6%) cases of pleural effusion. All the 100% cases of abdominal TB included in the study showed adrenal insufficiency. Amongst the 6 other types of TB, 4 (60%) showed adrenal insufficiency and these were 1 case each of tubercular mastitis, tubercular abscess, tubercular ascitis, and TB thyroid (Table 2).

There were 60 cases which had normal basal serum cortisol levels but an abnormal response to ACTH stimulation test, of these 31 (51.6%) cases were from group A and 29 (48.4%) cases were from group B (Table 3). On analysing the data, the sensitivity of basal serum cortisol level estimation in diagnosing adrenal insufficiency was observed to be 21.05%. Its specificity was 100% as it gave no false negative results. Positive predictive value was 100% and negative predictive value was 28.57%. Diagnostic accuracy of basal serum cortisol level estimation was observed to be 40%. This suggests that basal serum cortisol level estimation alone is liable to miss detection of adrenal insufficiency and therefore, all cases must be investigated for adrenal insufficiency by basal serum cortisol level estimation along with low dose ACTH stimulation test.

Table 3 – Distribution of cases with abnormal response to ACTH stimulation test with respect to the basal serum cortisol levels.

	Cases with abnormal response to ACTH stimulation test and with:	
	Low basal *S. cortisol* levels	Normal basal *S. cortisol* levels
Group A	6 (37.5%)	31 (51.6%)
Group B	10 (62.5%)	29 (48.4%)
Total	16 (100%)	60 (100%)

4. Discussion

Adrenal insufficiency in TB remains an under diagnosed disease co-morbidity. The high prevalence of adrenal insufficiency of 76% shows that it should be imperative to investigate patients for hypo-adrenalism in TB. This result corroborates with another study by Sharma et al. which observed adrenal insufficiency rates of nearly 50% in TB sample population.[2] This has important significance in the Indian scenario where the prevalence of TB is high and institution of rifampicin containing ATT is implicated in enzyme induction and enhancing cortisol metabolism, thus further predisposing to adrenal crisis.[2–7] The most likely explanation for this adrenal insufficiency is either functional hypopituitarism leading to poor ACTH stimulus for adrenal glands leading to hypoadrenalism or acquired adrenal insufficiency due to haematogenous spread of TB to adrenal glands. The adrenal glands could also be fatigued following an initial phase of hypersecretion of cortisol in acute disease induced stress condition giving way to chronic atrophic adrenals with low serum cortisol levels in chronic insidious TB.[8] Hypo-adrenalism can also be due to pituitary insufficiency due to TB infection but this is typically seen in TB meningitis.[9] Functional

Table 2 – Incidence of adrenal insufficiency in different types of extra pulmonary TB.

Type of extra-pulmonary TB ($n = 50$)	Total number of cases	Number of cases with adrenal insufficiency	Percentage
Tubercular pleural effusion	24	16	66.6%
Tubercular lymphadenitis	17	16	94.1%
Abdominal TB	3	3	100%
Others (tubercular abscess, tubercular empyema, tubercular mastitis, tubercular anterior chest wall mass, tubercular ascitis and TB thyroid)	6	4	60%
Total	50	39	78%

hypo-pituitarism in these patients can be explained by the active TB infection, however it should be kept in mind that most of the patients diagnosed with TB are clinically cachectic and suffer from some degree of malnutrition which is a well known cause of functional hypo-pituitarism. It should furthermore be appreciated that TB patients have poor immunity and may have associated suppressed pituitary function due to associated super-added infection.[8,10,11]

The incidence of adrenal insufficiency in TB patients in the present study group was demonstrated to be higher than expected possibly because of small sample size. There is a possibility that the low dose stimulation test that we used has higher sensitivity than the standard dose ACTH test. Standard dose ACTH stimulation test uses supra-physiological dose (250 μg) of synacthen for stimulation and this is suspected to be responsible for adrenal over drive and thus masking subclinical adrenal insufficiency.[12–17]

In our study of 100 cases (group A + group B), only 21% of the cases with adrenal insufficiency had low serum cortisol level while all the cases of adrenal insufficiency were identified on low dose ACTH stimulation test suggests that only investigating the patients for baseline serum cortisol levels is not enough to rule out Addison's disease and cases are liable to be missed in this manner. All patients, specially those with normal basal serum cortisol levels should be subjected to ACTH stimulation test to detect adrenal insufficiency. The reason for the apparent normal basal serum cortisol levels with abnormal response to ACTH stimulation test could possibly be explained by the fact that TB is diagnosed earlier in disease phase and the adrenal glands are still compensating and maintaining serum cortisol levels. This prevents adequate disease progression to involve the adrenal glands leading to adrenal fatigue and atrophy with low basal serum cortisol levels. While the abnormal ACTH stimulation response may be attributed to the fact that the acute response of the adrenal gland to bolus ACTH injection reflects ambient ACTH concentrations to which the gland has been exposed. The cortisol response to an acute ACTH injection will be blunted if the subject has experienced chronic pituitary ACTH hyposecretion with resultant adrenal atrophy and diminished cortisol reserve.[18–20]

In case of disease detection in early phase of TB, the serum cortisol levels will be maintained by cortisol hypersecretion on part of adrenals but they may not be having enough cortisol reserve to elicit an adequate response to ACTH stimulation testing. Thus, this plausibly explains that low number of cases identified with low basal serum cortisol levels and a greater number of cases detected with the low dose ACTH stimulation test. Hence, low dose ACTH stimulation test is advised in all TB cases along with basal serum cortisol estimation to detect adrenal insufficiency.

We observed that the incidence of adrenal insufficiency was high but similar in both pulmonary and extra-pulmonary disease. This suggests that level of stress induced by both pulmonary and extra-pulmonary disease can overwhelm the adrenals and lead to adrenal fatigue or pituitary function suppression. Among the extra-pulmonary cases (50 cases) in our study, greater prevalence of adrenal insufficiency was seen in tubercular lymphadenitis compared to tubercular pleural effusion. Bottasso et al. observed that immune-modulatory cytokines may contribute to the divergent profile of cytokine responses during the progression of TB and the hormonal alterations are consistent with and partly mediated by cytokines released during the immune response to *M. tuberculosis* and since these products are released in response to both pulmonary and extra-pulmonary TB, a similar pattern of incidence is seen in both the groups.[21]

The incidence of adrenal insufficiency in males and females, for both pulmonary and extra-pulmonary groups were compared. It was identified that females had a higher percentage of adrenal insufficiency in both groups, which was 75% and 92.3% respectively for group A and group B. The p value was 0.856 and 0.011 for group A and group B respectively. The p value for group B was statistically significant. The observations of our study suggest that there is a higher incidence of adrenal insufficiency in females afflicted with extra-pulmonary tuberculosis.

Gender distribution in tuberculosis reportedly shows male preponderance which is attributed to skewed sex ratio, lesser access to healthcare for women and under reporting of TB in women. However, Indian studies under RNTCP DOTS have documented greater prevalence of TB in men and despite facing greater stigma and inconvenience, women are more likely than men to access health services, be notified under DOTS and adhere to treatment.[22,23] In a study done by Willis et al. in Coventry, UK comparing gender distribution in Addison's disease they documented equal gender distribution in Addison's disease in tuberculosis and a female preponderance in Addison's disease of autoimmune etiology.[24] The possible cause for this gender discrepancy could be the associated endocrine changes in patients with TB which have more effect on the cortisol/DHEA ratio in women who may be testosterone deficient under chronic disease induced stress conditions.[25–27] When steroid metabolites were analyzed in 24 h urine samples of patients with TB the decreased levels of some androgens especially dehydroepiandrosterone (DHEA) was documented. DHEA also opposes many glucocorticoid effects. This could also attribute to the altered cortisol/DHEA ratio in TB.[8]

There is evidence that all the hormones involved in such altered endocrine response can affect immune processes, metabolic status and the accompanying inflammatory responses.[21,25–27]

5. Interpretation and conclusion

The incidence of subclinical adrenal insufficiency in TB cases attending chest department at a tertiary care hospital was higher than expected but comparable in both pulmonary and extra-pulmonary type of TB. Females in general and particularly those with extra-pulmonary TB are at increased risk of adrenal insufficiency. The Low dose ACTH stimulation test was able to identify those cases with adrenal insufficiency which was masked by normal basal serum cortisol levels. Screening all TB cases for adrenal insufficiency by measuring both morning basal serum cortisol levels and low dose ACTH stimulation test can help identify cases at risk and institute timely management, thus improving case outcome. Our impression, as suggested by the above findings is that all cases of TB whether pulmonary or extra-pulmonary and

irrespective of the type of extra-pulmonary TB involvement must undergo investigations for adrenal insufficiency. All patients should be subjected to basal serum cortisol estimation and low dose ACTH stimulation test, even if the serum cortisol levels come out to be normal so that no case of adrenal insufficiency is missed.

Conflicts of interest

The authors have none to declare.

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Original Article

Comparative study of effect of *Withania somnifera* as an adjuvant to DOTS in patients of newly diagnosed sputum smear positive pulmonary tuberculosis

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ABSTRACT

Background: Ashwagandha (*Withania somnifera* Linn.) a rejuvenative herb has long been used as an immunomodulator in Indian subcontinent. As immunity plays an important role in pathogenesis and treatment of tuberculosis (TB), so role of *W. somnifera* as an adjuvant has been studied on selected parameter.

Method: A randomized, double-blind placebo-control study was conducted in two groups of 60 newly diagnosed sputum smear positive pulmonary TB patients on Directly Observed Treatment – short course (DOTS) regime. *W. somnifera* root extract or placebo capsules were given as add-on therapy for duration of 12 weeks. Effects on sputum conversion, Hemoglobin (Hb), body weight, Erythrocyte Sedimentation Rate (ESR), RBC counts, WBC counts, CD4 and CD8 counts, Serum Glutamic-Oxaloacetic Transaminase (SGOT), Serum Glutamic-Pyruvic Transaminase (SGPT), serum uric acid and HRQL (Health Related Quality of Life) Index scores were studied.

Results: At the end of 8 weeks, sputum conversion was seen in 86.6% patients in study group and 76.6% in placebo group. At the end of 12 weeks a highly significant increase was seen in both CD4 and CD8 counts in study group. A raised SGOT and SGPT levels (>35 IU/L) were observed in 16.6% and 33.3% patients in study group; 43.33% and 53.33% in the placebo group of patients. Elevated serum uric acid levels (>6 mg/dl) were observed in 20% and 33.33% in study and placebo group respectively. Average gain in HRQL score was better in patients of study group.

Conclusion: Use of *W. somnifera* as an adjuvant in conjunction with anti-TB drugs used as DOTS showed a favorable effect on symptoms and immunological parameters in patients with pulmonary TB.

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1. Introduction

Tuberculosis (TB) has been a leading cause of death in the world for centuries. Today it ranks as the second leading cause of death from an infectious disease worldwide, after the human immunodeficiency virus. An estimated one third of the world population has been infected. India remains the highest TB burden country giving an estimated incidence of 2.2 million cases out of a global incidence of 9.6 million cases. Most of these people do not show signs of TB disease (termed latent infection). Approximately 1.5 million patients are put on antitubercular therapy every year, while approximately 0.3 million tubercular patients remain untreated.[1] Further, approximately 66,000 MDR-TB cases were diagnosed and put on treatment during the last three years.[2] It has also been reported that one infectious patient can infect 10–15 persons in a year unless effectively treated.

After entry into the lungs, tubercular bacilli have a series of encounters with different host defense mechanisms. Cell mediated immune responses play a pivotal role in host resistance to Mycobacterium tuberculi infection.[3,4] Cellular immunity against tubercular infection predominantly consists of T-lymphocytes that activate macrophages to produce agents such as reactive nitric oxide intermediates that are toxic to the harbored pathogens.[5,6] The progression and the final outcome of infection depend on the balance between outgrowth and killing of *Mycobacterium tuberculosis*. In most individuals, however, the immune response of the host usually merely manages to confine rather than eradicate the harbored microorganisms.[7] It is believed that the CD4+ T-cells releases interleukin-2 (IL-2), IL-4 and IFN-y and are believed to play an important role in immunity to intracellular infections and drive the secondary humoral response. The loss of CD4+ T cells in TB greatly increases susceptibility to both acute and reactivation TB.[8,9] In addition, CD8+ T cells are proved to be efficient in lysing infected cells and in reducing the number of intracellular bacteria.[11] The mechanisms of control of the bacterial load seem to be associated with granular exocytosis involving perforin and granzymes. So both CD4+ and CD8+ T cells provide protection against *M. tuberculosis*.[10,11] Efforts made to improve immunological status of the patient along with antitubercular drugs can have desired effect on treatment outcome.

From time to time, studies have been done where use of adjuvant like liquorice (*Glycyrrhiza glabra*), vitamin A (as retinyl acetate), zinc (as zinc sulphate), sylimarin, peppermint (*Mentha piperita*) essential oil inhalations, adaptogen (Spirulina), with Anti Tubercular Treatment (ATT) reported to have attenuated the side effects of ATT, hence increasing cure rate and improving drug compliance.[12–15] *Withania somnifera* or Ashwagandha (in Sanskrit), is a traditional herbal drug also called as ''Queen of Ayurveda'' and ''Indian ginseng''. The dried root is used in the traditional medicine systems of Ayurveda, Siddha, Sowa-Rigpa (Amchi), and Unani, medicine.[16] *W. somnifera* standards monographs published in the *Ayurvedic Pharmacopoeia of India* (Vol. I, 1989), *Unani Pharmacopoeia of India* (Vol. I, 2007), *Siddha Pharmacopoeia of India* (Vol. I, 2008), the World Health Organization (WHO) Monographs (Vol. 4, 2009), as well as in the currently valid editions of the *British Pharmacopoeia* (BP 2012), *Indian Pharmacopoeia* (IP 2014), and *United States Pharmacopoeia* (USP 36).[17,18] It contains a variety of pharmacologically and medically important constituents like withanolides, sitoindosides and other alkaloids which act on various systems of human body such as nervous system, immune system, reproductive system and endocrine system.[19–21] It has been used for multiple health benefits to get adaptogenic, aphrodisiac, immunomodulatory and anti-inflammatory effects.[22–27] It has also been studied in animals as a cytotoxic agent and has different Central Nervous System (CNS) applications.[28] The safety and efficacy of *W. somnifera* has been described in classical Ayurvedic texts and also in various preclinical and clinical studies.[29–32]

As immune system plays a key role in tubercular infection and response to drug therapy, the traditional and modem uses of this herb as an immunomodulator have prompted to use it in present study as an adjuvant in tubercular patients on DOTS (Directly Observed Treatment – short course).[33] The present research work was undertaken to study the effect of *W. somnifera* as an adjuvant to DOTS regime on immunological parameters and other health status indicators in sputum smear positive pulmonary TB.

2. Materials and methods

The study was conducted in accordance with the Indian Council for Medical Research Guidelines in humans (ICMR-GCP) and Declaration of Helsinki (2008) and was approved by the Institutional Ethics Committee (IEC).

2.1. *Patient selection and study design*

Present study was prospective, double blind, randomized, placebo controlled and a single-center study. It was conducted at Chest and TB hospital, Amritsar (Punjab) which is a university-affiliated, urban, tertiary care medical institute. The study included 60 (32 males and 28 females) newly diagnosed sputum smear positive patients of pulmonary TB of category I in DOTS under RNTCP (Revised National Tuberculosis Control Program – which is the state-run TB control initiative of the Government of India) within the age group of 15–65 years on first line antitubercular therapy in DOTS strategy (Fig. 1). Diagnosis was made on the basis of clinical examination and laboratory investigations including sputum for acid-fast bacilli. Detailed clinical history of all the patients regarding symptoms of TB such as cough, fever, expectoration, bodyaches and loss of weight were taken.

Patients on corticosteroids, barbiturates, hormones and having thyroid disorders, diabetes mellitus, cardiac disorders, obesity, pregnancy and lactation were excluded from the study. The written consent of patients was obtained after fully explaining them the details of study procedures in their vernacular language. They were strictly advised to complete their ATT course even after completion of this 12 week study.

2.2. *Randomization and treatment allocation*

The patients were divided into two groups, according to a pre-generated computerized randomization table. 30 patients were given *W. somnifera* root extract capsule 500 mg twice

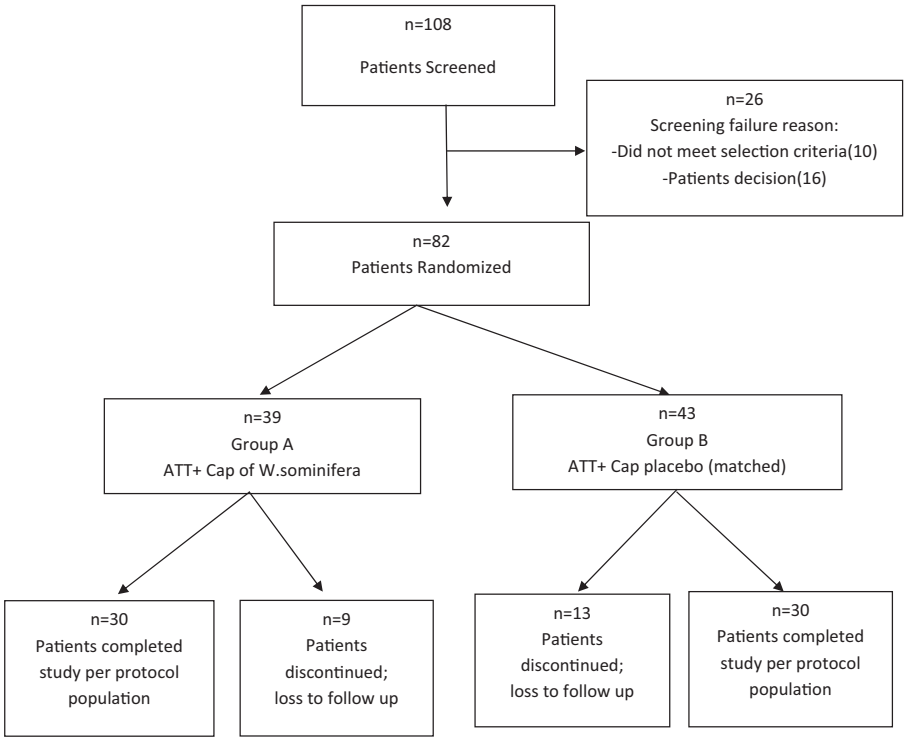

Fig. 1 – Disposition of patients.

daily with a glass of water plus first line antitubercular drugs 2 $(HRZE)^3 + 4(HR)^3$ where H = isoniazid, R = rifampicin, Z = pyrazinamide and E = ethambutol [the number before the letters, e.g. 2(HRZE), etc. refers to the number of months of treatment and subscript after the letters refers to the number of doses per week] as per of RNTCP guidelines and other 30 patients received matched placebo capsules containing dextrose powder along with similar first line antitubercular drugs. *W. somnifera* root extract capsules were provided by Prakash Pharmacy Pvt. Ltd. Amritsar (India), a registered pharmaceutical for manufacturing and selling Ayurvedic products.

These patients were monitored for any adverse drug reaction and therapeutic drug response. At the end of 12 weeks, blinding was opened and patients were placed in their respective groups as group-A antitubercular drugs with capsule *W. somnifera* and group-B antitubercular drugs with capsule matched placebo.

2.3. *Clinical assessment*

In present study investigations hemoglobin, RBC, WBC counts, Erythrocyte Sedimentation Rate (ESR), CD4 and CD8 counts and Serum Glutamic-Pyruvic Transaminase (SGPT), Serum Glutamic-Oxaloacetic Transaminase (SGOT) and serum uric acid were done on 0 week and 12 weeks. Sputum examination was done at 0 week and 8 week following RNTCP guidelines according to which sputum examination is repeated routinely at 8 week.

For adverse effects patients were monitored on 2, 4, 8 and 12 week. The patients were advised to report in case of any serious adverse effect. On reporting any of Adverse Drug Reaction (ADR) they will be managed appropriately; their record will be maintained and will be excluded from the study. In patients having side effects due to antitubercular drugs, standard protocol for management of adverse drug reaction will be followed.

2.4. *HRQoL score*

All the patients were subjected to Health Related Quality of Life (HRQoL) scores during treatment at 0 week, 4 week and 8 week by HRQoL questionnaire (modified HRQoL questionnaire, courtesy – Dhingra and Rajpal, 2003).[34] The questionnaire contained questions relating to symptoms (Symptom Score or Score I) as well as physiological, psychological and social interactions of patients (Socio-psychological and exercise adaptation Score or Score-II). These scores were combined and the composite score was expressed as total HRQoL score.

2.5. *Statistical analysis*

The analyses and graphical representation of the data was done with validated statistical software GraphPad StatMate 2.00 (http://www.graphpad.com). Student 't' test was used to compare the end-point values within both groups.

3. Results

The baseline characteristics in both study groups were comparable (Table 1). In present study more patients got relief from cough, fever, body aches and breathlessness in

Table 1 – Baseline characteristics of patients in study groups.

Characteristics[a]	Group A (n = 30)	Group B (n = 30)
Age (years)	39.27 ± 12.66	38.70 ± 13.82
Sex (M:F)	17:13	16:14
Hemoglobin (g/dl)	9.33 ± 0.79	9.41 ± 0.73
Red blood cell counts (/cmm)	4.24 ± 0.66	4.19 ± 0.69
White blood cell counts (/cmm)	11,738.67 ± 10,033.0	15,711.13 ± 18,150.88
ESR (mm after 1st hour)	83.53 ± 20.56	82.63 ± 21.02
CD4 cell counts (/cmm)	593.27 ± 216.65	530.30 ± 157.77
CD8 cell counts (/cmm)	484.07 ± 236.32	453.57 ± 248.67
SGOT (IU)	30.97 ± 6.17	30.20 ± 4.58
SGPT (IU)	33.36 ± 6.5	31.6 ± 4.47
S. uric acid (mg/dl)	5.11 ± 0.88	5.06 ± 0.75

[a] All characteristics are in mean ± SD.

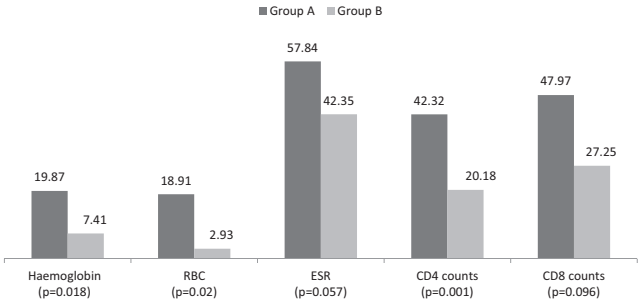

Fig. 2 – Percent change in various parameters at 12 weeks.

group A, i.e. W. *somnifera* group than group B, i.e. placebo group by the end of 12 weeks (Fig. 2). Most of the patient gained weight after starting the antitubercular treatment. Weight gain of less than 5 kg was found in 73.3% and 56.6%, weight gain of more than 5 kg in 13.33% and 3.33% patients in group A and group B respectively at the end of 12 weeks.

Sputum conversion was observed in 86.6% (26 out of 30) and 76.6% (23 out of 30) patients in group A and group B respectively at the end of 8 weeks (Table 2). Even the decrease in bacillary load was more in group A than group B.

Both groups showed a statistically significant increase in percentage change in hemoglobin and RBC count from 0 to 12 weeks. A highly significant percentage decrease in ESR from 0 to 12 weeks was observed in both groups. So statistically significant percentage changes were observed in all of above mentioned investigations in both study groups but the results were more significant in group A in comparison to group B (Fig. 2).

Table 2 – Patients with bacillary load at 0 and 8 weeks.

Bacillary load	Group A		Group B	
	0 week	8 week	0 week	8 week
+	7	4	9	5
++	21	0	17	2
+++	2	0	4	0

There was a significant increase in CD4 counts 42.32% and 20.18% from 0 to 12 weeks in group A and group B respectively and this increase in change was highly significant in group A patients. Likewise, a highly significant increase in CD8 counts was noticed from 0 to 12 weeks in group A while significant increase in group B was seen (Fig. 2). Number of patients with serum uric acid levels more than 6 mg/dI was 13.3% and 20% at 0 and 12 weeks respectively. In group B number of patients with serum uric acid levels more than 6 mg/dl were 13.3% and 33.33% at 0 and 12 weeks respectively. So, a noticeable difference in percentage change in serum uric acid was evident (Fig. 3).

W. *somnifera* as an adjuvant to DOTS showed better HRQoL scores at the end of intensive phase (Table 3). In group A and group B no patient presented with gastritis, Joint pains and Numbness in extremities at 0 day. At the end of 12 weeks, 6.67%, 6.67%, 10% and 20%, 33.3%, 26.66% had gastritis joint pains and numbness in extremities respectively. So the treatment emergent side effects with the use of W. *somnifera* and placebo at the end of 12 weeks have verified the role of W. *somnifera* in preventing possible ADRs (adverse drug reactions) of antitubercular drugs.

The present study has demonstrated favorable effects of W. *somnifera* as an add-on therapy to DOTS in tubercular patients. W. *somnifera* has shown better relief of symptoms and significantly favorable effects on liver transaminase levels and serum uric acid levels. It has also improved Health Related Quality of Life (HRQoL) scores in pulmonary TB patients.

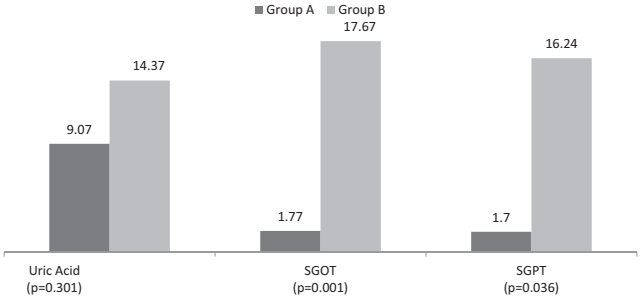

Fig. 3 – Percent rise in SGOT, SGPT and uric acid at 12 weeks.

Table 3 – Mean ± SD HQRL score in group A and group B.

	Mean ± SD HQRL score				'p' value	
	0 week	4 week	8 week	0-4 week	0-4 week	0-4 week
Group A	26.73 ± 2.083	30.77 ± 1.924	33.63 ± 1.903	<0.001; HS*	<0.001; HS*	<0.001; HS*
Group B	26.63 ± 2.428	28.50 ± 2.162	29.47 ± 2.432	<0.001; HS*	0.002; S**	<0.001; HS*

S** (significant) $p < 0.05$; HS* (highly significant) $p < 0.001$.

4. Discussion

TB is the most common infectious disease which is responsible for high mortality in developing countries. There has been very limited progress in TB diagnostics, no new drugs have been developed, MDR/XDR (multi/extensively drug-resistant tuberculosis) is spreading and millions still dying.

Non-compliance by the patients because of long duration of treatment and side effects of anti-TB drugs results in treatment failure or leading to resistant TB bacilli. By adopting DOTS strategy various causative factors for non-compliance have been overcome with the exception of side effects of anti-TB drugs.

This present study is an attempt to improve the compliance by enhancing the immunity and decreasing the side effects with use of W. *somnifera*, a well known Indian herb as an adjuvant to DOTS. W. *somnifera* has been reported to improve blood counts and produce relief of symptoms in TB patients. Ziauddin et al.,[24] has observed the effects of W. *somnifera* on myelosuppression induced mice. A significant increase in hemoglobin concentration, red blood cell counts, white blood cell counts, platelet counts and body weight was observed in W. *somnifera*-treated mice as compared with untreated (control) mice.

The administration of W. *somnifera* was associated with, better sputum conversion rate and low bacillary loads at the end of intensive phase. It has shown better relief of symptoms viz. cough, fever, bodyaches and other symptoms of TB and it may be due to additive type of synergism. W. *somnifera* has shown more favorable rise in immunological parameters such as body weight, hemoglobin, CD4 and CD8 counts, decrease adverse events of anti-TB drugs, less sustained rise in liver transaminases levels, better control of serum uric acid levels and improved Health Related Quality of Life Scores. Pandey et al.,[33] have studied role of W. *somnifera* as immunoadjuvant with chemotherapy in management of pulmonary TB and observed significantly better response in fever, weight gain, sputum conversion and increased T lymphocytes in patients treated with W. *somnifera* along with chemotherapy.

Based on the findings of this study, W. *somnifera* has been observed to produce favorable response in relief of symptoms, sputum conversion, attenuation of adverse effects, hepatoprotective actions and various parameters of immune system which is due to its immunostimulant actions. Statistically significant increase in CD4 and CD8 count with use of W. *somnifera* indicate its ability to increase immunity and phagocytic activity. Present study is also comparable to Mikolai et al.,[31] which reported significant increase in CD4 counts at 96 h over base line after giving 20 ml W. *somnifera* root extract in divided doses.

According to an estimate of World Health Organization (WHO), an approximately 85–90% of the world's population consumes traditional herbal medicines due to better tolerance and fewer adverse drug reactions.[35] We admit that Ayurvedic drugs are not a part of RNTCP. But still both general practitioners and specialists use various types of traditional medicines to support TB management. So Ayurveda can offer some solutions to these problems. Hence a systematic review was carried out to assess the role of W. *somnifera* for the management of TB. We conclude that the supervised use of W. *somnifera* as an adjuvant to DOTS therapy seems beneficial in pulmonary TB. A limitation of present study is the small study sample, so the results may be confirmed using wide cross-section of the population with larger multicenter trials.

Conflicts of interest

The authors have none to declare.

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Original Article

A case risk study of lactic acidosis risk by metformin use in type 2 diabetes mellitus tuberculosis coinfection patients

Keywords:
Type 2 diabetes mellitus–tuberculosis coinfection
Metformin
Lactic acidosis

ABSTRACT

Metformin (MET) has possibilities to be utilized as an adjunct of tuberculosis (TB) therapy for controlling the growth of *Mycobacterium tuberculosis* (*M. tuberculosis*). MET enhances the production of mitochondrial reactive oxygen species and facilitates phagosome–lysosome fusion; those mechanism are important in *M. tuberculosis* elimination. Moreover, MET-associated lactic acidosis (MALA) needs to be considered and the incidence of MALA in patients with type 2 DM–TB coinfection remains unknown. This result contributes much to our understanding about the clinical effect of MET use in type 2 DM–TB coinfection.

For the purpose of understanding the MET effect as an adjuvant therapy in TB therapy and insulin simultaneous therapy, an observational clinical study was done in type 2 DM newly TB coinfection outpatients at Surabaya Paru Hospital. Patients were divided into two groups. First group was MET group, in which the patients were given MET accompanying insulin and TB treatment regimens, the golden standard therapy of DM–TB coinfection. MET therapy was given for at least 2 months. Second group was non-MET group, in which the patients were given insulin and TB treatment regimens. The lactate levels in both groups were measured after 2 months.

Among 42 participants, there was no case of lactic acidosis during this study period. Data were normally distributed; thus, we continued analysis of the difference using paired *T*-test with 95% confidence. There was no difference in lactate levels ($p = 0.396$) after MET therapy compared to non-MET group.

In this study involving patients with TB pulmonary diseases, there is neither evidence that MET therapy induced lactic acidosis event nor that it increased lactate blood level. Thus, we concluded that MET use in type 2 DM–TB coinfection did not induce lactic acidosis.

1. Introduction

Tuberculosis (TB) remains a major cause of morbidity and mortality throughout the world; one-third of the world's population is estimated to be infected with *M. tuberculosis* whereby approximately nine million people develop the disease each year, and almost two million die annually as a result.[1] DM–TB coinfection is associated with poor glycemic control in DM patients, and thus elevated proinflammatory state.[2–4] People with DM had approximately three times the risk of developing TB disease as people without.[2,5–10]

Metformin hydrochloride (MET) MET, the biguanide, have been used for treating type 2 diabetes mellitus for more than 60 years. MET works by inhibiting the production of hepatic glucose, reducing intestinal glucose absorption, and improving glucose uptake and utilization.[11–14] Recently, by a comprehensive in silico study, MET was known to have possibilities of being utilized as a combination drug with existing antibiotics for TB therapy,[15] and by an extensive in vitro study, MET was reported to control the growth of drug-resistant *M. tuberculosis*

strains via production of mitochondrial reactive oxygen species and facilitating phagosome–lysosome fusion.[16,17]

MET is not metabolized by P450 enzymes[12,13,18]; thus, it has no interaction with rifampicin (RIF) that could decrease the therapy efficacy. However, interaction between MET and RIF increases the expression of organic cation transporter (OCT1) and hepatic uptake of MET, leading to enhanced lowering of glucose levels.[19,20]

In our previous study, MET was given to type 2 DM newly TB coinfection patients, which improved the superoxide dismutase (SOD) level (unpublished). SOD improvement after MET therapy is predicted to enhance antituberculosis efficacy and is considered to reduce the intracellular growth of *M. tuberculosis*. Collectively, these data indicate that MET is a promising candidate for host-adjunctive therapy for enhancing the effective treatment of TB.[15,21]

Although MET has several advantages in improving treatment of TB, MET use is still considered to be contraindication in many chronic conditions that may increase the risk of tissue anoxia, the development of MALA, a fatal metabolic condition, and especially pulmonary diseases due to the existence of potential hypoxia.[17,22,23]

Lactic acidosis is characterized by an elevated blood lactate concentration (>45.0 mg/dL or >5.0 mmol/L), decreased blood pH (<7.35), and electrolyte disturbances with increased anion gap[17,23–30]; it also has signs and symptoms of inadequate oxygen (hypoxia) such as shortness of breath, rapid breathing, paleness, sweating, nausea, muscle weakness, abdominal pain, and coma.[22,26,31]

The objective of this study is to assess the risk of lactic acidosis associated with MET use in patients with type 2 DM newly TB coinfection, as well as combination of MET with golden standard therapies, insulin, and TB treatment regimens. Another objective is to evaluate levels of blood lactate, measured at during treatment.

2. Materials and methods

2.1. Study design

The objective of this study was to identify clinical effect of MET to modulate host immune system and its ability to control the growth of intracellular *M. tuberculosis*. Thus, an observational clinical study was done and carried out at outpatient ward of Surabaya Paru Hospital. Patient's inclusion criteria were the following: (1) patients with DM with new case of TB coinfection, who were given insulin and TB treatment regimens; (2) positive *M. tuberculosis* in sputum smear; (3) age of 25–60 years; (4) has normal liver function and renal function; (5) not in hypoxia condition, and on presentation, peripheral oxygen saturation level must be higher than 92%.

During this clinical study, type 2 DM newly TB coinfection patients were divided into two groups. First group was MET group, in which the patients were given MET accompanying insulin and TB treatment regimens, the golden standard therapy of DM–TB coinfection. MET therapy was given for at least 2 months. Second group, a comparison group, was non-MET group, in which the patients were given insulin and TB treatment regimens.

We evaluated MET combined with insulin and TB treatment regimens. MET therapy was given for at least 2 months. During MET therapy, as a follow-up program, patients were physical examined weekly; thus, signs and symptoms for lactic acidosis were monitored. Lactate level was measured after 2-month MET therapy for MET group. For comparison, patients belonging to non-MET group, who were given insulin and TB treatment regimens, were also physical examined weekly and lactate level was measured after 2-month insulin and anti-TB therapy.

2.2. Diagnosis and management therapy

The diagnosis of TB was established by (1) clinical symptoms and signs of TB, such as chronic productive cough, unintentional weight loss; (2) positive sputum smear of acid-fast bacteria by microscopic Ziehl–Neelsen-stained sputum slides; and (3) chest radiographs with suggestive features of TB. Diagnosis of DM was established by fasting and 2 h after meal blood glucose levels. HbA1c was measured after 2 months of MET therapy, as evaluation.

Patients diagnosed with TB were registered and treated with TB treatment regimens for a period of 6 months in accordance to WHO guidelines.[32–34] Management therapy for achieving good glycemic control was insulin therapy.

These following drugs were used: MET (Metformin®), insulin (Humulin®), RIF, isoniazid (INH), pyrazinamide (PYR), and ethambutol (ETH). MET was given 1000–1500 mg in divided daily dose for at least two months or during intensive phase of TB treatment, accompanying insulin therapy and TB treatment regimens.

2.3. Lactate blood measurement

After at least 2 months therapy, whole blood samples, in both groups, were measured by using Biosen C-line glucose and lactate analyzer® to test lactate blood levels.[26]

3. Results

3.1. Characteristics of patients

During this study period, there were 476 cases of new TB infection and 156 cases (~30%) of what were type 2 DM newly TB coinfection. 42 patients, with equal number of males and females, were eligible and participated in this observational study (Table 1). The condition in both groups was homogenous ($p = 0.17$; $p > 0.05$) using *Saphiro Wilk test*. The youngest patient's age was 26 years.

Table 1 – Characteristics of patients' sex and ages.

Sex	MET group		Non-MET group	
	N	Age (X̄±SD)	N	Age (X̄±SD)
Male	11	44.29 ± 9.76	12	43.00 ± 9.14
Female	11	43.45 ± 9.10	8	49.63 ± 6.44
Total	22	43.78 ± 9.08	20	47.53 ± 7.53

Table 2 – Distribution of patient's eligibility criteria.

Parameters	MET group	Non-MET group	p (difference)
HbA1c (g/dL)	8.82 ± 1.91	9.52 ± 2.02	0.379
Oxygen saturation (SpO_2) (%)	98.06 ± 0.73	97.47 ± 0.83	0.308
BUN (mg/dL)	0.95 ± 0.16	0.93 ± 0.13	0.980
Creatinine serum (U/L)	23.92 ± 11.92	27.3 ± 12.01	0.103
SGOT (U/L)	17.63 ± 6.16	14.44 ± 6.48	0.354
SGPT (U/L)	19.22 ± 8.73	16.09 ± 7.56	0.509

Table 3 – Lactate blood level.

MET group (mmol/L)	Non-MET group (mmol/L)	p (difference)
1.77 ± 0.60	1.71 ± 0.54	0.240

Distribution of patient's eligibility criteria such as HbA1c, oxygen saturation, renal function (BUN and creatinine serum), and liver function (SGOT, SGPT) are shown in Table 2. All data were normally distributed using *Saphiro Wilk* test; thus, we continued analysis of the data for the difference using paired *T*-test statistics with 95% confidence.

Blood glucose condition for both groups was similar ($p = 0.26$); thus, we dismissed the influence of hyperglycemia condition on lactate blood level.[26,35]

3.2. *Lactate blood level*

After observational of MET therapy, on divided daily dose of 1000–1500 mg for at least 2 months accompanying insulin therapy and TB treatment regimens. Lactate blood levels were measured after 2 months of MET therapy.

There was no incidence of lactic acidosis event during this period. Additionally, other side effects of MET therapy such as gastrointestinal intolerance were also reported. Only two cases of mild gastrointestinal disturbance, such as mild frequent diarrhea and nausea/vomiting, were reported.

Lactate blood level in both groups was normally distributed using *Saphiro Wilk test* ($p = 0.24$; $p > 0.05$); then, we analyzed the difference between both groups using paired *T*-test (Table 3 and Fig. 1).

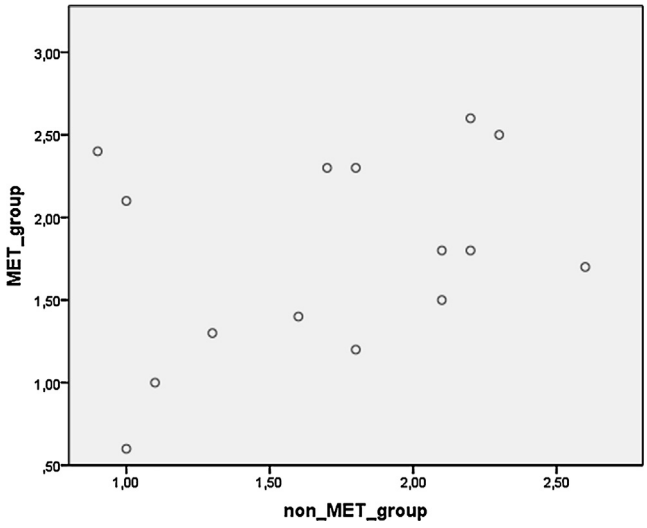

Fig. 1 – Lactate blood level (mmol/L).

Comparing MET group with non-MET group, we concluded there was no statistically significant difference of lactate blood level after at least 2 months of MET therapy ($p > 0.05$). The level of blood lactate was in the normal range (less than 2.50 mmol/L) both in MET group and also non-MET group.

4. Discussion

The optimum treatment strategy for DM–TB coinfection remained unclear to date. Uncontrollable chronic hyperglycemia in DM patients increases the incidence of TB therapy failure. Besides, DM is also associated with deaths due to TB infection and relapse of TB infection.[4,9,36–38] TB treatment for TB patients with DM is no different from treatment for patients without DM.[5] Insulin becomes the main therapy to control hyperglycemia condition. In this study, DM–TB patients got insulin and TB treatment, with TB regimen dose referring to World Health Organization (WHO).

Identification of new host-directed therapies that can improve clinical outcomes for DM–TB coinfection patients has been a priority by the WHO, leading to the study of immunomodulatory agents for adjunct treatment of TB.[21,39–41]

MET in some studies enhances *M. tuberculosis* – specific host immunity, reduces inflammation, and enhances efficacy of TB treatment. MET, which is not metabolized by P450[12,13,18] enzyme, does not decrease the efficacy of RIF. Interaction between MET and RIF increases OCT1 expression, which has its role in blocking *M. tuberculosis*[15,42] transcription. SOD is one essential factor to prevent INH resistency,[43] and MET has been known to increase SOD.[44–46] Hence, it can be concluded that MET possesses the potency to boost OAT effectiveness. MET treatment was associated with improved control of *M. tuberculosis* infection and decreased disease severity.[15,16]

The use of MET may cause side effects such as digestion problem (anorexia, nausea, vomit, and diarrhea), lactate level increase, vitamin B_{12} malabsorption, and kidney/heart function problem.[12,13] Though the incidence of MET-associated lactic acidosis (MALA) is low, it must be prevented as it threatens lives. In this study, MALA can occur in very rare situations such as (1) *drug-induced hepatitis* caused by OAT and/or MET and (2) lung damage, which becomes worse causing hypoxia.[47,48] MALA prevention in this study has been determined at the following precondition criteria: (1) minimal to moderate lung lesion; (2) oxygen saturation > 92%; (3) normal function of SGOT and SGPT, and normal kidney function (BUN and SK) (see Table 2). This study also provides consultation,

information, and education related to symptoms of *lactic acidosis*.

Lactic acidosis is also influenced by high glycemic index. To minimize the bias due to hyperglycemia, HbA1c measurement was done 2 months after the MET therapy accompanying insulin and TB treatment regimens for MET group. HbA1c, for non-MET group, was also performed after 2 months of insulin and OAT therapy, or after intensive TB therapy phase was done (see Table 2).

There were no MALA cases during this 2-month study, both for MET and non-MET groups. It was even proved that blood lactate level was in normal range (<2.50 mmol/L). The blend of MET, insulin, and TB treatment was relatively safe for DM–TB patients if some condition was controlled (see Table 3).

In this study, we also found that the participants (<5%) in MET group experienced mild gastrointestinal intolerance (nausea and vomit). This can be related to high concentrated MET or glucose metabolism change causing local irritation, fluid retention, and salt malabsorption, leading to loose stools and diarrhea.[17]

In this study, we were not yet involved TB patients non-type 2 DM, even in our knowledges MET, which has low hypoglycemic effect, could be beneficial in TB patients non-DM due to anti-inflammatory effect and increasing efficacy of TB treatment.[21,41] In future, after establishing MET clinical effect in type 2 DM–TB coinfection, we may combine MET therapy with anti-TB for TB patients with non-type 2 DM in order to evaluate the efficacy of MET therapy in immune modulation.

5. Conclusion

Lactic acidosis in MET therapy is a rare but important adverse event and clearly we need to prevent it. In this case risk study, there is no evidence of MALA. Elevation of levels of lactate, compared with placebo, also did not occur. Thus, we concluded that MET use in type 2 DM–TB coinfection did not induce lactic acidosis. Furthermore, this result, due to our limitation in number of participants involved in the study, needs to be confirmed in a cohort study.

Conflicts of interest

The authors have none to declare.

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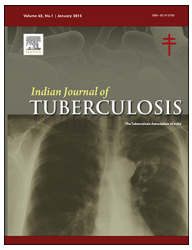

Case Report

Primary peritoneal tuberculosis, a forgotten localization. Case report

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ABSTRACT

We present a case report of a young nulliparous woman that presented with progressive ascites, night sweats and weight loss. Clinical and para-clinical findings were not suggestive of pulmonary tuberculosis (TB) or other peritoneal conditions. A laparoscopy revealed important ascites and granulomatous peritoneal infiltration with normal genital anatomy. Tests for tuberculosis revealed primary peritoneal involvement in absence of pulmonary TB. This was a case of TB with primary and limited localization in the peritoneum. A strength of this report is that it has adequate illustration of the macroscopic and microscopic findings. In this brief report, we argue that the peritoneal localization of TB has been forgotten, but in countries with a high incidence of this condition, it should always be taken into consideration by doctors from all specialities when making differential diagnosis.

1. Introduction

Peritoneal tuberculosis (PTB) is uncommon in developed countries, accounting 1–2% of all forms of tuberculosis (TB),[1] but it is expected to be much more frequent in countries with a higher incidence of TB. Pulmonary TB usually explains a secondary peritoneal process, but primary peritoneal involvement is often very difficult to diagnose. Symptoms of PTB are insidious and unspecific represented by ascites, fever, night sweats, anorexia, weight loss or abdominal pain and can delay the proper diagnosis to over four months.[2] Definite diagnosis requires peritoneal biopsy during laparoscopy or laparotomy as peritoneal fluid analysis for TB bacillus is often inconclusive.[3]

We report a case of primary peritoneal TB successfully diagnosed using a combination of invasive and imaging techniques in a young subject presenting with isolated ascites. A high index of suspicion is required for the correct diagnosis of PTB in countries with a high incidence of TB.

2. Case report

A 27-year-old nulliparous woman, physician, presents for progressive abdominal distention over a two months period,

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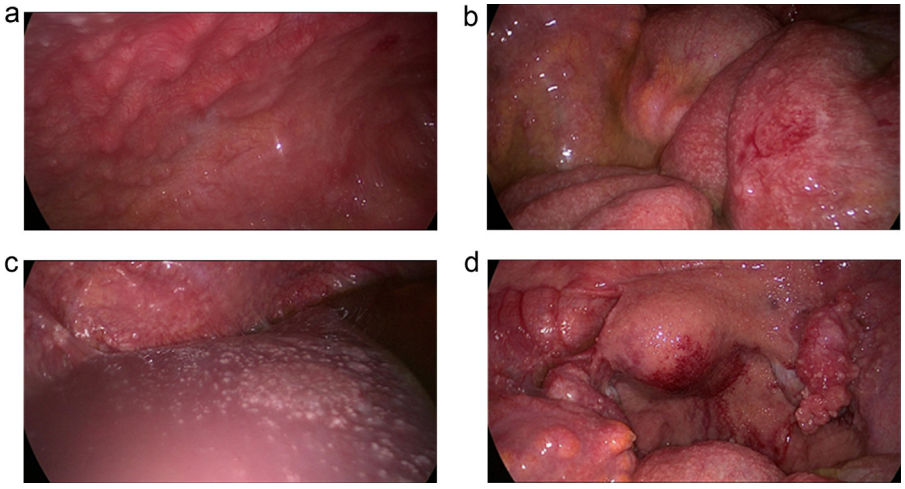

Fig. 1 – (a) Laparoscopic view of the anterior parietal peritoneum. (b) Laparoscopic view of the small intestine. (c) Laparoscopic view of the diaphragmatic surface of the liver. (d) Laparoscopic view of the uterus, fallopian tubes and ovaries.

cachexia of the limbs and a bloating abdomen. There was no personal history or contact history of TB nor symptoms of active pulmonary TB, neither any other pathology. The clinical examination revealed only ascites, no signs of liver, kidney or cardiac diseases or neoplasia. Examination of the respiratory system was within normal limits. Blood tests revealed leukopenia with lymphopenia, high levels of PCR and IgG, but normal results for infectious (Hepatitis B, C and HIV) and

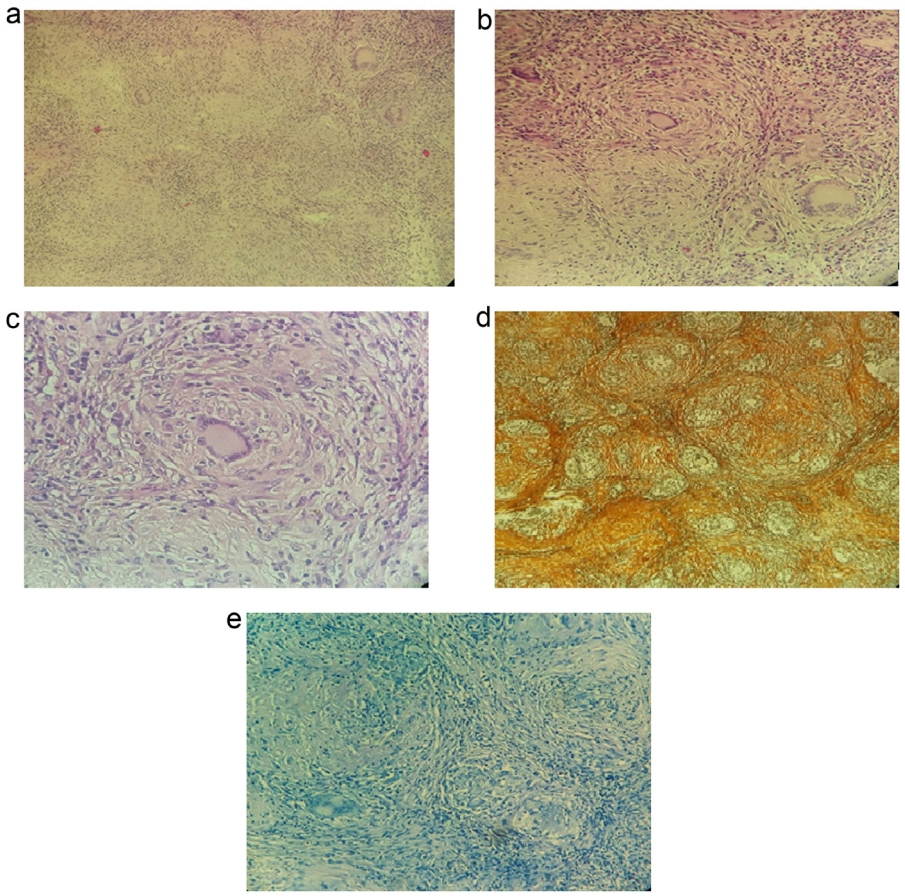

Fig. 2 – (a) Numerous non-caseating granulomas (Hematoxylin-Eosin stain, Ob. 40×). (b) Non-necrotizing granulomas composed of macrophages, epithelioid cells and giant cells, focally surrounded by lymphocytes (H&E Ob. 100×). (c) Giant cell displaying numerous nuclei arranged in horseshoe pattern (H&E, Ob. 200×). (d) Gömori stain showing collagen reticulin fibers (Ob 40×). (e) No acid-fast bacilli were detected on Ziehl-Neelsen staining (Ob. 100×).

rheumatologic conditions. The tumor markers, CA-125 and CA-153 were mildly elevated (220.9 UI/ml and 51.23 UI/ml respectively). Liver and kidney function tests were normal except for a mild reduction of the plasma protein level. Peritoneal fluid analysis revealed a transudative ascites with a high lymphocytes count (polymorphonucleocytes of 35%, big lymphocytes of 18%, medium lymphocytes of 24% and small lymphocytes of 23%) as well as a higher level of low density lipids (383 U/L), a higher protein gradient (5.9 g/dl) and a normal glucose level (85 mg/dl). Ascitic fluid adenosine deaminase level (ADA) was almost double the normal value (56.8 U/L), and IgM for *Chlamydia pneumonia* and *Mycoplasma pneumonia* were negative (ELISA). The quantiferon-TB test was positive (3.16 IU/ml). The chest X-rays showed minimal pleurisy, but no pulmonary TB signs. A contrast-enhanced nuclear magnetic resonance imaging of the abdomen and pelvis was performed and revealed moderate to high ascites but no abdominal or pelvic masses. The parietal and visceral peritoneum was noted to be thickened (3–4 mm) with a granulomatous hyposignal in T2 and contrast positive. The differential diagnosis at this stage included PTB, sarcoidosis and neoplasia (mesothelioma). The patient was started on the standard anti-tuberculosis regimens for one week and a laparoscopy was performed. The intraoperative findings noted 2200 ml ascites and multiple nodular deposits on both the visceral and parietal peritoneum (Fig. 1a–d). Biopsy specimens revealed granulomatous inflammation with caseous necrosis compatible with TB infection (Fig. 2a–e). The diagnosis of peritoneal TB was confirmed by TB genome identification in the biopsy specimen. There were no other sites of TB involvement. On the standard anti-tuberculosis treatment the patients had complete clinical recovery.

3. Discussions

As Romania has the highest incidence of TB in the European Union,[4] a high index of suspicion for unusual locations of TB infectious process has to be taken into account. Extrapulmonary TB represents 11.3%[5] and the most frequent localizations include nodal, genitourinary, bone and joint, miliary, meningeal and gastrointestinal tract. Moreover, clinical presentation of PTB is non-specific making the preliminary workup very challenging. Ascites has been reported to be the most frequent presenting sign in PTB (in 95.2% of the affected patients) followed by fever and night sweats (53.8%), anorexia (46.9%), weight loss (44.1%) and abdominal pain (35.9%).[6] However these symptoms are unspecific and ascitic fluid analysis is not pathognomonic. Although in our case ascites associated with high levels of tumor markers (CA 125 and CA 153), raised the suspicion of ovarian carcinomatosis,[1,7] quantiferon-TB test positive brought into discussion PTB, preventing unnecessary hysterectomy with bilateral anexectomy at a young nulliparous subject. Peritoneal biopsy taken either by laparoscopy or laparotomy, represent the gold standard for the correct diagnosis of PTB.[8,9]

In conclusion, our case emphasizes the diagnostic challenge of PTB as it is a forgotten localization. A high index of suspicion is required in young patients presenting with ascites residing in endemic areas. Therefore, PTB should be taken into consideration as differential diagnosis in young females in order to avoid further complications or surgery that could lead to infertility. Thus laparoscopy approach for biopsy is essential for diagnosis and management.

Conflicts of interest

The authors have none to declare.

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Case Report

Tuberculosis of knee joint mimicking giant cell tumor – A case report

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ABSTRACT

A 50-year-old woman presented with pain, swelling, and reduced range of motion of right knee joint since one year. Radiograph of knee joint revealed eccentric, expansile, geographic lytic lesion on the medial epiphyseal region of tibia mimicking giant cell tumor (GCT). She underwent minimally invasive biopsy, which was positive for acid-fast bacilli and revealed necrotizing chronic granulomatous lesion, diagnostic of tuberculosis (TB). This case emphasizes to consider tuberculosis arthritis as differential diagnosis when a case of destructive giant cell tumor is encountered.

1. Introduction

Osteoarticular tuberculosis (TB) is commonly encountered infection in our country. They can affect any joints but most commonly affect spine, weight bearing joints and characteristically monoarticular.[1] They have broad spectrum of presentation and non-specific radiographic features. The TB can spread to joints by hematogenous dissemination through subsynovial vessels or indirectly from metaphysis in children and epiphysis in adults.[2] There are mimickers of other conditions like pyogenic arthrirtis, tumors of synovium and bone or inflammatory conditions.[3,4]

Informed consent – Patient was informed in her own language that her data will be published in a journal and her written consent was obtained. Ethical clearance also was obtained.

2. Case report

A 50-year-old female patient presented to our clinic, with insidious onset of pain, swelling of right knee joint since one year. She was unable to walk or stand and she had fixed flexion deformity of 45° and further flexion of 40° was present with pain. She had tenderness over medial knee joint line and medial condyle of tibia. Minimal synovial thickening with muscle wasting was noted. She had no other systemic affection. Her CRP was 8.40 (0.05–0.33) and ESR was 41 (0–20 mm/h). Her radiographs revealed eccentric, expansile, geographic type of lytic lesion was noted on the epiphysis of medial condyle of tibia mimicking giant cell tumor (Fig. 1). She underwent minimal invasive biopsy, which was positive for acid-fast bacilli and revealed necrotizing chronic granulomatous lesion favoring TB. She was not allowed to bear weight on the affected side for 6 months and following antitubercular

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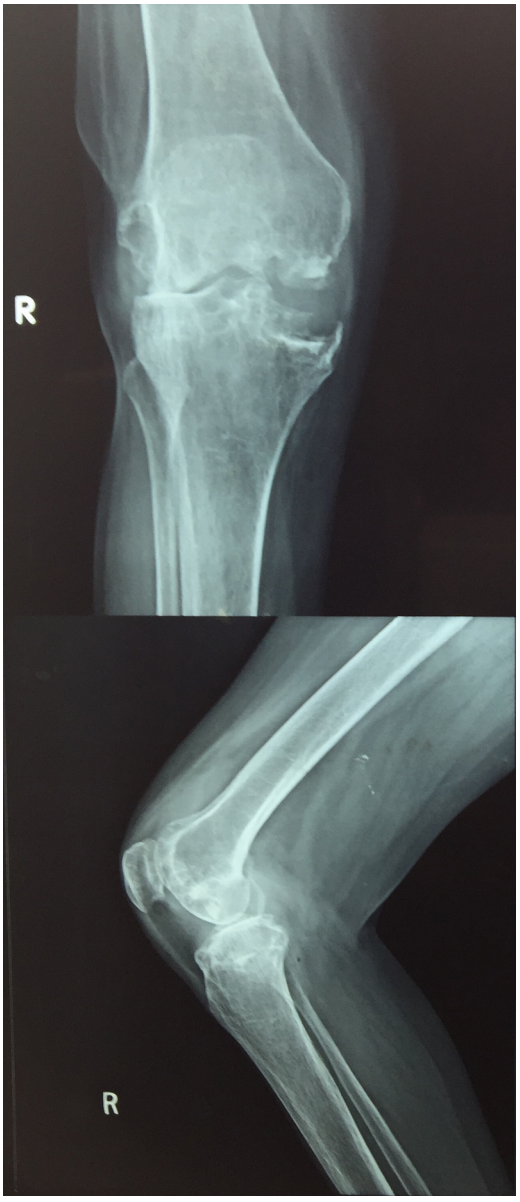

Fig. 1 – Plain radiograph of right knee joint – expansile, lytic, eccentric lesion located on medial aspect of epiphysis of tibia.

drugs was give for 1 year – Isoniazid 300 mg OD, Rifampicin 600 mg OD, Pyrazinamide 1500 mg OD, Ethambutol 1000 mg OD, and Pyridoxine 10 mg OD. Her symptoms subsided clinically and at 1 year follow up, she still had 20° fixed flexion deformity of knee, range of motion had improved to 90° and bony defect on medial condyle persisted. She is awaited for total knee replacement.

3. Discussion

Tuberculosis is most commonly encountered in underdeveloped and developing countries. There is always a delay in diagnosis of osteoarticular TB because of non specific symptoms and mimics other conditions.[5,6]

The classical radiological features of TB are juxta-articular osteopenia, joint space narrowing, and erosions.[7] Most common mimickers described are pigmented villonodular synovitis,[8] pyogenic arthritis, tumors and inflammatory conditions.[3,4]

The typical sites of occurrence of osteoclastoma are knee (50–65%), distal radius (10–12%) followed by sacrum and vertebrae. They are typically seen in adulthood between ages of 20–50 years. Characteristic radiographic features are, occurs close to closed growth plate, abuts articular surface, non-sclerotic margin and eccentric. Broader zone of transition is noted in aggressive GCT.[9]

In our case the radiograph lacked the features of typical TB and were in favor of GCT.

We like to conclude that tuberculosis of knee can also be considered as differential diagnosis for GCT. Joint TB should always be suspected in case of chronic monoarticular joint pain.

Conflicts of interest

The authors have none to declare.

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Case report

An unusual presentation of primary myelofibrosis

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ABSTRACT

Extramedullary hematopoisis (EMH) normally occurs in fetal life, but it is pathological in later life and most of the time because of underlying marrow diseases. Sometimes EMH tissue can present with large masses which can cause compressive and constitutional symptoms. They can be wrongly diagnosed as malignancy and pulmonary tuberculosis. Here in this case report we are reporting a case with mediastinal EMH because of underlying mylofibrosis.

1. Introduction

Extramedullary hematopoiesis (EMH) is a compensatory mechanism by which the body compensates for chronic deficient hematopoiesis in the bone marrow (BM) or increased destruction of erythrocytes and refers to deposits of erythroid precursors in regions other than the BM and peripheral blood.[1] A common example of EMH is ectopic erythropoiesis seen in liver or spleen stimulated by chronic hypoxia and increased erythropoietin production.[1]

Rarely EMH can present with posterior mediastinal mass and is frequently confused with other mediastinal tumors – benign or malignant.[2]

Mediastinal EMH is a very rare condition and only very few cases have been reported in literature.

Herein, we report a case presenting as a symptomatic paravertebral mediastinal mass diagnosed on computed tomography (CT) scan, which on histopathology turned out as an extramedullary hematopoietic mass secondary to the primary myelofibrosis.

2. Case report

A 45-year-old, non-smoker male walked into our outpatient department with complaints of dry cough, shortness of breath, which was insidious during onset and was gradually worsening, and loss of body weight (5 kg) and appetite for 4 months. There was no history of hemoptysis and fever.

The patient was evaluated for the above complaints by a local physician one year ago and was diagnosed with pulmonary

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tuberculosis. The patient was treated for the same for 6 months. Since the symptoms kept worsening, the patient reported to our institute for further evaluation and management.

On examination, he was severely anemic at the time of presentation, and he had splenomegaly without associated hepatomegaly and lymphadenopathy.

Chest X-ray showed cardiomegaly with mediastinal widening and paravertebral masses on both sides (Fig. 1a).

Contrast enhanced computed tomography (CECT) chest showed well-defined minimally enhancing, lobulated paravertebral soft tissue lesions in posterior mediastinum bilaterally (Fig. 1b). No obvious bony destruction or intraspinal extension was delineated. No vascular compromise was noted. Multiple hypodense faintly enhancing lesions were seen in the spleen (Fig. 1c). CT-guided biopsy from the posterior mediastinal mass revealed EMH (Fig. 2a).

Laboratory investigations revealed hemoglobin level was 5.3 g%, total leukocyte count (TLC) was 5100/mm^3, platelet count was 2.4 lakh/mm^3, and erythrocyte sedimentation rate (ESR) was 160 mm/h.

BM evaluation revealed hypocellular marrow with scanty hematopoietic cells consistent with myelofibrosis (Fig. 2b). Hence, the diagnosis of primary myelofibrosis (*Intermediate Risk-1*) with EMH was made. Breakpoint cluster region – Abelson was undetectable and *jak2* was found to be mutated for *V617F* mutation.

After confirming the diagnosis and discussing the case in our specialty board, the patient was started on Lenalidomide therapy (Tab. Lenalidomide 5 mg once a day) and was reassessed after 3 months. No toxicity was observed with Lenalidomide.

Repeat CECT chest (Fig. 1d) showed around 50% reduction in the size of the mediastinal masses. His hemoglobin levels improved to 11 g%. The patient continued the same drug therapy and was asymptomatic on clinical follow-up for a period of two years.

3. Discussion

EMH is formation of blood cells outside the medullary spaces of the BM and can be microscopic or can present as a mass lesion, as noted in our case.[3]

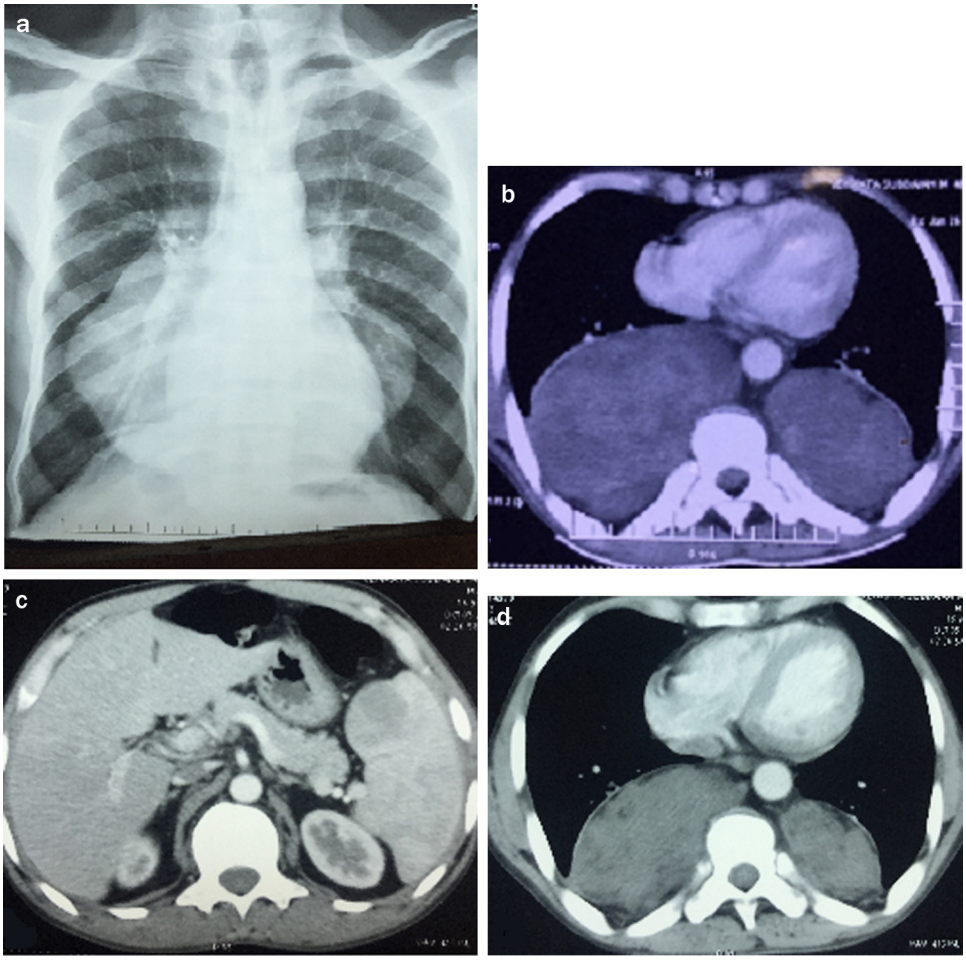

Fig. 1 – (a) Chest X-ray PA view showing cardiomegaly with mediastinal widening and paravertebral masses on both sides. (b) CECT chest showing large well-circumscribed inhomogenously enhancing bilateral paravertebral soft tissue masses with no underlying bony involvement. (c) CECT abdomen showing hypodense nodular lesions in the spleen. (d) CECT chest post-treatment showing significant reduction in the size of the bilateral paravertebral masses.

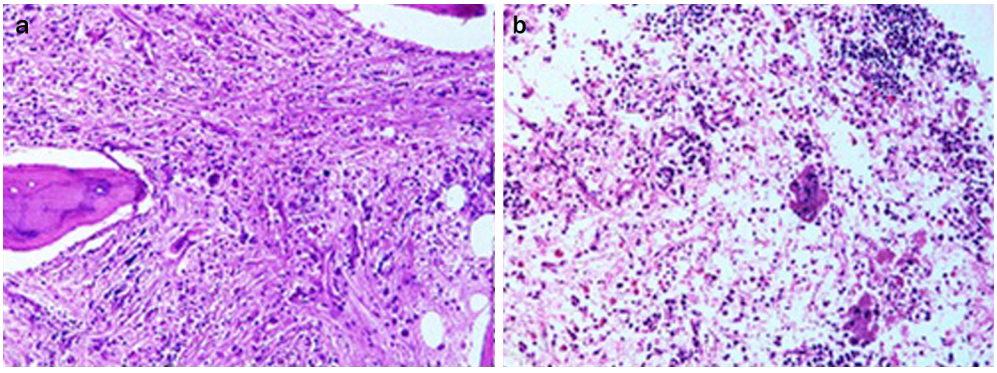

Fig. 2 – (a) Photomicrograph of bone marrow trephine biopsy showing increased cellularity, increased reticulum fibrosis, and granulocytic and atypical megakaryocytic proliferation (H&E, 100×). (b) Photomicrograph of biopsy from mediastinal mass showing extramedullary hematopoiesis (H&E, 100×).

To explain the pathogenesis, 4 major theories are documented, which involve changes in stem cells and/or their surrounding environment: (i) severe marrow failure; (ii) myelostimulation; (iii) tissue inflammation, injury, and repair; and (iv) abnormal production of chemokines.[4]

There is cross talk between hematopoietic stem cells (HSCs) and their niches (found in varies part of the body) to maintain steady-state hematopoiesis in the marrow. However, in pathological situations, hematopoiesis occurs in these niches where microenvironments are still poorly defined and can occur in any organ.[5]

Spleen and liver are the most common sites for EMH. Other less common sites include the lymph nodes, retroperitoneum, spinal cord, kidneys, adrenal glands, gastrointestinal tract, lung, breasts, and very rarely the posterior mediastinum, where they form large paravertebral masses and produce constitutional and compressive symptoms because of mechanical compression.[6]

EMH can be active or passive. In fetal life, yolk sac is the place where hematopoiesis starts first (YS) followed by aorta–gonads–mesonephros (AGM), placenta, liver, and spleen before lodgment in the BM – this is an example of active EMH.[2]

In contrast, the EMH can develop after marrow failure – in liver, spleen, and other peripheral organs, and this secondary activation of hematopoiesis is called passive form of EMH.[7] Secondary EMH is seen in patients with myelofibrosis, myeloproliferative disorders, and hemoglobinopathies.[2] Similar to our case, EMH developed because of underlying primary myelofibrosis and chronic anemia.

Primary myelofibrosis is classified under Philadelphia-negative chronic myeloproliferative disorders.[8] It is characterized by displacement and mobilization of stem and progenitor cells. These displaced cells occupy different organs, especially liver and spleen, as alternative sites of hematopoiesis. Simultaneously, the BM stem cell niche is altered and it no longer supports normal hematopoiesis.[9]

Another important feature of primary myelofibrosis is production of inflammatory cytokines such as stromal cell derived factor-1, hepatocyte growth factor, interleukin 6, interleukin 8, stem cell factor, and vascular endothelia growth factor (VEGF), and also factors that promote fibrosis and angiogenesis (β-fibroblast growth factor, transforming growth factor-β, platlet factor 4, VEGF, etc.). These cytokines are produced mainly by hematopoietic cells and induce changes in the medullary and extramedullary niches.[10]

Paravertebral EMH is commonly noted in the lower paravertebral regions and are usually multiple and bilateral. Destruction of adjacent ribs and vertebrae is not seen. Similar to this case, there was a large mass with compressive symptoms without local destruction or infiltration.

Pathologically, the masses are soft, deep red, and look similar to splenic tissue on the cut surface. Histologically, they are composed of hematopoietic cells mixed with adipose tissue.[11]

4. Conclusion

Mediastinal EMH represents a rare phenomenon associated with several hematological disorders. This diagnosis should be kept in mind in cases of posterior mediastinal masses in a patient with unexplained anemia and respiratory symptoms in order to avoid surgical interventions.

More research is needed to discover useful strategies for controlling unwanted EMH and chronic inflammation.

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Conflicts of interest

The authors have none to declare.

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Case report

Tubercular biliary hilar stricture: A rare case report

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ABSTRACT

Localized hepatic tuberculosis (TB) with or without bile duct involvement is a rare form of hepatobiliary tuberculosis; accounting for less than 1% of all tuberculous infections. We report an uncommon case of cholestatic jaundice with disseminated TB in an immunocompetent male who presented with simultaneous involvement of liver and biliary system.

1. Introduction

Hepatic involvement by tuberculosis (TB) is mainly of 3 types.[1] Commoner ones being generalized military TB (15–80% cases) and tuberculous hepatitis with granuloma formation. Third is a rare form of localized hepatic TB with or without bile duct involvement. This form of hepatobiliary tuberculosis (HTB) accounts for less than 1% of all tuberculous infections.[2] We report an uncommon case of cholestatic jaundice with disseminated TB in an immunocompetent male who presented with simultaneous involvement of liver and biliary system.

2. Case report

A 22-year-old male symptomatic since 3 months with low grade fever, anorexia and significant weight loss; presented with painless cholestatic jaundice without cholangitis for last 1 month. Physical examination revealed icterus, hepatomegaly with cervical and axillary lymphadenopathy.

On investigations, hemoglobin was 11.8 g/dl, total leukocyte count was 5400/cumm, erythrocyte sedimentation rate 35 mm/h, serum bilirubin 4.1 mg/dl, direct bilirubin 2.7 mg/dl, aspartate transaminase – 98 units/l, alanine transaminase – 104 units/l, serum alkaline phosphatase – 777 IU/l, serology for hepatitis B, hepatitis C and human immunodeficiency virus were negative and chest X-ray showed inhomogenous bilateral upper lung zones opacities which were later confirmed as active pulmonary TB on contrast enhanced CT thorax. Ultrasonography (USG) abdomen showed hepatomegaly with multiple small ill-defined hypoechoic areas and dilated intrahepatic biliary radicles. Magnetic resonance cholangiography (MRCP) (Fig. 2) was suggestive of cut off at the level of confluence of left and right hepatic bile duct with proximal biliary dilatation. Patient underwent fine needle aspiration (FNA) from cervical lymphnodes, which showed granuloma with langheran giant cells. USG guided FNA from

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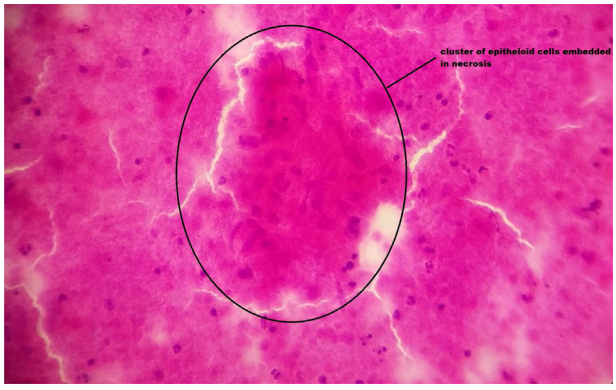

Fig. 1 – Fine needle aspiration cytology from liver lesion.

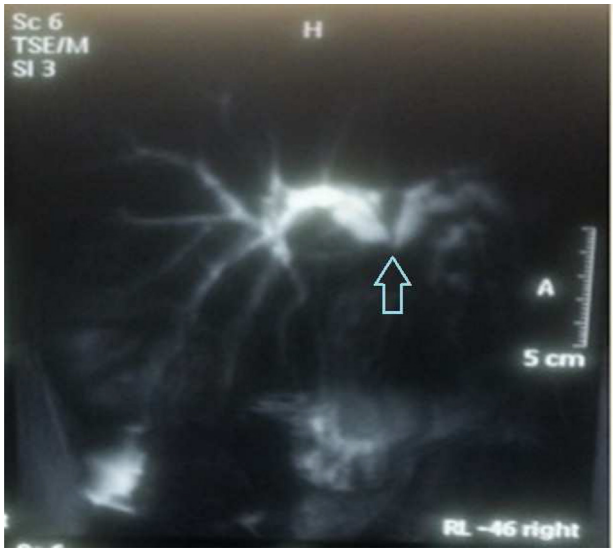

Fig. 2 – MRCP showing hilar stricture with proximal biliary radical dilatation.

liver lesions (Fig. 1) showed clusters of epitheloid cells with central caseating necrosis in the background of hepatocytes with acute inflammatory exudates. Patient was started on quadruple antitubercular therapy and after 8 weeks of follow up showed significant clinical and biochemical improvement

3. Discussion

Although hepatic involvement in pulmonary TB quite common; however biliary obstruction due to TB presenting as jaundice is very rare.[3–5] Essop et al. published a 6 year study of 96 patients out of which 10 patients had localized hepatobiliary tuberculosis.[6]

Biliary obstruction in TB patients can be due to either extrinsic lymph nodal compression or formation of biliary stricture. Former being much more common compared to later. Recently, Amrapurkar et al. published a case series of 242 TB patients out of which 15.7% had hepatobiliary tuberculosis.[7] In this study, approximately 5% cases had biliary obstruction secondary to lymph nodal compression while only 1.2% cases presented with tubercular biliary stricture. Similarly, 10-year study by Kok et al. described only four cases of biliary strictures due to TB.[8] Tubercular biliary stricture can involve any part of common bile duct but hilar strictures are most common.[9]

Our case was unique in respect that there was simultaneous involvement of liver in the form of tuberculomas and tubercular biliary stricture at the level of hilum with evidence of disseminated TB.

In most of the reported cases, the biliary stricture does not resolve with medical therapy alone and requires endoscopic intervention.[10,11] However in our case, patient had no evidence of cholangitis or intractable pruritis and hence no endoscopic intervention was done. Further, complete resolution of tubercular biliary stricture by quadruple treatment alone without surgery or biliary drainage procedure has also been described in published literature.[12,13] In our case, patient became asymptomatic with normal liver function test after 2 months of antitubercular treatment.

In conclusion, although most common cause of hilar biliary stricture is malignancy but in a country like ours, TB should be kept as a differential while evaluating a young patient especially with evidence of TB elsewhere.

Conflicts of interest

The authors have none to declare.

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Letter to the Editor

Daily regimens: Seeing beyond conventional DOTS

Dear Editor,

Tuberculosis (TB) related stigma is known since ages, and contributes to delay in seeking medical advice and non-adherence to prescribed treatment.[1,2] The issue has not been addressed satisfactorily, and its impact on final treatment outcomes continues.[2] A mere thought of reporting to the directly observed treatment short course (DOTS) centre for getting medications, on recommended days could be stressing, as is the 'unknown fear' of being recognized by someone known in the social circle. Data is accumulating highlighting the need to combat social stigma, and concentrate on mental health of TB patients.[3]

Adopting daily regimens for treating TB may mark a revolution in the history of TB.[4] It is expected to have a hidden but strong impact on adherence to treatment by reducing TB related stigma. A hallmark in the treatment of TB, the administration of DOTS has expanded its horizon in the new recommendations.[4] Direct observation of therapy by a treatment supporter close to patient's residence or even a family member will bring a dramatic change in the attitude of the society towards TB.[4] In India, with improvement in basic education levels, increased understanding of the disease, its transmission, prevention and treatment strategies is expected.[5] Age old taboos/notions about TB can now be openly discussed with the patients and family members and myths leading to stigma can be managed, if specifically targeted at.

Adopting a 'patient centred approach', the cornerstone of treatment of any disease, is a highly appreciable move.[4] Self realization on the part of the patient for his own treatment is very important, as he has to fight with the disease, problems which may be inadvertently associated with treatment and various psychosocial issues which may be encountered during timeline of management. A health care worker/physician can only assist the patient in management. If the patient is not convinced to take medications, any means of administering a prolonged treatment is bound to increase chances of non-adherence and end in failure. Besides, even in a compliant patient, because of his professional/family/societal obligations, it may not be feasible to go to the DOTS centre on the specified days. Compulsion to maintain the same station just to take medications might be too difficult for some patients. Latest recommendations had tried to address these small, intricate but important issues. Besides community and family-centred DOT, intelligent deployment of information communication technology (ICT) is expected to yield encouraging results, keeping the physician/health care worker and patient in a close unison.[4] This patient friendly approach will prevent the patient from missing work/daily wages.[3] This will add to the confidence in patients, family members and society, decrease humiliation and social stigma, thus addressing the psychosocial aspects silently. The disease will thus be managed in totality. Special concern will be given to each and every aspect of patient's problems, with immediate interventions, whenever required.

Everyone should unite hands and work in cohesion to reduce physical, social and mental sufferings related to TB and achieve a TB free India, TB free world, and thus end TB.

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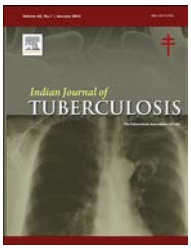

Abstracts

Microbiologic outcome of interventions against *Mycobacterium avium* complex pulmonary disease: A systematic review

Diel R, Nienhaus A, Ringshausen FC, Richter E, Welte T, Rabe KF, Loddenkemper R. *Chest*. 2018;153(4):888–921. https://doi.org/10.1016/j.chest.2018.01.024

Objective: Pulmonary disease (PD) caused by *Mycobacterium avium* complex (MAC) is increasing worldwide. We conducted a systematic review of studies that include microbiologic outcomes to evaluate current macrolide-based treatment regimens.

Methods: We searched literature published before April 2017 by using the MEDLINE, Cochrane, and Embase databases. Risk of bias in randomized trials was assessed using the Cochrane tool.

Results: We retrieved 333 citations and evaluated 42 studies including 2748 patients: 18 studies were retrospective chart reviews, 18 were prospective, and six were randomized. The weighted average proportion of sputum culture conversions in macrolide-containing regimens after subtracting posttreatment microbiologic recurrences was 52.3% (95%CI, 44.7–59.9%). Using the triple-drug regimens recommended by the American Thoracic Society (ATS) achieved treatment success in 61.4% (95%CI, 49.7–72.5%), which further increased to 65.7% (95%CI, 53.3–77.4%) when drugs were taken for at least 1 year by patients who were macrolide susceptible and had previously untreated MAC. The overall risk of bias was low in five of the six randomized trials. However, selective outcome reporting because of a posteriori exclusion of initially included patients (14.0%), uncompleted treatment (17.6%), and inconsistent use of outcome parameters (17 definitions of treatment success) hampered the comparison of nonrandomized trials.

Conclusions: To date, randomized studies on treatment outcome in patients with MAC PD are scarce. Long-term treatments with ATS-recommended regimens for patients who are macrolide susceptible are superior to other macrolide-based therapies. A standardized definition of treatment success and genotypic distinction between reinfection and relapse by means of pretreatment and posttreatment identification of MAC species in cases of microbiologic recurrences may help to optimize evaluation of treatment regimens in the future.

Conflicts of interest

The authors have none to declare.

https://doi.org/10.1016/j.ijtb.2018.05.003

Treatment outcomes and tolerability of the revised WHO anti-tuberculosis drug dosages for children

Nansumba M, Kumbakumba E, Orikiriza P, Bastard M, Mwanga JA, Boum Y, de Beaudrap P, Bonnet M. *Int J Tuberc Lung Dis*. 2017;22(2):151–7. https://doi.org/10.5588/ijtld.17.0535

Background: In 2010, the World Health Organization (WHO) revised the paediatric dosages of anti-tuberculosis drugs, increasing rifampicin to 15 mg/kg, isoniazid to 10 mg/kg and pyrazinamide to 35 mg/kg. We assessed treatment outcomes, safety and adherence among children treated with the new recommended dosages.

Methods: Prospective cohort of children started on anti-tuberculosis treatment in Uganda with 12 months of follow-up, including alanine aminotransferase (ALT) monitoring. Treatment intake was observed.

Results: Of 144 treated children, 81 were male (56.3%), 106 (73.6%) were aged <5 years, 30 (22%) had moderate to severe malnutrition and 48 (33.3%) had human immunodeficiency virus infection. Treatment outcomes were as follows: 117 (81.3%) successes, 3 (2.1%) failures, 4 (2.8%) lost to follow-up, 19 (13.2%) deaths and 1 (0.7%) transferred out. There was no relapse. Severe malnutrition (adjusted hazard ratio 8.76, 95% confidence interval [CI] 1.59–48.25) was the only predictor of death. Two serious adverse events were attributed to treatment: one case of increased ALT and one with peripheral neuropathy. Median ALT values at baseline and at weeks 2, 4 and 8 were respectively 24 (interquartile range [IQR] 16–39), 26 (IQR 18–38), 28 (IQR 21–40) and 27 (IQR 19–38) international units/l. Treatment adherence was above 85% on all visits.

Conclusion: We confirm the good tolerability of and adherence to the new treatment recommendations. The increased risk of fatal outcome among severely malnourished children requires attention.

Conflicts of interest

The authors have none to declare.

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Did diabetes mellitus affect treatment outcome in drug-resistant tuberculosis patients in Pakistan from 2010 to 2014?

Latif A, Ghafoor A, Wali A, Fatima R, ul-Haq M, Yaqoob A, Abdullah Z, Najmi H, Khan NM. *Public Health Action*. 8(1):14–9. https://doi.org/10.5588/pha.17.0098

Settings: All hospitals managing drug-resistant tuberculosis (DR-TB) according to national guidelines in Pakistan.
Objectives: To assess the effect of diabetes mellitus (DM) and factors associated with unfavourable outcomes in DR-TB.
Methods: A cross-sectional study based on a retrospective record review of patients enrolled on DR-TB treatment from 2010 to 2014 in Pakistan. DR-TB data reported to Pakistan's National TB Control Programme on a monthly basis were used for the study.
Result: Among 5811 patients enrolled on second-line drugs, 8.8% had DM. Overall, 68.9% had favourable outcomes. No association was found between DM and DR-TB treatment outcomes (risk ratio 0.90, 95%CI 0.74–1.05). Unfavourable outcomes were more frequent among DR-TB patients with human immunodeficiency virus (HIV) co-infection (OR 11.58, 95%CI 2.20–60.72), extensively drug-resistant TB patients (OR 5.36, 95%CI 1.00–28.72), patients with exposure to both first-line and second-line anti-tuberculosis drugs (OR 2.45, 95%CI 1.21–4.97) and those with a previous history of treatment in the private sector (OR 1.53, 95%CI 1.16–2.02).
Conclusion: Although there were limitations to correctly measuring DM and its management, DM appears not to be a risk factor for unfavourable outcomes in DR-TB patients in our study. DR-TB and HIV co-infection, second-line drug resistance and history of treatment in the private sector were nevertheless more frequently associated with adverse outcomes.

Conflicts of interest

The authors have none to declare.

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Normalised quantitative polymerase chain reaction for diagnosis of tuberculosis-associated uveitis

Barik MR, Rath S, Modi R, Rana R, Reddy MM, Basu S. *Tuberculosis*. 2018;110. https://doi.org/10.1016/j.tube.2018.03.005

Polymerase chain reaction (PCR)-based diagnosis of tuberculosis-associated uveitis (TBU) in TB-endemic countries is challenging due to likelihood of latent mycobacterial infection in both immune and non-immune cells. In this study, we investigated normalised quantitative PCR (nqPCR) in ocular fluids (aqueous/vitreous) for diagnosis of TBU in a TB-endemic population. Mycobacterial copy numbers (*mpb64* gene) were normalised to host genome copy numbers (*RNAse P* RNA component H1 [*RPPH1*] gene) in TBU ($n = 16$) and control ($n = 13$) samples (discovery cohort). The *mpb64*:*RPPH1* ratios (normalised value) from each TBU and control sample were tested against the current reference standard, i.e. clinically-diagnosed TBU, to generate receiver operating characteristic (ROC) curves. The optimum cut-off value of *mpb64*:*RPPH1* ratio (0.011) for diagnosing TBU was identified from the highest Youden index. This cut-off value was then tested in a different cohort of TBU and controls (validation cohort, 20 cases and 18 controls), where it yielded specificity, sensitivity and diagnostic accuracy of 94.4%, 85.0%, and 89.4% respectively. The above values for conventional quantitative PCR (≥1 copy of *mpb64* per reaction) were 61.1%, 90.0%, and 74.3% respectively. Normalisation markedly improved the specificity and diagnostic accuracy of quantitative PCR for diagnosis of TBU.

Conflicts of interest

The authors have none to declare.

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Impact of switching from Caucasian to Indian reference equations for spirometry interpretation

Chhabra SK, Madan M. *Int J Tuberc Lung Dis*. 2017;22(3):342–8. https://doi.org/10.5588/ijtld.16.0646

Background: In the absence of ethnically appropriate prediction equations, spirometry data in Indian subjects are often interpreted using equations for other ethnic populations.
Objectives: To evaluate the impact of switching from Caucasian (National Health and Nutrition Examination Survey III [NHANES III] and Global Lung Function Initiative [GLI]) equations to the recently published North Indian equations on spirometric interpretation, and to examine the suitability of GLI-Mixed equations for this population.
Materials and methods: Spirometry data on 12 323 North Indian patients were analysed using the North Indian equations as well as NHANES III, GLI-Caucasian and GLI-Mixed equations. Abnormalities and ventilatory patterns were categorised and agreement in interpretation was evaluated.
Results: The NHANES III and GLI-Caucasian equations and, to a lesser extent, the GLI-Mixed equations, predicted higher values and labelled more measurements as abnormal. In up to one third of the patients, these differed from Indian equations in the categorisation of ventilatory patterns, with more patients classified as having restrictive and mixed disease.
Conclusion: The NHANES III and GLI-Caucasian equations substantially overdiagnose abnormalities and misclassify ventilatory patterns on spirometry in Indian patients. Such errors of interpretation, although less common with the GLI-Mixed equations, remain substantial and are clinically unacceptable. A switch to Indian equations will have a major impact on interpretation.

Conflicts of interest

The authors have none to declare.

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The global tuberculosis epidemic and progress in care, prevention, and research: An overview in year 3 of the End TB era

Floyd K, Glaziou P, Zumla A, Raviglione M. *Lancet Respir Med*. 2018;6(4):299–314. https://doi.org/10.1016/S2213-2600(18)30057-2

Tuberculosis is the number one cause of death from infectious disease globally and drug-resistant forms of the disease are a

major risk to global health security. On the occasion of World Tuberculosis Day (March 24, 2018), we provide an up-to-date review of the status of the tuberculosis epidemic, recommended diagnostics, drug treatments and vaccines, progress in delivery of care and prevention, progress in research and development, and actions needed to accelerate progress. This Review is presented in the context of the UN Sustainable Development Goals and WHO's End TB Strategy, which share the aim of ending the global tuberculosis epidemic. In 2016, globally there were an estimated 10.4 million new cases of tuberculosis, and 600 000 new cases with resistance to rifampicin (the most powerful first-line drug). All countries and age groups are affected by tuberculosis, but most cases (90%) in 2016 were in adults, and almost two-thirds were accounted for by seven countries: India, Indonesia, China, Philippines, Pakistan, South Africa, and Nigeria. The sex ratio (male to female) was 1.9 and 10% of patients with newly diagnosed tuberculosis were also HIV-positive. There were 1.7 million deaths from tuberculosis in 2016, including 0.4 million deaths among people co-infected with HIV (officially classified as deaths caused by HIV/AIDS). Progress in care and prevention means that the global mortality rate (deaths per 100 000 people per year) is decreasing by 3.4% per year and incidence (new cases per 100 000 people per year) is decreasing by 1.9% per year. From 2000 to 2016, the annual global number of tuberculosis deaths decreased by 24% and the mortality rate declined by 37%. Worldwide, an estimated 53 million deaths were averted through successful treatment. Nonetheless, major gaps in care and prevention remain. For example, the 6.3 million new cases of tuberculosis reported globally in 2016 represented only 61% of the estimated incidence; only one in five of the estimated number of people with drug-resistant tuberculosis was enrolled in treatment. Pipelines for new diagnostics, drugs, and vaccines are progressing, but slowly. Actions needed to accelerate progress towards global milestones and targets for reductions in the burden of tuberculosis disease set for 2020, 2025, 2030, and 2035 include closing coverage gaps in testing, reporting of cases, and overall access to health care, especially in countries that account for the largest share of the global gap; multisectoral efforts to reduce prevalence of major risk factors for infection and disease; and increased investment in research and development.

Conflicts of interest

The authors have none to declare.

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A high throughput methodology for susceptibility testing of *Mycobacterium tuberculosis* isolates

Rampersad T, Makume M, Sobia P, Willem Sturm A. *J Microbiol Methods*. 2018;146:64–7. https://doi.org/10.1016/j.mimet.2018.02.001

MICs for 11 anti-TB drugs with *Mycobacterium tuberculosis* isolates were obtained by means of agar dilution with multi-point inoculation. The results were compared with classic agar dilution and the MTT assay. The multi-point inoculation method was reproducible with all drugs and correlated with classic agar dilution and MTT assay. This methodology can be used for routine breakpoint drug susceptibility testing (DST) and for MIC determination.

Conflicts of interest

The authors have none to declare.

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Diagnostic accuracy of GenoType® MTBDR*sl* VER 2.0 in detecting second-line drug resistance to *M. tuberculosis*

Yadav R, Saini A, Kaur P, Behera D, Sethi S. *Int J Tuberc Lung Dis*. 2017;22(4):419–24. https://doi.org/10.5588/ijtld.17.0663

Setting: A tertiary care hospital in North India.

Objective: To evaluate the GenoType® MTBDR*sl* VER 2.0 assay for rapid diagnosis of second-line drug resistance to *Mycobacterium tuberculosis*.

Design: The MTBDR*sl* VER 2.0 assay was performed on 431 multidrug-resistant *M. tuberculosis* clinical isolates and specimens. The results were compared with phenotypic drug susceptibility testing (DST) and DNA sequencing. Molecular characterisation of drug resistance using DNA sequencing was performed for *gyr*A, *gyr*B, *rrs* and *eis*.

Results: Of the 415 isolates, respectively 176 (42.4%) and 40 (9.6%) were resistant to levofloxacin (LVX) and kanamycin (KM). The sensitivity and specificity of MTBDR*sl* VER 2.0 compared with phenotypic DST in detecting LVX resistance were respectively 97.2% (95%CI 93.5–99.1) and 99.1% (95%CI 97–99.9), and for KM resistance they were respectively 92.5% (95%CI 79.6–98.4) and 99.5% (95%CI 98.1–99.9).

Conclusion: The MTBDR*sl* VER 2.0 assay showed very high sensitivity and specificity for the detection of second-line drug resistance, suggesting it has potential for the rapid, early detection of such cases.

Conflicts of interest

The authors have none to declare.

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Outcomes of HIV-infected versus HIV-non-infected patients treated for drug-resistance tuberculosis: Multicenter cohort study

Bastard M, Sanchez-Padilla E, du Cros P, Khamraev AK, Parpieva N, Tillyashaykov M, Hayrapetyan A, Kimenye K, Khurkhumal S, Dlamini T, Perez SF, Telnov A, Hewison C, Varaine F, Bonnet M. *Plos One*. 2018. https://doi.org/10.1371/journal.pone.0193491

Background: The emergence of resistance to anti-tuberculosis (DR-TB) drugs and the HIV epidemic represent a serious threat for reducing the global burden of TB. Although data on HIV-negative DR-TB treatment outcomes are well published, few data on DR-TB outcomes among HIV co-infected people is available despite the great public health importance.

Methods: We retrospectively reported and compared the DR-TB treatment outcomes of HIV-positive and HIV-negative patients treated with an individualized regimen based on WHO guidelines in seven countries: Abkhazia, Armenia, Colombia, Kenya, Kyrgyzstan, Swaziland and Uzbekistan.

Results: Of the 1369 patients started DRTB treatment, 809 (59.1%) were multi-drug resistant (MDR-TB) and 418 (30.5%) were HIV-positive. HIV-positive patients were mainly from African countries (90.1%) while HIV-negative originated from Former Soviet Union (FSU) countries. Despite a higher case fatality rate (19.0% versus 9.4%), HIV-positive MDR-TB patients had a 10% higher success rate than HIV-negative patients (64.0% versus 53.2%, $p = 0.007$). No difference in treatment success was found among polydrug-resistant (PDR-TB) patients. Overall, lost to follow-up rate was much higher among HIV-negative (22.0% versus 8.4%). Older age and not receiving ART were the only factors associated with unfavorable treatment outcome among HIV-positive patients.
Conclusions: As already known for HIV-negative patients, success rate of DR-TB HIV-positive patients remains low and requires more effective DR-TB regimen using new drugs also suitable to HIV-infected patients on ART. The study also confirms the need of ART introduction in HIV co-infected patients.

Conflicts of interest

The authors have none to declare.

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Effectiveness of WHO's pragmatic screening algorithm for child contacts of tuberculosis cases in resource-constrained settings: A prospective cohort study in Uganda

Martinez L, Shen Y, Handel A, Chakraburty S, Stein CM, Malone LL, Henry Boom W, Quinn FD, Joloba ML, Whalen CC, Zalwango S. *Lancet Respir Med*. 2018;6(4):276–86. https://doi.org/10.1016/S2213-2600(17)30497-6
Background: Tuberculosis is a leading cause of global childhood mortality; however, interventions to detect undiagnosed tuberculosis in children are underused. Child contact tracing has been widely recommended but poorly implemented in resource-constrained settings. WHO has proposed a pragmatic screening approach for managing child contacts. We assessed the effectiveness of this screening approach and alternative symptom-based algorithms in identifying secondary tuberculosis in a prospectively followed cohort of Ugandan child contacts.
Methods: We identified index patients aged at least 18 years with microbiologically confirmed pulmonary tuberculosis at Old Mulago Hospital (Kampala, Uganda) between October 1, 1995, and December 31, 2008. Households of index patients were visited by fieldworkers within 2 weeks of diagnosis. Coprevalent and incident tuberculosis were assessed in household contacts through clinical, radiographical, and microbiological examinations for 2 years. Disease rates were compared among children younger than 16 years with and without symptoms included in the WHO pragmatic guideline (presence of haemoptysis, fever, chronic cough, weight loss, night sweats, and poor appetite). Symptoms could be of any duration, except cough (>21 days) and fever (>14 days). A modified WHO decision-tree designed to detect high-risk asymptomatic child contacts was also assessed, in which all asymptomatic contacts were classified as high risk (children younger than 3 years or immunocompromised [HIV-infected]) or low risk (aged 3 years or older and immunocompetent [HIV-negative]). We also assessed a more restrictive algorithm (i.e., assessing only children with presence of chronic cough and one other tuberculosis-related symptom).
Findings: Of 1718 household child contacts, 126 (7%) had coprevalent tuberculosis and 24 (1%) developed incident tuberculosis, diagnosed over the 2-year study period. Of these 150 cases of tuberculosis, 95 (63%) were microbiologically confirmed with a positive sputum culture. Using the WHO approach, 364 (21%) of 1718 child contacts had at least one tuberculosis-related symptom and 85 (23%) were identified as having coprevalent tuberculosis, 67% of all coprevalent cases detected (diagnostic odds ratio 9.8, 95%CI 6.8–14.5; $p < 0.0001$). 1354 (79%) of 1718 child contacts had no symptoms, of whom 41 (3%) had coprevalent tuberculosis. The WHO approach was effective in contacts younger than 5 years: 70 (33%) of 211 symptomatic contacts had coprevalent disease compared with 23 (6%) of 367 asymptomatic contacts ($p < 0.0001$). This approach was also effective in contacts aged 5 years and older: 15 (10%) of 153 symptomatic contacts had coprevalent disease compared with 18 (2%) of 987 asymptomatic contacts ($p < 0.0001$). More coprevalent disease was detected in child contacts recommended for screening when the study population was restricted by HIV-serostatus (11 [48%] of 23 symptomatic HIV-seropositive child contacts vs two [7%] of 31 asymptomatic HIV-seropositive child contacts) or to only culture-confirmed cases (47 [13%] culture confirmed cases of 364 symptomatic child contacts vs 29 [2%] culture confirmed cases of 1354 asymptomatic child contacts). In the modified algorithm, high-risk asymptomatic child contacts were at increased risk for coprevalent disease vs low-risk asymptomatic contacts (14 [6%] of 224 vs 27 [2%] of 1130; $p = 0.0021$). The presence of tuberculosis infection did not predict incident disease in either symptomatic or asymptomatic child contacts: in symptomatic contacts, eight (5%) of 169 infected contacts and six (5%) of 111 uninfected contacts developed incident tuberculosis ($p = 0.80$). Among asymptomatic contacts, incident tuberculosis occurred in six (<1%) of 795 contacts infected at baseline vs four (<1%) of 518 contacts uninfected at baseline, respectively ($p = 1.00$).
Interpretation: WHO's pragmatic, symptom-based algorithm was an effective case-finding tool, especially in children younger than 5 years. A modified decision-tree identified 6% of asymptomatic child contacts at high risk for subclinical disease. Increasing the feasibility of child-contact tracing using these approaches should be encouraged to decrease tuberculosis-related paediatric mortality in high-burden settings, but this should be partnered with increasing access to microbiological point-of-care testing.
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Conflicts of interest

The authors have none to declare.

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Involving private practitioners in the Indian tuberculosis programme: A randomised trial

Yellappa V, Battaglioli T, Gurum SK, Narayanan D, Van der Stuyft P. *Trop Med Int Health*. 2018;23(5):570–9. https://doi.org/10.1111/tmi.13053
Objectives: To assess a multicomponent intervention to improve private practitioners (PPs) involvement in referral of presumptive pulmonary TB (PTB) cases to the Revised National TB Control Programme (RNTCP) for sputum examination.

Methods: Randomised controlled trial. We randomly allocated all 189 eligible PPs in Tumkur city, South India, to intervention or control arm. The intervention, implemented between December 2014 and January 2016, included two sets of activities, one targeted at health system strengthening (building RNTCP staff capacity to collaborate with PPs, provision of feedback on referrals through SMS) and one targeted at intervention PPs (training in RNTCP, provision of referral pads and education materials and monthly visits to PPs by RNTCP staff). Crude and adjusted referral and PTB case-finding rate ratios were calculated with negative binomial regression.
Results: PPs referred 836 individuals (548 from intervention and 169 from control arm PPs) of whom 176 were diagnosed with bacteriologically confirmed PTB. The proportion (95% confidence interval) of referring PPs [0.59 (0.49, 0.68) *vs.* 0.42 (0.32, 0.52) in the intervention and control arm, respectively], mean referral rate per PP-year [(5.7 (3.8, 8.7) *vs.* 1.8 (1.2, 2.8)] and smear-positive PTB case-finding rate per PP-year [(1.5 (0.9, 2.2) *vs.* 0.6 (0.3, 0.9)] were significantly higher in the intervention than the control arm. Stratifying by qualification, a statistically significant difference in the above indicators remained only among GPs and internists. Overall, surgeons, paediatricians and gynaecologists referred few patients. PP referrals contributed to 20% of the sputum smear positive PTB cases detected by RNTCP in Tumkur city (14% were from intervention arm PPs).
Conclusions: We demonstrated the effectiveness of a health system-oriented intervention to improve PP's referrals of presumptive PTB cases to RNTCP.

Conflicts of interest

The authors have none to declare.

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