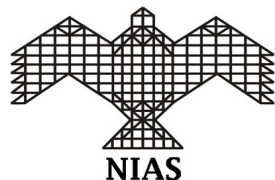# Tuberculosis
Newsletter

Brought to you by Open Source Pharma Foundation, National Institute of Advanced Studies and South East Asia Region of The UNION

OPEN SOURCE PHARMA FOUNDATION

NIAS

The Union

SEAR - UNION

TBINFO

Articles

Pathways to End Tuberculosis – Overcoming Challenges to Achieve Global Health Goals

Dr. Nibedita Rath, Scientific Director, Open Source Pharma Foundation, Bengaluru, India, Vice President, Union Lung Health, South East Asia Region, New Delhi, India

Dr. M Sai Baba, Honorary Visiting Professor, School of Natural Science and Engineering, National Institute of Advanced Studies, IISc Campus, Bengaluru, India

Tuberculosis (TB) remains a pressing global health challenge, with millions of people falling ill and losing their lives to this infectious disease each year. Despite significant progress in TB control efforts, there are still formidable challenges to be addressed on the path to achieving TB elimination by 2030. The articles presented shed light on the complexities of TB care, including issues such as stigma, mental health implications, drug resistance, underdiagnosis, and the impact of socioeconomic factors and the COVID-19 pandemic.

Dr. Bernd discusses the importance of addressing potential pitfalls and show-stoppers in drug development early on, utilizing a Target Product Profile (TPP) to navigate the regulatory landscape effectively. It emphasizes the reverse planning technique, starting with the end goal in mind: improving the accessibility of life-saving medications for patients worldwide. This approach can help developers mitigate risks and increase the chances of successful translation from bench to bedside.

Dr. Katiyar et al. have discussed the challenges posed by drug resistance, underdiagnosis, and treatment adherence, which underscore the need for innovative approaches in TB care. Rapid diagnostic tests, effective treatment regimens, and increased investment in research and development are essential to address these challenges. The articles emphasize the importance of a multi-sectoral approach involving all stakeholders, including governments, healthcare providers, community organizations, and individuals affected by TB, to collectively work towards the goal of TB elimination.

The efforts and achievements of Kerala in the fight against Tuberculosis (TB) are highly commendable and serve as a beacon of success in the global battle against this infectious disease. Dr. Nair has discussed Kerala's proactive approach towards TB elimination, involving innovative strategies, successful public-private partnerships, improved case management, and the rollout of TB preventive therapy, and how it has set a remarkable example for other states and countries to follow.

Dr. Arora and Dr. Chopra have discussed India's National Tuberculosis Elimination Program and how it has made significant strides in TB control efforts. However, challenges persist, particularly in addressing the socio-economic factors that influence TB outcomes. Political commitment, rapid molecular diagnostics, effective treatment regimens, and consistent supervision and monitoring are key to successful TB control programs. Collaboration and collective efforts are essential to overcome these challenges and achieve the TB elimination target by 2025.

The impact of the COVID-19 pandemic on TB control efforts serves as a stark reminder of the fragility of global health systems and the need for resilient and adaptable healthcare systems. As we continue to navigate the challenges posed by TB and other infectious diseases, it is imperative that we prioritize investments in public health infrastructure, research, and innovation to build a more resilient and prepared healthcare system for the future.

One of the key themes highlighted in these articles by Dr. Arora and Dr. Rath discussed the critical role of education and awareness in combating TB stigma and promoting mental health support for individuals affected by the disease. Efforts to dispel myths and misunderstandings surrounding TB, as well as the integration of mental health services into primary healthcare, can contribute significantly to improving treatment outcomes and reducing the burden of both TB and mental health conditions.

Dr. John discussed the economic burden of tuberculosis in India and how it is a pressing issue that disproportionately affects low-income households and tribal populations. The high out-of-pocket expenses and catastrophic costs associated with TB treatment contribute to financial strain and impoverishment among affected individuals. Initiatives like the AB-PMJAY scheme show promise in reducing these financial barriers, but more research is needed to assess their impact and effectiveness. A multi-faceted approach that addresses the economic challenges of TB is necessary to ensure access to affordable and quality care for all individuals in India.

In conclusion, the journey towards TB elimination is a complex and multifaceted one, requiring collaboration, innovation, and unwavering commitment from all stakeholders. By addressing the challenges outlined in these articles and working together towards our shared goal of ending TB, we can pave the way for a healthier and more equitable future for all.

From Innovation to Medication – Planning for Patients' Access to Life-saving Medication Right from the Beginning of Drug Development

Dr. Bernd Eisele, M.D., Freelance Consultant for Regulatory Authorities and University Hospitals in the Field of Infectious Diseases and Oncology, Former CEO VPM (Vaccine Project Management GmbH, Hannover, Germany)

Abstract

In the field of drug development, successful translation from bench to bedside is crucial for bringing new and innovative treatments to patients in need. However, many promising drug and vaccine candidates face pitfalls and show-stoppers that prevent them from reaching clinical application. By addressing potential issues early in the planning process and utilizing a Target Product Profile (TPP) as a roadmap, developers can navigate the regulatory landscape more effectively and increase the chances of success. This reverse planning technique, starting with the end goal in mind, can help to identify and mitigate risks throughout the development process, ultimately improving the accessibility of life-saving medications for patients worldwide.

Image Credit : The Blue Diamond Gallery

4

Introduction

Tuberculosis (TB) continues to be a major global health challenge. The development of multi-drug resistance contributes to the need for new and improved treatment options. Thus, current research activities which result in innovative treatment regimens and the repurposing of marketed antimicrobials and other drugs for TB are urgently needed [1,2]. Unfortunately, promising drug and vaccine candidates often face unforeseen pitfalls when translating them from bench to bedside. Many urgently needed and potentially life-saving medications never make it to clinical application.

The Target Product Profile outlines the desired 'profile' or characteristics of a target product that is aimed at a particular disease or disease [5]. TPPs state the intended use of a product, target populations and other desired attributes including safety and efficacy-related characteristics.

Pitfalls and show-stoppers

There are various reasons why promising drug and vaccine candidates fail on their way from bench to patients and people in need. When asking regulators from National Regulatory Authorities (NRAs) about the most often seen reasons for development failures, it turns out that very often candidates do not fail early but rather late in the translational development process. The main causes are as follows: in some cases, they are clinical development-related (e.g. fatal flaws in the design or inappropriate key efficacy endpoints in the pivotal phase III trial). In other cases, they are manufacturing process-related. But even though the show-stopper may come into effect late in the development process, the mistake that finally caused the failure might have been done already at the bench level. One well-known example of this is the use of fetal calf serum (FCS) when building up the master cell bank for a vaccine candidate. In principle there is nothing wrong with that, but, unfortunately, scientists doing lab research are often not aware that later in the development when permission for clinical trials in humans is applied for, the Regulatory Authority will request from the applicants that they have a certificate at hand that confirms that the FCS was sourced from a country that was TSE/BSE free [3]. Likewise critical is, if a biological (i.e. a vaccine or monoclonal antibody) needs a change in its composition or production process. This may happen if a replacement for the contract manufacturer or a supplier of an important ingredient, e.g. the adjuvant or a stabilizer, becomes necessary during the development process. Due to the fact that with biologicals the process as such is seen as the product, this change will severely jeopardize the marketability and hence the accessibility of the medication for patients and people in need. In other cases, the reasons for failure may be purely related to the marketed product. A drug may simply be too big to swallow or it may contain ingredients that are not acceptable for patients or societies. This would be the case e.g. in Muslim countries if a medicinal product contained porcine ingredients.

Reverse planning – starting with the goal in mind

To avoid these pitfalls and potential show-stoppers, it is advisable to address them early in the planning process, i.e. already when setting up the translational project development plan. Specifically, the plan should follow a label-oriented regulatory strategy that starts with the final product that will be suitable and available for patients in need. In this respect, defining the Target Product Profile (TPP) as a first step in the translational planning process is a straightforward starting point. Originally, the TPP was issued by the FDA as a guidance document for industry and review staff [4].

The Target Product Profile
The TPP outlines the desired 'profile' or characteristics of a target product that is aimed at a particular disease or disease [5]. TPPs state the intended use of a product, target populations and other desired attributes including safety and efficacy-related characteristics. In principle, the compilation of a TPP by the applicant is voluntary. However, I'd like to encourage any drug-developing party to design a TPP early in the planning process of the project. The reasons are as follows:

The benefit of a TPP
First and foremost, the TPP provides a valuable format for discussions between a sponsor and Regulatory Authorities (FDA/ EMA/ NRAs) that can be used throughout the entire drug development process as well as for post-marketing programs to pursue new indications. Second, a TPP embodies the notion of beginning the project planning with the goal in mind. Furthermore, it documents the specific studies that are planned to support the intended label. Ideally, the final version of the TPP will be identical to the annotated draft labelling submitted with a new Marketing Authorization Application.

In a nutshell, it can be stated that a TPP assists in a constructive dialogue with the Regulatory Authorities. The applicant learns the Regulatory position already during the early stages of development. The risk of unforeseen regulatory issues at the late stages of the product's life cycle is substantially reduced.

TPP - the starting point for the project planning process
Once the TPP has been designed and discussed with the Regulatory Authorities, it is advisable to use it as the starting point when the translational project plan gets designed. Subsequently, the design of the pivotal phase III trial will be drafted, with the intention that you, as the applicant will get market authorisation if the key efficacy endpoint is met and the investigational medicinal product (IMP) is found to be efficacious and safe. As the next step, the design of the phase II trial will be drafted that allow a transition into phase III, if successfully completed. Then the design of the phase I trial will be designed and subsequently the pre-clinical studies and experiments will pave the way to the phase I (first-in-human) trial.

The advantage of the reverse planning technique
Starting with the goal in mind and planning the developing process from patients' access to the marketed medication back to the bench of the laboratory will substantially reduce the risk that "unknown unknowns" will show up and become show-stoppers late in the development and life cycle of a drug. Therefore, the reverse-planning tool will increase the chances for drug candidates to successfully pass the translational R&D process and become accessible to patients and people in need.

Conclusion
Successful translation of promising drug and vaccine candidates from bench to bedside is essential for bringing innovative treatments to patients in need. By addressing potential pitfalls and show-stoppers early in the planning process and utilizing a Target Product Profile (TPP) as a roadmap, developers can navigate the regulatory landscape more effectively and increase the chances of success. The reverse planning technique, starting with the end goal in mind, can help identify and mitigate risks throughout the development process, ultimately improving the accessibility of life-saving medications for patients worldwide. By implementing the TPP as the starting point for project planning, developers can engage in constructive dialogues with Regulatory Authorities and reduce the risk of unforeseen regulatory issues late in the product's life cycle. This approach enhances the likelihood of successful market authorization and ensures that new treatments reach those who need them most.

References

1. N. Rath (2022) Yes! we can end TB. TB Newsletter December 2022 vol. 2 (1) p.3
2. M. Ramanna (2022). Anti-Tuberculosis League in Bombay City, 1912. TB Newsletter December 2022 v0l.2 (1) p.4
3. Jochems, C. E., van der Valk, J. B., Stafleu, F. R., & Baumans, V. (2002). The use of fetal bovine serum: ethical or scientific problem?. Alternatives to laboratory animals : ATLA, 30(2), 219–227. https://doi.org/10.1177/026119290203000208.
4. https://www.fda.gov.
5. https://www.who.int/observatories/global-observatory-on-health-research-and-development/analyses-and-syntheses/target-product-profile/who-target-product-profiles.

Shorter Drug-Resistant Tuberculosis Regimen: Implications with High Fluoroquinolone Resistant Tuberculosis and Weak Healthcare Systems

Dr. S. K. Katiyar, Formerly Professor and Head, Department of Tuberculosis & Respiratory Diseases, G.S.V.M. Medical College & C.S.J.M. University, Kanpur, Uttar Pradesh, India

Dr. Sandeep Katiyar, Pulmonologist, Apollo Spectra Hospital, Kanpur, Uttar Pradesh, India

Abstract

The prevalence of drug-resistant pulmonary tuberculosis (DR-TB) in India, particularly Multidrug-resistant and Rifampicin-resistant TB (MDR-TB and RR-TB), poses a significant challenge to the country's efforts in controlling and eliminating the disease. The high incidence of FLQ-R in MDR-TB cases further complicates management and leads to poor outcomes. The implementation of Shorter Course Chemotherapy (SCC) for MDR-TB, including all-oral regimens, faces uncertainties in the Indian context due to the high prevalence of FLQ-R, limited healthcare system capacities, and challenges in detecting resistance. The BPaLM regimen recommended by the WHO for MDR/RR-TB cases, including those with FLQ-R, may be a more suitable option for India. However, the feasibility and appropriateness of newer regimens in the Indian setting require careful evaluation, along with the development of tailored strategies and guidelines to optimize treatment outcomes and prevent the development of further drug resistance. Addressing these complexities is crucial for the success of India's National Tuberculosis Eradication Program and the overall management of DR-TB in the country.

Introduction

Drug-resistant pulmonary tuberculosis (DR-TB) poses a significant challenge to India's efforts to control and eliminate this longstanding disease, placing a substantial burden on the country's ongoing initiatives. In 2022, the World Health Organization (WHO) estimated 410,000 cases of Multidrug-resistant and Rifampicin-resistant TB (MDR-TB and RR-TB) worldwide, with India accounting for approximately 26% of these cases. Some important forms of drug resistance include Hr-TB, RR-TB, MDR-TB, Pre-XDR-TB, and XDR-TB. Prognosis in MDR and XDR TB cases is notably poor, ranging from 17–24% and 23–61%, respectively. The Pre-XDR-TB is new addition which includes MDR-TB with additional fluoroquinolone resistance (FLQ-R). The pivotal role of FLQ-R in all these cases is a major factor contributing to their bleak prognosis [1].

The prevalence of MDR-TB in India varies from 2.4% to 5.6% in newly diagnosed cases and 11.6% to 35.8% in previously treated cases of tuberculosis [2-6]. Managing these cases is crucial, not only because they are challenging to treat, but also because they pose a significant infectious risk to their contacts, often leading to primary MDR-TB. These cases also remain infectious for longer periods. In the current era, diagnosing DR-TB is not enough; identifying resistance patterns through drug susceptibility testing (DST) and tailoring specific treatments are equally essential. This approach yields better results and prevents the progression or acceleration of drug resistance. However, treating these cases requires extended regimens with challenges of increased toxicity, difficulty in tolerance, high costs, and poor therapy outcomes. Addressing these complexities is vital in India for the success of the ambitious National Tuberculosis Eradication Program (NTEP), aiming to make the country TB-free by 2025.

Challenges and Uncertainties Surrounding FLQ-R Management
In the past decade, significant transformations have reshaped the approach to tackling tuberculosis, particularly with the introduction of Shorter Course Chemotherapy (SCC) for MDR-TB. However, in the Indian context, uncertainties surround this therapy. Challenges arise from the high prevalence of MDR-TB, issues related to FLQ-R, and the current limitations of the healthcare system in dealing with these intricate cases. Despite advancements, addressing these concerns remains pivotal to the successful implementation of SCC, ensuring its optimal impact on MDR-TB management in India.

Fluoroquinolones (FLQs), particularly newer ones like Levofloxacin (LFX) and Moxifloxacin (MFX), exhibit remarkable efficacy against Mycobacterium tuberculosis (MTB) in both drug-sensitive (DS-TB) and DR-TB cases. They demonstrate an early bactericidal activity (EBA) comparable to Isoniazid (INH) and are considered safe for long-term use as anti-tuberculous (Anti-TB) agents without cross-resistance to other companion drugs. Treatment regimens incorporating FLQs, where organisms are sensitive to it, result in higher treatment success rates with lower mortality, and have better safety profiles. For over two decades, FLQs have held a core position in MDR-TB treatment, as indicated by the WHO guidelines. Despite numerous changes, additions, and deletions in drug recommendations, FLQs persist as indispensable Group A agents for both short and long-term MDR-TB regimens, whether in the form of all-oral or injection-containing therapies. [7-9] Fluoroquinolone resistance significantly impacts outcomes in MDR-TB cases, complicating management and leading to poor results. Identifying resistance to this crucial drug is essential for improving prognosis and devising treatment strategies that enhance survival rates.

Regrettably, the prevalence of FLQ-R in India among MDR-TB cases has reached alarming levels, standing at 24.14% in newly diagnosed and 20.91% in treated cases [3]. Reports from NTEP in 2021 and 2022 using second-line Line Probe Assays (SL LPAs) indicate FLQ-R rates of 28.4% and 29.8% in RR/MDR-TB cases [10]. Various other studies have consistently shown FLQ-R in RR/MDR-TB cases ranging from 36% to 69.2%, employing diverse methodologies [11-15].

In 2022, the World Health Organization (WHO) estimated 410,000 cases of Multidrug-resistant and Rifampicin-resistant TB (MDR-TB and RR-TB) worldwide, with India accounting for approximately 26% of these cases.

Image Credit: Pix4free

The widespread misuse of FLQs in India, both as an antibiotic, even in suspected tuberculosis cases, and as an Anti-TB drug, is a significant concern contributing to the high incidence of FLQ-R. The attractiveness of FLQs lies in their efficacy, easy availability, low cost, excellent tolerability, and a favourable safety profile, leading to their frequent misuse as antibiotics. In the context of DS-TB, FLQs are often misused as an additional drug to enhance therapy, replacing rifampicin or pyrazinamide to improve overall tolerance, or as an add-on drug to failing regimens. These practices contribute significantly to the development of high FLQ-R in MTB.

Data from studies and meta-analyses indicate that the key determinants of treatment success in MDR-TB regimens include the baseline susceptibility to fluoroquinolones, pyrazinamide, and second-line injectables. The probability of successful treatment is highest among participants with MDR-TB susceptible to both fluoroquinolones and pyrazinamide, and lowest in those with resistance to both. Notably, individuals with pyrazinamide resistance but sensitivity to fluoroquinolones fare better than those resistant to fluoroquinolones but sensitive to pyrazinamide [16].

Detecting FLQ-R in all MDR-TB cases is imperative, not only to enhance outcomes but also to prevent the escalation of drug resistance. Despite the widespread implementation of shorter all-oral regimens in the public sector, efficient methods for detecting FLQ-R, such as Xpert MTB/XDR, Next-Generation Sequencing (NGS), or Whole Genome Sequencing (WGS), are yet to be integrated. While the latter requires proper validation and cannot be directly applied to clinical specimens, its potential in the present time remains limited. Reducing the turnaround time for SL-LPA and ensuring its availability for patients on newer regimens is crucial. Accelerating the reporting time of Xpert MTB is also essential for early MDR-TB diagnosis to prevent lesion aggravation and spread, making patients unsuitable for shorter regimens. These constraints pose challenges to FLQ-R detection, vital information required before initiating newer shorter regimens, as resistance to FLQ has become a pivotal factor in managing MDR/RR-TB cases.

The WHO implemented SCC for MDR-TB in 2016, initially with injectables, later transitioning to an all-oral regimen in 2019 by replacing injections with bedaquiline (BDQ). However, both all-oral and injection-containing regimens, as outlined in the guidelines, are not recommended in the presence of FLQ-R. This limitation narrows treatment options, or otherwise overall poor outcomes, if FLQ-R is not detected before start of therapy [17]. Furthermore, these regimens are only appropriate when the disease in the lungs is not extensive, and there is no severe extra-pulmonary tuberculosis (EXPTB). Additionally, the patient should not have received second-line drugs in the regimen for over one month. Unfortunately, in India, with a large number of MDR-TB cases, a high prevalence of FLQ-R, limited facilities for early detection in public sector, and validated facilities in the private sector, along with cases often presenting with extensive disease, this therapy option seems less applicable and is largely not indicated in most cases. Udwadia et al. (2019) reported at a tertiary care hospital in Mumbai that less than 5% of MDR-TB patients were considered suitable for the Short Injectable MDR regimen [18]. Similar observations have been made in other countries, with suitability ranging from 10% to 50% of their MDR/RR-TB cases [19]. Moreover, the WHO's recommendation for an all-oral bedaquiline-containing regimen comes with very low certainty. Addressing these shortcomings in the implementation of newer regimens requires strategic interventions, policy changes, and further upgrades and optimizations of diagnostic facilities for more effective management. It also demands consideration of alternative therapies based on prevailing drug resistance patterns, patient characteristics, and healthcare infrastructure.

For India, the new 6-month BPaLM regimen, a recent addition to the shorter regimens by WHO, which includes bedaquiline, pretomanid, linezolid, and moxifloxacin, recommended in 2022, appears well-suited to prevalent conditions. Specifically designed to address MDR/RR-TB and pre-XDR-TB (with additional FLQ-R) in individuals aged over 14 years, it covers extensive extrapulmonary TB cases, excluding those with central nervous system, osteoarticular, and disseminated tuberculosis. Notably, this therapy has been recommended even in cases with FLQ-R. Until the feasibility of this therapy is assessed in Indian conditions, it might be worthwhile to continue with conventional long-term regimens using all oral drugs. Although drug susceptibility testing for FLQ is encouraged with this regimen, it is mainly to guide decisions on whether moxifloxacin should be retained or dropped based on sensitivity to FLQs. This aims to prevent undue delays in initiating the BPaLM regimen. In cases of documented resistance to FLQ, the BPaL regimen without moxifloxacin is recommended [18].However, it's vital to emphasize that even these recommendations are conditional and come with very low certainty of evidence, as per WHO (2022).

Implementing a short course regimen for MDR/RR-TB necessitates a robust healthcare system, with careful consideration to avoid premature and hasty decisions in implementing these newer therapies. This highlights the ongoing need for research, monitoring, and further evidence generation to refine and strengthen treatment recommendations for MDR/RR-TB in Indian contexts. Unfortunately, social factors such as education, living conditions, nutritional status, alcohol abuse, and smoking habits also adversely impact overall therapy outcomes in our scenario. The healthcare infrastructure, first, must be well-equipped with trained professionals and facilities to ensure effective implementation and monitoring of the short course regimen, especially regarding its feasibility and managing adverse drug reactions. Cardiac monitoring is particularly essential for drugs known to prolong the QT interval, seen in many newer drugs, optimizing patient care and treatment outcomes.

Equally vital is preventing the development of resistance to the crucial drug FLQ, a core component in DR-TB management. Achieving this goal involves multifaceted interventions, encompassing strict regulations on over-the-counter sales, judicious antibiotic use, preserving FLQ for anti-TB purposes, robust surveillance to gauge drug resistance prevalence, and heightened awareness among both healthcare professionals and the public. Proactively preventing FLQ-R ensures its continued effectiveness in benefiting a growing number of MDR/RR-TB cases.

Conclusion
Considering the prevalent FLQ resistance burden, compounded by India's substantial share of DR-TB cases, coupled with the existing challenges within healthcare services tailored for these cases, the adoption of shorter treatment regimens may not be the most fitting choice within the Indian context. As guidelines continue to evolve, it becomes imperative to judiciously evaluate their feasibility and appropriateness in our unique conditions, steering clear of potential harm. It is well within our capabilities to develop tailored strategies and guidelines that align with our unique setup, ensuring sustained benefits in the long run for our patients.

References

1. Bagcchi S. (2023). WHO's Global Tuberculosis Report 2022. The Lancet. Microbe, 4(1), e20. https://doi.org/10.1016/S2666-5247(22)00359-7.

2. Ramachandran, R., Nalini, S., Chandrasekar, V., Dave, P. V., Sanghvi, A. S., Wares, F., Paramasivan, C. N., Narayanan, P. R., Sahu, S., Parmar, M., Chadha, S., Dewan, P., & Chauhan, L. S. (2009). Surveillance of drug-resistant tuberculosis in the state of Gujarat, India. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease, 13(9), 1154–1160.

3. Ministry of Health and Family Welfare GoI. Report of the first national anti-tuberculosis drug resistance survey: India 2014–16, 2018, https://tbcindia.gov.in/showfile.php?lid=3315

4. Goyal, V., Kadam, V., Narang, P., & Singh, V. (2017). Prevalence of drug-resistant pulmonary tuberculosis in India: systematic review and meta-analysis. BMC public health, 17(1), 817. https://doi.org/10.1186/s12889-017-4779-5.

5. Lohiya, A., Suliankatchi Abdulkader, R., Rath, R. S., Jacob, O., Chinnakali, P., Goel, A. D., & Agrawal, S. (2020). Prevalence and patterns of drug resistant pulmonary tuberculosis in India-A systematic review and meta-analysis. Journal of global antimicrobial resistance, 22, 308–316. https://doi.org/10.1016/j.jgar.2020.03.008.

6. Charan, J., Tank, N., Reljic, T., Singh, S., Bhardwaj, P., Kaur, R., Goyal, J. P., & Kumar, A. (2019). Prevalence of multidrug resistance tuberculosis in adult patients in India: A systematic review and meta-analysis. Journal of family medicine and primary care, 8(10), 3191–3201. https://doi.org/10.4103/jfmpc.jfmpc_542_19.

7. WHO Guidelines for the programmatic management of drug-resistant tuberculosis-2006, 2008,2011.https://www.who.int/publications/i/item/9789241501583

8. Falzon, D., Schünemann, H. J., Harausz, E., González-Angulo, L., Lienhardt, C., Jaramillo, E., & Weyer, K. (2017). World Health Organization treatment guidelines for drug-resistant tuberculosis, 2016 update. The European respiratory journal, 49(3), 1602308. https://doi.org/10.1183/13993003.02308-2016.

9. WHO consolidated guidelines on drug-resistance tuberculosis treatment-2018, Annex 3-9, https://www.who.int/publications/i/item/9789241550529.

10. India TB report, 2022, https://tbcindia.gov.in/WriteReadData/IndiaTBReport2022/TBAnnaulReport2022.pdf

11. Dreyer, V., Mandal, A., Dev, P., Merker, M., Barilar, I., Utpatel, C., Nilgiriwala, K., Rodrigues, C., Crook, D. W., CRyPTIC Consortium, Rasigade, J. P., Wirth, T., Mistry, N., & Niemann, S. (2022). High fluoroquinolone resistance proportions among multidrug-resistant tuberculosis driven by dominant L2 Mycobacterium tuberculosis clones in the Mumbai Metropolitan Region. Genome medicine, 14(1), 95. https://doi.org/10.1186/s13073-022-01076-0.

12. Jain, A., Dixit, P., & Prasad, R. (2012). Pre-XDR & XDR in MDR and Ofloxacin and Kanamycin resistance in non-MDR Mycobacterium tuberculosis isolates. Tuberculosis (Edinburgh, Scotland), 92(5), 404–406. https://doi.org/10.1016/j.tube.2012.05.010.

13. Selvakumar, N., Kumar, V., Balaji, S., Prabuseenivasan, S., Radhakrishnan, R., Sekar, G., Chandrasekaran, V., Kannan, T., Thomas, A., Arunagiri, S., Dewan, P., & Swaminathan, S. (2015). High rates of ofloxacin resistance in Mycobacterium tuberculosis among both new and previously treated patients in Tamil Nadu, South India. PloS one, 10(3), e0117421. https://doi.org/10.1371/journal.pone.0117421.

14. Mamatha, H. G., & Shanthi, V. (2018). Baseline resistance and cross-resistance among fluoroquinolones in multidrug-resistant Mycobacterium tuberculosis isolates at a national reference laboratory in India. Journal of global antimicrobial resistance, 12, 5–10. https://doi.org/10.1016/j.jgar.2017.08.014.

15. Sharma, R., Sharma, S. K., Singh, B. K., Mittal, A., & Kumar, P. (2019). High degree of fluoroquinolone resistance among pulmonary tuberculosis patients in New Delhi, India. The Indian journal of medical research, 149(1), 62–66. https://doi.org/10.4103/ijmr.IJMR_1220_17.

16. Ahmad Khan, F., Salim, M. A. H., du Cros, P., Casas, E. C., Khamraev, A., Sikhondze, W., Benedetti, A., Bastos, M., Lan, Z., Jaramillo, E., Falzon, D., & Menzies, D. (2017). Effectiveness and safety of standardised shorter regimens for multidrug-resistant tuberculosis: individual patient data and aggregate data meta-analyses. The European respiratory journal, 50(1), 1700061. https://doi.org/10.1183/13993003.00061-2017.

17. WHO consolidated guidelines on tuberculosis: Module 4: treatment – Tuberculosis care and support. (2022). World Health Organization.

18. Udwadia, Z. F., Tornheim, J. A., Ganatra, S., DeLuca, A., Rodrigues, C. S., & Gupta, A. (2019). Few eligible for the newly recommended short course MDR-TB regimen at a large Mumbai private clinic. BMC infectious diseases, 19(1), 94. https://doi.org/10.1186/s12879-019-3726-8.

19. Riccardi, N., Saderi, L., Borroni, E., Tagliani, E., Cirillo, D. M., Marchese, V., Matteelli, A., Piana, A., Castellotti, P., Ferrarese, M., Gualano, G., Palmieri, F., Girardi, E., Codecasa, L., & Sotgiu, G. (2021). Therapeutic strategies and outcomes of MDR and pre-XDR-TB in Italy: a nationwide study. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease, 25(5), 395–399. https://doi.org/10.5588/ijtld.21.0036.

Tuberculosis Elimination Efforts in Kerala: Successes, Challenges, and the Way Forward

Dr. Sanjeev Nair, Professor, Department of Pulmonary Medicine, Government Medical College, Thrissur

Kerala has one of the lowest notification rates for TB in India, at 67/100,000 compared to the National notification rate of 172/100,000, indicating a lower incidence of TB compared to the rest of the country.

Abstract

This article discusses the efforts and achievements of Kerala, a state in the south of India, in the fight against Tuberculosis (TB). Despite being the highest TB burden country in the world, India has made significant progress towards TB elimination, with Kerala leading the way. The state has implemented various innovative strategies, including involving local governments, establishing successful public-private partnerships, improving case management, and rolling out TB preventive therapy. However, challenges such as high mortality rates, a high percentage of extra-pulmonary TB cases, and limited diagnostic capacity remain. Overall, Kerala is well-positioned to achieve TB elimination, but continued efforts and interventions are needed to address the remaining challenges.

Introduction

India is the highest Tuberculosis (TB) burden country in the world, accounting for more than one-fourth of the estimated incidence, mortality and multi-drug resistant (MDR) TB. WHO estimates that there were 2.8 million incident cases of TB in India in 2022, including 110,000 cases of MDR TB. There were an estimated 342,000 deaths due to TB in India in 2022, as per WHO estimates [1]. India is committed to the END TB strategy and aims to eliminate TB. The national TB program of India, now named the National TB Elimination Program (NTEP), aims to achieve the 2030 targets of the END TB strategy by 2025.

Kerala state, in the south of India, with a population of about 35 million, is known for its achievements in the health sector. The model of good performance in various indicators despite a low resource setting is known all over the world as the "Kerala model of Health" [2]. The infant mortality rate, under-5 mortality rate, and life expectancy are comparable to those of developed countries despite the low health expenditure per capita.

The state is also known for its achievements in the TB program. It was one of the states which took part in the pilot study for the Revised National TB Control Program (RNTCP) in 1992-93. It was one of the first states to implement the RNTCP in all districts of the state in 2000. Many other "newer" initiatives of the RNTCP / NTEP were initially implemented in Kerala, including various private-public partnership schemes, diabetes-TB cross referral mechanisms, TB preventive therapy, etc. Kerala has one of the lowest notification rates for TB in India, at 67/100,000 compared to the National notification rate of 172/100,000, indicating a lower incidence of TB compared to the rest of the country.

TB Elimination Efforts in Kerala

The Kerala government was the first in India to formulate strategies for TB elimination. This was part of the state's overall efforts to achieve the SDG targets for all diseases. The state devised a strategy in 2017, the Aardram mission, with the objective to completely transform the public health sector in the backdrop of the Sustainable Development Goals (SDGs) 2030 [3]. During the same time, the state came out with its strategy document for TB elimination, the guidance document for the people's movement against Tuberculosis in Kerala: "Kerala TB Elimination Mission" [4].

The document emphasises on how the difference in demographics and disease conditions in Kerala necessitates a different strategy for TB elimination in Kerala as opposed to the rest of the country. Kerala state has an older population, higher life expectancy, and a high proportion of non-communicable diseases, particularly diabetes, in the community. The proportion of TB patients in the "older" age groups, already higher when compared to the rest of the country, is further increasing. The proportion of TB patients in the 0-14 years and 15 – 24 years reduced by 20% and 33%, respectively, between 2004 and 2014, whereas the proportion in the 55 – 64 years and >65 years increased by 17% and 9% respectively in the same period. The state also notified a low proportion of HIV coinfection and a low proportion of MDR TB among newly diagnosed cases.

The core principles listed in the Kerala TB Elimination Mission document included: 1) Stopping new TB infections; 2) Preventing the active breakdown of disease among the infected; 3) Diagnosing TB early and completely, mainly through mapping TB vulnerable individuals in the community and actively searching for TB among vulnerable; 4) Treating TB correctly and completely, particularly with Drug Susceptibility Testing (DST) guided regimens; 5) Prevent the emergence of resistance, particularly by judicious use of anti-TB drugs and regimen. Further strategies were listed (ten in number) on how these principles would be achieved.

Activities undertaken in Kerala for TB Elimination

After the formulation of the strategy for TB elimination strategy for the state, the state moved forward towards implementing some of the strategies. One of the main successes in the state was the involvement of the local government in TB elimination efforts. The state already had an empowered local governance system, with decentralization of power and finances, including health care institutions. This advantage was used to take TB elimination efforts to local government levels much more decentralized than what was conceived at the National level at that time (the then central government document spoke of district-level TB task forces, whereas in Kerala, it was done at the Panchayat level).

The local government stewardship in TB elimination is documented elsewhere [5]. While the attempts at involving local government in TB control in Kerala started in 2003, they were done systematically after the TB elimination strategy was formulated as a joint initiative of the health and the local government departments. 98.1% of all LG heads were formally sensitised about the TB Elimination Mission. A single overriding communication objective of "My TB Free Panchayat" was used. Decentralised surveillance data of case-finding and outcomes were captured LG-wise, analysed and presented as maps for easy understanding. The state government honoured those LGs which had zero TB among those aged <5 years (561 in number), those who had zero lost to follow-up during treatment of TB (688 in number) and those who had zero drug-resistant TB (709 in number) in 2019.

These activities had initial results regarding presumptive TB testing, which increased from 1,105/100,000 in 2015 to 1,461/100,000 in 2019. TB notifications went up in 2018 and 2019. LGs provided a leadership role for periodic active case-finding by mobilising volunteers and ensuring acceptance of the interventions in the community. They also strengthened TB diagnostic infrastructures by establishing 127 new TB diagnostic laboratories based on local needs and enhancing screening in populations which previously had poor accessibility. Over 22 million "vulnerable individuals" at risk of developing TB were mapped by a task force under the LG. The total loss to follow-up rate among diagnosed TB patients fell in the state to 2% in 2020 from 4.5% in 2015. LGs also helped ensure continuity of services during the pandemic and lockdowns by extending social support to TB patients [5].

Private sector involvement
Kerala was at the forefront of Private Public partnership (PPP) schemes in TB. The initial Kannur and Punalur PPM models, initiated in 2000-2003, were proven to be successful in improving case finding. The IMA-RNTCP project for the involvement of the doctors of the state started in 2005 and later became the model for the National project [6]. The projects for private sector involvement kept evolving as per the needs and the priorities of the National program, and Kerala was at the forefront of such projects. The latest model in Kerala, the STEPS model, has also been a success and replicated in other states of India [7]. One of the significant factors for the success of various PPP schemes in Kerala has been the willingness of private practitioners, including TB specialists, to work closely with the program.

Activities for improving case management
The TB program in Kerala has also implemented various innovations to improve case holding and case management. These include decentralised care of DS and DR TB, involvement of patient groups and communities for case holding, and clinical care at the PHC level, including support for the management of comorbidities, particularly diabetes and COPD. One of the successes has been screening for risk factors and early detection of adverse effects (ADR). For example, while the NTEP does not include a liver function test in the pretreatment evaluation of DS TB, this is done for all patients in Kerala. Patients also undergo screening for ocular toxicity, given increased reporting of adverse visual effects. One of the major successes has been decentralised care for DR TB. From the onset of the PMDT services in Kerala in 2008, pretreatment evaluation was done at the district level, and treatment initiation began at the district level. This model was later replicated in other states of India. The state was quick in implementing new regimes and the use of newer drugs like Bedaquline (BDQ) and Delamanid as soon as they were available. The state is prepared to take up the newer, shorter regimes, the WHO-approved six-month regimes for DR TB (BPaL and BPaLM), as and when the regimes are made available. These activities have resulted in high success rates for DR TB in Kerala. The success rate for the regime for INH resistance was 82% that for the shorter DR TB regime (9-11 months BDQ containing regime) was 78%, and that of longer DR TB regimes (18-20 months BDQ containing regime) was 76%. This is higher than the national average success rates for these regimes. The success rate in XDR TB, though small numbers were there, was 89% (16/18).

TB preventive therapy
Kerala was the first state in India to roll out TB preventive therapy. In fact, the services were initiated even before the national guidelines were formulated. Kerala initiated TB preventive therapy with a "test and treat" strategy, using Interferon Gamma Release Assays (IGRA) for testing for TB infection, wherever indicated. The regime for children and adolescents selected was 3HR (INH and Rifampicin, daily for three months), whereas that for adults and other high-risk groups was 3HP (3 months of weekly INH and Rifapentine), while HIV patients continued on 6H (6 months of daily INH). Kerala was the only state in India to use the 3HR regime, and the success of the same led to the rollout of the regime in some other states, too. Kerala was one of the first states to use Rifapentine for TB preventive therapy.

Challenges for the TB program in Kerala

Despite the successes of the TB program in Kerala, there are multiple challenges as well. The mortality rate for notified TB cases in Kerala is 8.1% (2021 cohort), which is much higher than the national average [8]. About 33% of TB patients have diabetes, and patients are much older in Kerala, with other comorbidities also being common. About 34% of notified TB patients had extra-pulmonary TB, requiring a different diagnostic algorithm and greater access to tests other than sputum examination [8]. The capacity for mycobacterial culture in the state needs to improve, with only two state reference laboratories offering MGIT services. These issues need to be addressed urgently if the state has to make a successful plan to eliminate TB.

Epidemiology of TB in Kerala, in the context of TB elimination

Kerala had the lowest prevalence of TB as per the National TB prevalence survey report [9]. The estimated prevalence of microbiologically pulmonary TB in Kerala was 115 / 100,000, compared to the national average of 316 / 100,000. However, the prevalence-to-notification ratio was a poor 3.3, worse than the national average of 2.84. The state had 54% of people with symptoms of TB consulting a doctor when they developed symptoms, which is much higher than the national average of 36%, indicating better health-seeking behaviour. The report shows that Kerala is best placed among the states of India in achieving TB elimination.

Conclusion

Kerala state is best placed among the states of India to achieve TB elimination. Significant innovations and success stories have been made for the TB program in Kerala, including decentralised care of TB, local government involvement, strong PPP models, etc. However, there are newer challenges which need to be addressed, including a high mortality rate, a high proportion of EP TB and diagnostic capacity for EP TB and a high proportion of comorbidities, particularly diabetes, in an ageing population.

References

1. TB profile [Internet]. [cited 2024 Mar 3]. Available from: https://worldhealthorg.shinyapps.io/tb_profiles/?_inputs_&entity_type=%22country%22&iso2=%22IN%22&lan=%22EN%22
2. Book-Kerala-Health-Making-the-SDG-a-reality-1.pdf [Internet]. [cited 2024 Mar 3]. Available from: https://dhs.kerala.gov.in/wp-content/uploads/2021/02/Book-Kerala-Health-Making-the-SDG-a-reality-1.pdf
3. Aardram – National Health Mission [Internet]. [cited 2024 Mar 3]. Available from: https://arogyakeralam.gov.in/2020/04/01/aardram/
4. Kerala TB Elimination Mission. [cited 2024 Mar 11]. Available from: https://dhs.kerala.gov.in/wp-content/uploads/2021/01/KeralaTB-Elimination-Mission_Strategy-activity-plan-and-budget..pdf
5. Rakesh PS, Nair S, Kamala R, Manu MS, Mrithunjayan SK, Valamparampil MJ, et al. Local government stewardship for TB elimination in Kerala, India. Public Health Action. 2023 Mar 1;13(1):44–50.
6. Nair S, Philip S, Varma RP, Rakesh PS. Barriers for involvement of private doctors in RNTCP – Qualitative study from Kerala, India. J Fam Med Prim Care. 2019 Jan;8(1):160.
7. Balakrishnan S, Ps R, M S, Sankar B, Ramachandran R, Ka A, et al. STEPS: A Solution for Ensuring Standards of TB Care for Patients Reaching Private Hospitals in India. Glob Health Sci Pract. 2021 Jun 30;9(2):286–95.
8. Annual report of the NTEP. 5646719104TB_AR_2023_04-04-2023_LRP_final.pdf [Internet]. [cited 2024 Mar 11]. Available from: https://tbcindia.gov.in/WriteReadData/l892s/5646719104TB_AR_2023_04-04-2023_LRP_final.pdf
9. National TB Prevalence Survey Report. 25032022161020NATBPSReport.pdf [Internet]. [cited 2024 Mar 11]. Available from: https://tbcindia.gov.in/WriteReadData/l892s/25032022161020NATBPSReport.pdf

Pathways to End TB - Challenges

Dr. V. K. Arora, Union Lung Health, South East Asia Region, New Delhi; The Tuberculosis Association of India, New Delhi, India

Dr. Kamal Kishore Chopra, New Delhi Tuberculosis Centre, Jawaharlal Nehru Marg, Delhi Gate, New Delhi, India

Abstract

Tuberculosis (TB) remains a major global health challenge, with India being one of the high burden countries. Despite significant progress in TB control efforts, there are still challenges to be addressed, such as underdiagnosis, drug resistance, treatment outcomes influenced by socio-economic factors, and the impact of the COVID-19 pandemic. Efforts to achieve TB elimination by 2025 require intensified research, innovation, and significant investment. A multi-sectoral approach involving all stakeholders is essential to end TB. India's National Tuberculosis Elimination Program has made significant strides, but challenges persist. It is crucial to maintain political commitment, utilize rapid diagnostic tests and effective treatment regimens, and ensure consistent supervision and monitoring. Collaboration and collective efforts are needed to achieve the TB elimination target by 2025.

Although Tuberculosis (TB) is considered preventable and curable. In the year 2022, it was the world's secondleading cause of death from a single infectious agent, after coronavirus disease (COVID-19), and it caused almost twiceas many deathsas HIV/AIDS. More than 10 million people

The WHO released a list of 30 high burden countries worldwide for TB, HIV_TB, and MDR/RR-TB, with India being listed in all above categories, requiring improved diagnosis, treatment, and clinical management [1].Universal health coverage (UHC) is necessary to ensure that everyone can obtain the health services they need without suffering financial hardship. India has committed to ending TB by 2025. India's National TB elimination program is one of the largest public health programs. It has scaled up access to free rapid molecular diagnostics, treatment, and nutritional support to patients. The Government of India is making significant efforts in introducing new tools for quality diagnosis and therapeutics, as well as revised plans for their implementation to improve standards for TB care. Pathways to end TB require seeking out and screening patients with the help of diagnostic algorithms and providing them with appropriate treatment and medical care.

Despite these outstanding achievements, there is still a long way to go to achieve a significant reduction in TB incidence and prevalence. The path to reach the TB elimination goal is full of challenges at the administrative and community level. The End TB Strategy aims toend the global TB epidemic by 2030. However,the rate of decline of TB burden has been slow, at a rate of 1.5–2% per year [4]. The large TB infection pool, along with risk factors for active disease,ageing, slow and insufficient case detection, low cure rates, and drug resistance, favors the slow decline in incidence.

One challenging issue in TB diagnosis is the wide gap between the estimated number of people who develop TB each year (incident cases) and the number of people newly diagnosed and officially reported as a TB case.

TB treatment outcomes are also influenced by socioeconomic factors such as poverty, overcrowding, poorly ventilated spaces, vulnerable populations including those living with HIV, diabetes, malnutrition, alcohol abuse, and drug and tobacco use, as well as migrants,refugees, and prisoners. Povertyand TB often go hand in hand. Without adequate nutrition, we will be unable to improve TB outcomes. There should be strong, reliable, multi-sectoral interventions and a global health approach to reach the End TB Target.

One challenging issue in TB diagnosis is the wide gap between the estimated number of people who develop TB each year (incident cases) and the number of people newly diagnosed and officially reported as a TB case. Therefore, many people are underdiagnosed with TB and underreported, which may be attributed to lack of awareness, human resources, and poor health infrastructure. Drug-resistant TB poses a significant challenge. Detecting drug resistance requiresconfirming the presence of TB bacteria throughbacteriological testing and conducting drug resistance tests usingrapid molecular diagnostics, culture methods, or sequencing technologies. A current challenge in drug susceptibility testing is that Fluoroquinolone (FQ) resistance on drug susceptibility testing (DST) does not correlate with actual resistance, resulting in patients not benefiting from shorter regimen treatment [5]. Patients in need of longer, individualized regimens require a more comprehensive DST profilefor proper regimenconstruction. Limited DST results may lead to the inclusion of ineffective and more toxic drugs and the exclusion of effective ones. Delayed DST results can also lead to the development of additional drug resistance mutations and the transmission of Drug Resistance TB (DRTB).

Although the efficacy of drug regimens has improved over time, challenges related to side effects, adverse drug reactions, longer treatment duration, low tolerability, and treatment adherence persist, posing ongoing challenges in treating patients with drug–resistant TB. Therefore, there is a need for treatment regimens with minimal drug combinations for a shorter duration, such as the BPaL regimen [6].

Newer technologies, such Whole Genome Sequencing, which can identify all known resistance mutations simultaneously, can overcome some limitations of culture-based DST. However, implementing this technology as a point-of-care test at primary centers is expensive and requires technical expertise.

TB preventive treatment (TPT) also plays a crucial role in achieving the goal of ending TB. There are interventions available to reduce the risk of TB infection progressing to active TB disease. The current scenario requires an intensification of TPT efforts and increased investment to expand its coverage.

Achieving universal health coverage, including financial risk protection and access to quality essential healthcare services, affordable essential medicines, and vaccines for all, remains another significant challenge.

The economic burden of tuberculosis on households is known to be high and poses one of the major challenges. The national strategic plan for the elimination of TB 2017 to 2025 aims to ensure zero catastrophic cost for affected families [7]. This is especially devastating for people with low income, causing delays in diagnosis as these patients often do not seek treatment until they are severely ill.

Meeting the targets of the End TB Strategy requires intensified research, innovation such as the development of new vaccines, and significant investment. A multi-sectoral approach involving all stake- holders, government departments, the private sector, community engagement, and survivor groups is essential to end TB.

Progress in reducing the burden of TB was reversed due to the global COVID-19 pandemic, causinga major setbackthat undid previousgains. In conclusion, India has a robustand well-functioning TB program, the National Tuberculosis Elimination Program (NTEP). The program includes defined guidelines for identifying presumptive TB cases, rapid and sensitive molecular diagnostic tests, efficient diagnostic algorithms, well-established treatment regimens with newer anti-TB drugs, and a large network of service delivery infrastructure. However, implementting all theseinitiatives has presented numerous challenges. Nonetheless, its essential to acknowledge the unprecedented highest-level political commitment, rapid molecular diagnostics, effective treatment regimens, consistent supervision and monitoring, and the continuous supply of high quality medicines throughout the history of TB controlprograms. Therefore, if we cannot now stop and reverse the TB epidemic, we should not hope to achievethis in the future. Let's work togetherto achieve the TB elimination targetof 2025.

References

1. World Health Organization (WHO). Global Tuberculosis Report 2023. Geneva: WHO; 2023.
2. Houben RM, Dodd PJ. The global burden of latent tuberculosis infection: a re- estimation using mathematical modelling. PLoS Med. 2016;13(10), e1002152.
3. Tiemersma EW, van der Werf MJ, Borgdorff MW, Williams BG, Nagelkerke NJ. Natural history of tuberculosis: duration and fatality of untreated pulmonary tuber- culosis in HIV negative patients: a systematic review. PLoS One. 2011;6(4), e17601.
4. World Health Organization (Who). Global Tuberculosis Report 2021. Geneva:WHO; 2021. www.who.int/publications/i/item/978924003702.
5. Arora a VK, Jindal b SK, Katiyar C SK, et al. Nikam m n, anirvan chatterjee O, and agam vora. "Genomic revolution: transforming tuberculosis diagnosis and treatment with the use of Whole Genome sequencing - a consensusstatement. Indian J Tubercul. 2023;70(4):383–389. https://doi.org/10.1016/j.ijtb.2023.10.002. ISSN 0019-5707.
6. van de Berg SEJ, Pelzer PT, van der Land AJ, et al. Acceptability, feasibility, and likelihood of stakeholders implementing the novel BPaL regimen to treat extensively drug-resistant tuberculosis patients. BMC Publ Health. 2021;21:1404. National Strategic Plan for Tuberculosis Control. CentralTB Division, Ministryof Health and Family Welfare, GoI; 2017.
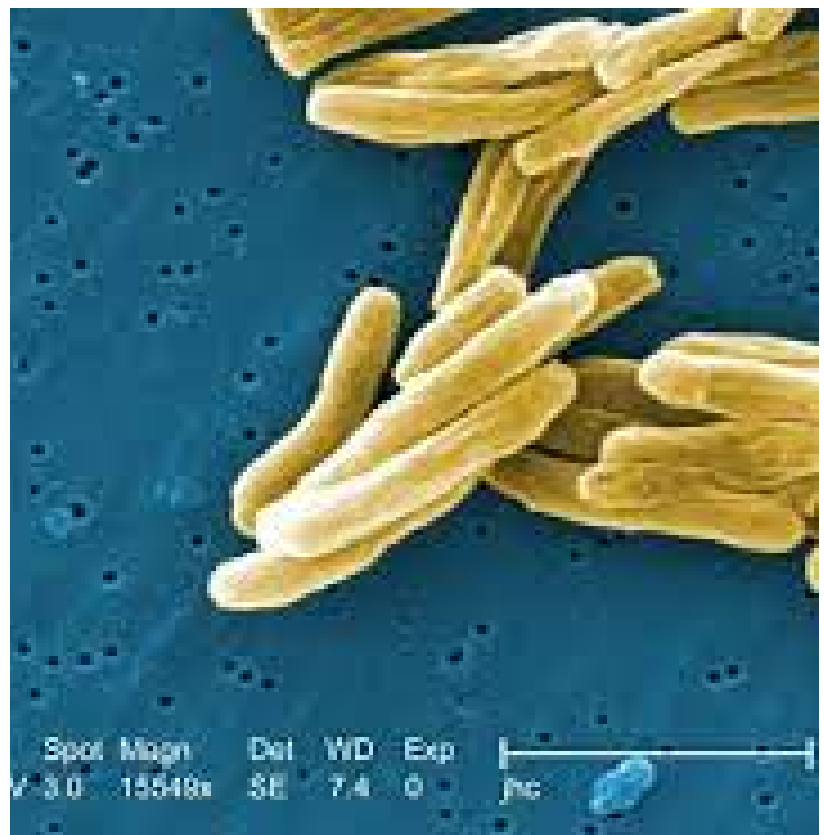
Image Credit : Flickr

Stigma, Tuberculosis and Mental Health

Dr. V. K. Arora, Union Lung Health, South East Asia Region, New Delhi, India; The Tuberculosis Association of India, New Delhi, India

Dr. Nibedita Rath, Scientific Director, Open Source Pharma Foundation, Bengaluru, India, Union Lung Health, South East Asia Region, New Delhi, India

Image Credit : Openclipart

Abstract

Tuberculosis (TB) has long been stigmatized, leading to social isolation, discrimination, and mental health challenges for affected individuals. The intersection of TB stigma and mental health is complex, with stigma hindering treatment outcomes and exacerbating mental health issues. Efforts to address stigma and mental health must be integrated into TB care, focusing on education, community support, integrated healthcare, and responsible media engagement. By adopting a holistic approach, we can create a supportive environment that promotes understanding, reduces stigma, and enhances the overall well-being of individuals affected by TB.

Introduction

Over the years Tuberculosis has been on the forefront of infectious disease that has caused enormous suffering in the humanity. Morbidity and mortality both had led to societal stigma from the disease. Tuberculosis (TB) and mental health are two distinct domains often overshadowed by stigma in the society. Here we explore, the intersection of stigma associated with TB and its impact on mental health, highlighting the need for a holistic approach to address the challenges faced by individuals grappling with both.

Stigma Surrounding Tuberculosis

TB has long been stigmatized due to historical misconceptions and fears related to the disease. Misinformation, coupled with a lack of awareness, leads to social isolation and discrimination against those affected. Individuals with TB may face prejudice, adding an extra layer of distress to their health struggles [1].

Efforts aimed at controlling tuberculosis rely heavily on the attitudes and awareness of the individuals affected by the disease. A lack of understanding and positive perception surrounding TB can lead to poor health-seeking behavior, treatment adherence, and delays in diagnosis. Research indicates that areas with inadequate knowledge, attitudes, and preventive practices regarding TB are more likely to exhibit stigma towards the disease. Stigmatization can discourage individuals from seeking medical care, getting tested, and taking preventive measures to stop the outspread of TB. The amplifying connection between TB and HIV/AIDS also contributes to increased stigma, further hindering efforts to seek treatment and follow through with medication. Stigma not only impacts individuals socially by isolating them from their social circles but also economically by limiting their job prospects and ability to manage the costs of treatment. Dealing with TB stigma requires tailored interventions that address community awareness, perspective, and sensitivity. Assessing the extent of stigmatizing attitudes towards TB can help identify the problem and guide strategies to reduce stigma and enhance TB control efforts.

Impact on Mental Health

The stigma surrounding TB can take a toll on mental health [2], exacerbating anxiety, depression, and feelings of isolation. The fear of rejection and judgment can deter individuals from seeking timely medical care, hindering treatment outcomes and perpetuating the cycle of stigma and mental health challenges.

The presence of co-morbid mental illness poses a significant hurdle to TB care and prevention, often leading to poor health-seeking behavior and treatment adherence among affected individuals. Research suggests that up to 70% of TB patients also experience mental health issue, which can result in more severe health outcomes and increased social and physical disabilities. Factors such as hardship, addiction, and homelessness contribute to the higher prevalence of both TB and mental health issue among marginalized populations.

Recognizing the link between mental illness and TB presents opportunities for intervention. Strategies such as individual psychotherapy, TB support groups, and group therapy with psychotropic medications have shown promise in improving treatment outcomes for TB patients with mental health issues. By addressing both the physical and mental health needs of TB patients, the spread of infection can be reduced, benefiting the broader community.

Implementing mental health interventions for TB patients in diverse settings like the Asia-Pacific region presents challenges due to limited resources, infrastructure, and cultural differences in the perception of mental distress. Efforts to address co-morbid mental illness and TB must be sensitive to cultural nuances and existing stigma surrounding both conditions.

Image Credit : Flickr

It is essential to consider the ethical implications of addressing mental health in TB care, ensuring interventions are tailored to each specific setting to be effective and culturally appropriate. By integrating mental health support into TB treatment, we can improve patient outcomes and reduce infection transmission, ultimately advancing global health.

Addressing Stigma and Mental Health

1.Education and Awareness:

Initiatives aimed at dispelling myths surrounding TB are crucial. Public education campaigns can foster understanding, reducing the fear and discrimination associated with the disease.

Studies have consistently found that stigma surrounding mental illness can act as a barrier to individuals seeking help for their psychological health [3]. Negative perceptions and a lack of understanding about mental health issues can contribute to this stigma, leading to a reluctance to seek support.

Efforts to increase mental health awareness have been shown to reduce stigma and promote help-seeking behavior. By educating the public and challenging misconceptions about mental health, individuals may feel more comfortable seeking help when they need it. This is particularly important for young adults, who may face additional challenges due to stigma and a lack of awareness about mental health resources.

Research indicates that individuals may avoid seeking treatment for mental health issues due to fears of being labeled or experiencing embarrassment. Addressing these concerns and creating a supportive environment for those struggling with mental health is essential in ensuring that individuals can access the care they need.

2. Community Support:

Establishing support networks within communities can create safe spaces for individuals affected by TB. This helps combat isolation and promotes mental well-being.

When it comes to tuberculosis (TB) and mental health, it is important to recognize that health goes beyond just physical well-being and involves overall wellness. To tackle health and social disparities related to TB and mental health, it is crucial to utilize resources from various sources such as families, caregivers, workplaces, schools, social services, institutions, and communities [4]. By implementing community-based mental healthcare strategies, we can enhance well-being and address the structural factors impacting TB-related mental health.

A Cochrane review from 2015 highlighted three key beliefs that should guide community interventions in this area. These beliefs emphasize the importance of understanding the socio-ecological factors influencing mental health, engaging community participation to access valuable insights and resources, and prioritizing community mental health and social outcomes for effective interventions. Adhering to these principles can help us improve overall well-being and address the root causes of TB-related mental health issues.

3.Integrated Healthcare:

A comprehensive healthcare approach that addresses both physical and mental health is essential [5]. Integrated care models can ensure that individuals receive holistic support, acknowledging the interconnected nature of TB and mental health.

Incorporating mental health services into primary healthcare offers a multitude of advantages. When mental health support is integrated at the primary care level, individuals can receive prompt treatment without any disruptions. This can lead to enhanced health outcomes, quicker recovery, and stronger ties to their community.

Primary healthcare facilities are typically the initial point of contact for individuals seeking medical assistance. By making mental health care available at these local settings, it becomes more easily accessible to individuals, reducing obstacles such as distance. Proximity to home enables people to access services conveniently, maintain their daily routines, and stay connected to their support networks, reducing the risk of financial strain.

Furthermore, primary healthcare services are generally more cost-effective than specialized mental health care, alleviating the financial burden on those in need of assistance. The integration of mental health services into primary care settings can also help diminish stigma and discrimination linked to mental health issues, as well as prevent potential violations of human rights in institutionalized care settings.

Merging mental health into primary healthcare presents numerous benefits, rendering mental health services more accessible, cost-effective, and acceptable for individuals seeking assistance. This collaborative approach has the potential to enhance the overall quality of care for individuals, including those affected by TB.

4. Media Engagement:

Responsible media reporting plays a pivotal role in shaping public perceptions. Collaboration with media outlets to disseminate accurate information can contribute to destigmatizing TB and promoting mental health awareness.

As technology continues to advance, social media is increasingly being utilized as a tool for raising awareness and educating individuals on important social issues. Platforms such as Facebook, Twitter, and Instagram enable wide-reaching communication and have revolutionized how we interact with one another. Social media has become an effective means for delivering online courses and classes, making it easier to reach a broad audience [6].

One significant area where social media can have a substantial impact is in promoting mental health awareness. It offers a cost-efficient way to disseminate crucial information and resources to those in need. By leveraging social media platforms, we can reach diverse populations and tailor health promotion messages to specific groups.

Social networking sites also serve as a hub for connecting with others and sharing valuable information, which can be particularly beneficial in advocating for mental health. People often turn to social media for relaxation and opportunities to connect with others, making it an ideal space for hosting campaigns aimed at promoting behavior change and mental health awareness.

Social media can play a pivotal role in promoting tuberculosis related mental health awareness and can be a valuable tool for hosting campaigns and disseminating critical information.

Conclusion

The stigma surrounding tuberculosis not only affects the physical health of individuals but also significantly impacts their mental well-being. A multifaceted approach, encompassing education, community support, integrated healthcare, and responsible media engagement, is vital to breaking down barriers and fostering a more inclusive and understanding society. Only by addressing the intersection of stigma related to TB and mental health can we hope to create an environment that supports the holistic health of affected individuals.

Image Credit : The Wire Science

References

1. Junaid, S. A., Kanma-Okafor, O. J., Olufunlayo, T. F., Odugbemi, B. A., & Ozoh, O. B. (2021). Tuberculosis stigma: Assessing tuberculosis knowledge, attitude and preventive practices in surulere, Lagos, Nigeria. Annals of African medicine, 20(3), 184–192. https://doi.org/10.4103/aam.aam_40_20
2. Mason PH, Sweetland AC, Fox GJ, Halovic S, Nguyen TA, Marks GB. Tuberculosis and mental health in the Asia-Pacific. Australas Psychiatry. 2016 Dec;24(6):553-555. doi: 10.1177/1039856216649770. Epub 2016 May 20. PMID: 27206468; PMCID: PMC5332205.
3. Lanfredi, M., Macis, A., Ferrari, C., Rillosi, L., Ughi, E. C., Fanetti, A., Younis, N., Cadei, L., Gallizioli, C., Uggeri, G., & Rossi, R. (2019). Effects of education and social contact on mental health-related stigma among high-school students. Psychiatry research, 281, 112581. https://doi.org/10.1016/j.psychres.2019.112581.
4. Castillo EG, Ijadi-Maghsoodi R, Shadravan S, Moore E, Mensah MO 3rd, Docherty M, Aguilera Nunez MG, Barcelo N, Goodsmith N, Halpin LE, Morton I, Mango J, Montero AE, Rahmanian Koushkaki S, Bromley E, Chung B, Jones F, Gabrielian S, Gelberg L, Greenberg JM, Kalofonos I, Kataoka SH, Miranda J, Pincus HA, Zima BT, Wells KB. Community Interventions to Promote Mental Health and Social Equity. Curr Psychiatry Rep. 2019 Mar 29;21(5):35. doi: 10.1007/s11920-019-1017-0. PMID: 30927093; PMCID: PMC6440941.
5. Funk, M., Saraceno, B., Drew, N., & Faydi, E. (2008). Integrating mental health into primary healthcare. Mental health in family medicine, 5(1), 5–8.
6. Latha, K., Meena, K. S., Pravitha, M. R., Dasgupta, M., & Chaturvedi, S. K. (2020). Effective use of social media platforms for promotion of mental health awareness. Journal of education and health promotion, 9, 124. https://doi.org/10.4103/jehp.jehp_90_20.

Zero Catastrophic Costs Goal for Tuberculosis Patients in India: Are We There Yet?

Dr. Denny John, Professor, Faculty of Life & Health Sciences, M S Ramaiah University of Applied Sciences, Bangalore, India

Abstract

This article gives insight into the financial burden of tuberculosis (TB) in India, with a specific emphasis on low-income households and tribal people who endure significant out-of-pocket spending, catastrophic costs, and impoverishment. The article emphasizes the challenges encountered by low-income households and tribal populations, the frequent use of private health facilities for tuberculosis care, and the impact of poverty on the results of tuberculosis treatment. It also explores the impact of AB-PMJAY scheme towards reducing financial obstacles in tackling tuberculosis.

Introduction

Tuberculosis (TB) is a contagious disease that requires long treatment and care and strongly associated with social stigma, poverty, illiteracy, unemployment, and catastrophic cost. The government of India provides free diagnosis and treatment to all registered TB patients; however various studies have reported high out-of-pocket expenses and catastrophic costs related to TB [1].

Financial Strain and Tuberculosis

A financial strain on low-income households is one of the main effects of poverty, which is both a risk factor and a result of tuberculosis. Poverty and tuberculosis may be linked negatively, with consequences including delayed care seeking, increased default rates, and poor treatment outcomes. The costs associated with the condition for affected persons and their families are one of the factors contributing to low treatment compliance and a low treatment success rate. Financial ruin could result from these expenses, which affect about 18% of the Indian population overall in terms of catastrophic medical costs [2].

Financial troubles experienced by a patient or family are indicated by a catastrophic cost, which is defined as the total cost of tuberculosis care surpassing 20% of the household's yearly income. The elimination of catastrophic costs by linking eligible TB patients with social welfare schemes including providing nutritional support is a stated objective of the National Strategic Plan (NSP) 2017-2025, the Centre's plan to eliminate TB in India by 2025.

Analysis using various National Sample Survey Office (NSSO) rounds (2004-2018) show the out-of-pocket expenditure (OOPE) has doubled for outpatient care and hospitalisation in the country [3]. During this period nearly 50% of households were exposed to catastrophic health expenditure.

TB Economic Burden and Hardship Financing

One additional aspect to consider towards economic burden of TB in the country is the aspect of hardship financing. Hardship financing occurs in a household when expenditures towards health are met through borrowings (mainly with repayment and interest) or sale of assets. In 2018, 26.7% of inpatient and 3.5% of outpatient cases experienced hardship financing [4]. This translates to an average of 25.9% or one in 4 patients had to sell assets or use borrowings for financing TB expenses.

It is well-known that there is a symbiotic relationship between TB and poverty. New TB infections are not just a product of poverty, but also creates poverty. The economic impact of TB is seen to be many times greater on poor households. However, the effects of TB expenditure are now to be seen among middle-class households as well. In 2018 almost 50% of the patients belonging to the middle-income category fell below the poverty line due to hospitalisation related OOPE [4].

Another matter of concern is the high use of private health facilities for TB treatment with almost half of all TB patients seeking private health facilities. Median treatment costs towards diagnosis and treatment of TB in private sector is almost double when compared to the public sector [5]. Patients seeking private health facilities for TB treatment have shown higher exposure to hardship financing and catastrophic health expenditure, and impoverishment [4].

Catastrophic health expenditure among tribal populations

Tribals comprise of 8.6% (translating to 110.4 million people) of our total population. Tribal populations have shown higher prevalence of TB compared to national average. 10.4% of all TB notified patients in the county belong to tribal communities [6]. Since 2005 the National TB program have prioritized tribal subgroup population through various Tribal Action Plans. Despite these efforts various studies have highlighted TB to be a major cause of catastrophic health expenditure among tribal populations in the country [6]. These expenses can be as high as 10% in relation to annual family income. Impoverishment among tribal populations due to OOPE for TB hospitalisation has shown substantial increase from 2004 to 2018 [6].

Image Credit : The Wire Collin Key

Impact of AB-PMJAY on TB care in India

The National Health Assurance Scheme 'Ayushman Bharat-Pradhan Mantri Jan Arogya Yojana' (AB-PMJAY) has been launched by the Government of India in 2018 to address the financial and economic barriers, including TB. This scheme provides health cover of Rs 5 lakhs per family per year for secondary and tertiary care hospitalisation. While TB has the lowest rate of hospitalisation (50 per 100,000 people) in the country, only 1% of the mean expenditure on TB hospitalisation has been reimbursed in 2018 [7].

Very few studies exist of the impact of AB-PMJAY towards reducing OOPE and catastrophic health expenditure for TB [8]. Recent study published with The Lancet Regional Health-Southeast Asia focused on impact of integrating AB-PMJAY (scheme is called Arogya Karnataka scheme or ArK) with National Tuberculosis Elimination Program [9]. This study reported an average cost per TB patient at US$124.5 per patient compared to US$159 per patient in 2018 [8,9]. The study also claims reduction in catastrophic costs incurring due to TB due to its gatekeeping mechanism.

This study, however, has major flaws. For example, in Table 3 the authors present analysis of average cost per TB patient using amount spent and number of patients [10]. This methodology is flawed as it does not convey whether these costs are direct costs or indirect costs. Indirect costs account for about 55.5% of total costs among TB patients [11]. The authors also claim reducing the catastrophic cost of TB treatment without explaining the methodology used for its measurement.

Modeling studies have shown that improvements in treatment packages have potential to reduce patient-incurred costs in the future [12,13]. These studies clearly point out that the 2025 targets of the End TB strategy for reducing catastrophic health expenditures would not be achieved by implementing any one intervention. Expanding access to care for tuberculosis services in the country has the potential to substantially reduce patient-incurred costs in the country.

Conclusion

Overall, the economic burden of tuberculosis in India is significant, especially for low-income households and tribal populations. The need for comprehensive strategies to address the financial barriers to treatment is crucial. While initiatives like the National Health Assurance Scheme aim to provide financial protection, more can be done to reduce out-of-pocket expenses and catastrophic costs for TB patients. Integrating programs like AB-PMJAY with the National Tuberculosis Elimination Program shows promise, but further research is needed to assess their impact on reducing economic burden. Overall, a multi-faceted approach is necessary to address the economic challenges of TB in India.

It is well-known that there is a symbiotic relationship between TB and poverty. New TB infections are not just a product of poverty, but also creates poverty. The economic impact of TB is seen to be many times greater on poor households

References

1. Chatterjee S, Das P, Shikhule A, Munje R, Vassall A. (2023) Journey of the tuberculosis patients in India from onset of symptom till one-year post-treatment. PLOS Glob Public Health 3(2): e0001564
2. Chandra A, Kumar R, Kant S, Parthasarathy R, Krishnan A. (2020). Direct and indirect patient costs of tuberculosis care in India. Trop Med Int Health 25(7):803-812
3. Yadav J, John D, Allarakha S, Menon GR. (2021). Rising healthcare expenditure on tuberculosis: Can India achieve the End TB goal? Trop Med Int Health 26: 1256–1275
4. Yadav J, John D, Menon, G R. (2019). Out of pocket expenditure on tuberculosis in India: do households face hardship financing?. Indian Journal of Tuberculosis, 66(4), 448-460
5. Suseela RP, Shannawaz M. (2023). Engaging the Private Health Service Delivery Sector for TB Care in India-Miles to Go! Trop Med Infect Dis 8(5):265
6. John, D., Yadav, J., Ray, D., Bhattacharya, P., Mukherjee, N., Patil, R., ... & Hansda, M. (2024). Hospitalisation expenditure on tuberculosis among tribal populations in India: a repeated cross-sectional analysis of national sample survey data, 2004 to 2018. Public Health in Practice, 100490
7. Kastor, A. and Mohanty, S. K. (2018). Disease-specific out-of-pocket and catastrophic health expenditure on hospitalization in India: do Indian households face distress health financing?. Plos One, 13(5), e0196106
8. Bhargava, A., Bhargava, M., & Meher, A. (2020). Universal health coverage and tuberculosis care in India in the times of covid-19: aligning Ayushman Bharat (national health assurance scheme) to improve case detection, reduce deaths and catastrophic health expenditure. The National Medical Journal of India, 33(5), 298
9. Shastri SG, Sancheti P, Nagaraja SB, Dayananda GG, Srinivas PK, Jayaprakash M, Ninge Gowda SN, Krishnamurthy A, Srinivasa BP, Singarajipura A, Devendiran R. (2023). Averting catastrophic tuberculosis costs in an Indian state: integration of Ayushman Bharat Arogya Karnataka with National Tuberculosis Elimination Program. Lancet Reg Health Southeast Asia 22:100327
10. Sharma, P., Zadey, S., & Mor, N. (2024). Integrating schemes could be beneficial but requires supportive evidence. The Lancet Regional Health - Southeast Asia, 23, 100386
11. Sinha, P., Carwile, M., Bhargava, A., Cintron, C., Acuña-Villaorduña, C., Lakshminarayan, S., ... & Hochberg, N. (2020). How much do Indians pay for tuberculosis treatment? a cost analysis. Public Health Action, 10(3), 110-117
12. Menzies, N., Gomez, G., Bozzani, F., Chatterjee, S., Foster, N., Baena, I., ... & Vassall, A. (2016). Cost-effectiveness and resource implications of aggressive action on tuberculosis in China, India, and South Africa: a combined analysis of nine models. The Lancet Global Health, 4(11), e816-e826
13. Verguet, S., Riumallo-Herl, C., Gomez, G., Menzies, N., Houben, R., Sumner, T., ... & Vassall, A. (2017). Catastrophic costs potentially averted by tuberculosis control in india and south africa: a modelling study. The Lancet Global Health, 5(11), e1123-e1132

For more information regarding this newsletter or to contribute, please contact Nibedita Rath nibedita.rath@ospfound.org or visit www.ospfound.org,

M. Sai Baba
msaibaba@nias.res.in

Newsletter designed by
Wengsi Chiu
wengsi.chiu@ospfound.org