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Tuberculosis Newsletter

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Articles

Editorial

Integrating Innovation and Policy: A Multi-faceted Approach to Tuberculosis Control

Dr. Nibedita Rath, Scientific Director, Open Source Pharma Foundation, Bengaluru, India, 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 one of our most formidable public health challenges. Despite extensive global initiatives, strides in TB control are persistently obstructed by factors like drug resistance, missed diagnoses, and the financial burden on patients. A nuanced understanding of these challenges, coupled with groundbreaking research and innovative approaches, promises a brighter future for TB management. Several recent articles in the current issue have shed light on these multi-dimensional efforts, offering insights into the contemporary landscape of TB control and possible pathways forward.

In "Mathematics and Statistics of, for and against Tuberculosis," Dr. Gaurav D. Sankhe outlines the indispensability of integrating mathematics and statistics in TB research. The piece elucidates how these quantitative sciences can enhance our understanding of TB's biology and contribute to developing new therapeutic targets. A pivotal focus is on the gut microbiome dynamics in TB patients undergoing treatment, highlighting how microbiome disruptions can exacerbate treatment outcomes. The detailed exploration of mathematical models and statistical analyses provides a blueprint for leveraging data to unravel complex biological interactions, thereby positioning mathematics and statistics as critical complements to traditional biological research.

Dr. Radha Munje and Dr. Neha Pachbhai, in "Diagnosing the Missing Millions: Connecting TB Patients to Care," tackle the pervasive issue of undiagnosed TB cases. Their exploration into the barriers ranging from stigma to healthcare access paints a bleak picture of the current diagnostic landscape. They compellingly argue for the inclusion of private healthcare providers in national TB programs, suggesting that bridging the public-private divide is essential for comprehensive TB control. Moreover, the authors emphasize the financial burden TB imposes on patients, advocating for robust social protection measures. The article effectively underscores that addressing TB requires not just medical but also sociopolitical solutions.

Image Credit: Global Fund

Dr. K. K. Chopra and Dr. Sanjay Rajpal bring an urgent perspective in their article "Salvage Regimen for DR TB treatment" by highlighting the challenges of treating drug-resistant TB (DR-TB). Salvage therapies combining new and repurposed drugs offer hope for those who do not respond to conventional regimens. Notably, their discussion on BPaL regimens—a combination of bedaquiline, pretomanid, and linezolid—underscores the promise of these advanced therapies. However, they caution that systemic issues such as drug availability and the need for individualized treatment plans remain key hurdles. This piece serves as a clarion call for accelerated efforts in drug development and regimen optimization tailored to resistant TB strains.

In "Artificial Intelligence in TB Control," Dr. V. K. Arora and Dr. Sanjay Rajpal explore the revolutionary potential of AI in TB diagnostics and treatment. The article presents an exciting vista of technological integration into TB control, from AI-powered chest X-rays to drone deliveries of samples in remote areas. The promise of AI in enhancing diagnostic accuracy, optimizing treatment regimens, and improving patient adherence through electronic monitors is palpable. However, the authors are mindful of AI adoption's ethical and implementation challenges, advocating for a balanced approach that ensures patient privacy and data security.

Dr. Nasser Yusuf's "Tuberculosis Recrudescence of Thoracic Surgery" revisits the resurgence of surgical interventions in TB management, particularly in cases of drug-resistant TB where medical treatments fall short. The piece traces the history of thoracic surgery in TB treatment, highlighting its evolving role amidst the rise of MDR-TB and XDR-TB. Dr. Yusuf presents a compelling argument for the integration of surgical options alongside medical therapy, emphasizing that a multidisciplinary approach is vital for comprehensive care. The call for early surgical intervention, before the disease progresses irreversibly, spotlights the need for timely referrals and collaborative care models.

Finally, Dr. M. Sai Baba's "The World of TB: Advances in Detection, Cure and Outreach" captures the cutting-edge innovations and outreach efforts reshaping TB control. From the development of a new 3D culture system by Indian researchers to track TB bacteria, to the introduction of new treatment regimens like BPaLM under India's National TB Elimination Program, this article celebrates the advances transforming TB management. Additionally, the piece highlights the ongoing trials for new vaccines as a promising avenue for prevention, while emphasizing the continued challenge of subclinical TB detection and community outreach to reduce stigma.

Together, these articles illustrate that the fight against TB is multifaceted, requiring scientific advancements, policy innovation, financial investment, and public health strategies. The integration of diverse approaches, from advanced diagnostics and treatment regimens to AI-driven technologies and surgical interventions, is pivotal. Additionally, addressing the social determinants of health, such as stigma, financial barriers, and access to care, is paramount in forging a holistic TB control strategy.

Investment in research and development must be paralleled by policies that facilitate equitable access to cutting-edge diagnostics and therapies. Public-private partnerships can play a crucial role in expanding healthcare access and improving case reporting. Moreover, the potential of AI and machine learning must be harnessed responsibly, with stringent safeguards to protect patient data and ensure ethical utilization.

In conclusion, while TB remains a stubborn global health challenge, the convergence of innovation, policy, and social action heralds a promising trajectory towards its control and eventual elimination. By adopting a comprehensive, integrated approach, we can hope to bridge the remaining gaps and make significant strides in eradicating this age-old scourge.

Mathematics and Statistics of, for and against Tuberculosis

Dr. Gaurav D. Sankhe, Research Associate, Immunology Program, Sloan Kettering Institute, 1275 York Ave, New York, USA

Emerging MDR TB strains have invigorated the need of finding novel mechanisms of adaptation of the pathogen in order to suggest strategies of intervention against it.

Abstract

After a brief dip in Tuberculosis (TB) incidence and mortality driven by Covid-19 pandemic, Mycobacterium tuberculosis (Mtb) emerged yet again as one of the leading cause of deaths in humans across globe. The rise of Multi Drug Resistant TB (MDR-TB) exacerbates the success of "end TB strategy". Thus, the statistics of TB clearly highlight the requirement for stepping up efforts for comprehensive health initiatives and concerted action plan to combat TB. Two-pronged approach could be by, on one hand, hitting the pathogen Mtb at its adaptability by gleaning into its mechanisms of adaptation and on the other, by reinforcing the host immune onslaught and pressures against Mtb. With two research stories, one involving mathematics and statistics for TB and other against TB, this article accentuates the merit of integrating mathematics and statistics with the biology of host as well as pathogen for performing data-backed theoretical investigations to not only further mechanistic insights but also suggest potential novel targets against TB.

Image Credit: Global Fund

Tuberculosis recently regained its position of the leading cause of deaths in humans from single infectious agent. Till date it is the most prevalent disease across the globe. A quick glance over the recent UN world tuberculosis report [1] brings in some hope but with much more disappointment. After the Covid-19 driven dip or pause in Tuberculosis incidence and mortality across all demographics, the sharp rise in sheer numbers has stretched the "End tuberculosis" timelines beyond the predicted temporal plots. In 2022, there were approximately 10.6 million new TB cases globally, with the disease claiming around 1.6 million lives. India, which is one of the high TB burden countries, reported about 2.9 million new TB cases and an estimated 0.5 million TB-related deaths in the same year. These statistics highlight the urgent need for comprehensive public health initiatives and concerted efforts to combat tuberculosis, particularly in regions with a high burden like India [1]. The rise of multidrug-resistant TB (MDR-TB) reported as ~5% of total global incidence ushers scare and despair. These statistics of TB burden strongly suggest that we are falling short of our efforts, and we have to step up our "endgame" against the TB causing pathogen Mycobacterium tuberculosis (Mtb). Broadly, the strategies of intervention stretch from finding druggable targets against vital mechanisms of adaptation and survival of the pathogen on one side and exploring avenues to reinforce host immune pressure and pathogen specific onslaught on the other. Mathematics and Statistics comes in handy for pursuing both strategies. The following research stories would, presumably, highlight the significance of knowledge of mathematics and statistics that could be fused with underlying biology to sharpen our tools in the battle against Tuberculosis.

The current regimen for DSTB (Drug Sensitive TB) includes Rifampicin (RIF), Isoniazid (INH), Pyrazinamide (PZA), and Ethambutol (EMB). Treatment typically spans 6 to 9 months, starting with an intensive phase of all four drugs for 2 months, followed by a continuation phase with RIF and INH for 4 to 6 months. MDR-TB is defined as resistance to at least two of the four, Rifampicin (RIF) and Isoniazid (INH), the two most potent anti-tubercular drugs. These antibiotics exert collateral damage on the other symbiotic bacteria in the gut collectively called as the gut microbiome. Recently a clinical study on gut microbiome dysbiosis and dynamics performed over time for DS-TB and MDR-TB patients [2] revealed that the TB-driven inflammation lead strong interrelation between gut microbiome and TB clearance. Microbiome disruption leading to pathobiont (troublemaker bacteria) dominance and evolution of resistance in commensals (gut friendly bacteria) further establishing their dominance in the microbiome provides a mechanistic understanding of the temporal fate of TB antibiotic driven gut microbiome dysbiosis. Fecal-microbiota transplantation of antimicrobial resistant commensal microbiome presents a unique solution for avoiding or mitigating TB drugs-driven inflammation thus reducing inertia for TB drug administration by patients over the prolonged due course. Now, in this clinical trial to determine the effect of antibiotics used in TB treatment on the composition of fecal microbiome (proxy for gut microbiome), and peripheral blood transcriptomics (signatures for TB-driven inflammation) used to model TB disease progression and resolution, involved hardcore mathematics and statistics. For instance fecal microbiome characterization informed enrichment in gut commensals (measured as NES, normalized enrichment score) as a function of microbiome dynamics, and mycobacterial load reduction (TTP) was defined for a particular hallmark pathway or TB signature obtained from blood peripheral transcriptomics yielding expression levels of common inflammatory signatures like interferon (IFN)-α, IFN-γ, interleukin-6 (IL-6) and Janus Kinase(JAK)-signal transducer and activator of transcription 3 (STAT3). Briefly, NES for a particular TTP is considered a general nonlinear function (the random forest) is applied to TTP and species relative abundances X in a particular sample say i as fixed effects and 1/ID (Internal expression differences) indicates random effects to account multiple samples from the same patient. Mixed-effects random forest regression modeling where NES for particular i was fit as a nonlinear function of (TTP and X) i + 1/ID, was applied to determine model-inferred associations [2]. Linear mixed-effects models were also run to identify significant associations between sex, age, and treatment kinetics on microbiome diversity to microbiome composition. These models were used to identify microbial species, pathways, and host genes associated with sex, age and treatment duration. This study appreciates the power of mathematics and statistics for correlating and delineating underlying effects of a complex phenomenon resulting into crucial insights presented by tangible results [2].

The study explored changes in the gastrointestinal microbiome associated with MDR TB treatment by using metagenomic sequencing of stool samples. Principal coordinate analysis on centered log-ratio transformed data was used to address compositionality in species and metabolic pathway abundance. Significant differences in microbial composition and gene content were identified between baseline and treatment completion samples compared to those collected at 2 weeks, 2 months, and 6 months. This was evidenced by PERMANOVA ($P < 0.05$) [3]. Notably, 23.6% of [Fig.1C] the variation in species abundance and 40.1% [Fig.1D] in pathway abundance on the first axis were linked to treatment-induced microbiome changes in the first 6 months. The second axis highlighted variability in early treatment response among different individuals.

The study explored the impact of MDR TB treatment on microbial species and metabolic pathways, comparing findings to pretreatment and drug-sensitive TB treatment results. MDR TB therapy, with the exception of increasing Flavonifractor plautii, significantly depleted the GI microbiome within the first six months (FDR < 0.05). Key species such as Bacteroides uniformis, Blautia spp., Clostridium bolteae, and others, known for producing bioactive metabolites and transforming bile acids, were notably reduced [2, 4].

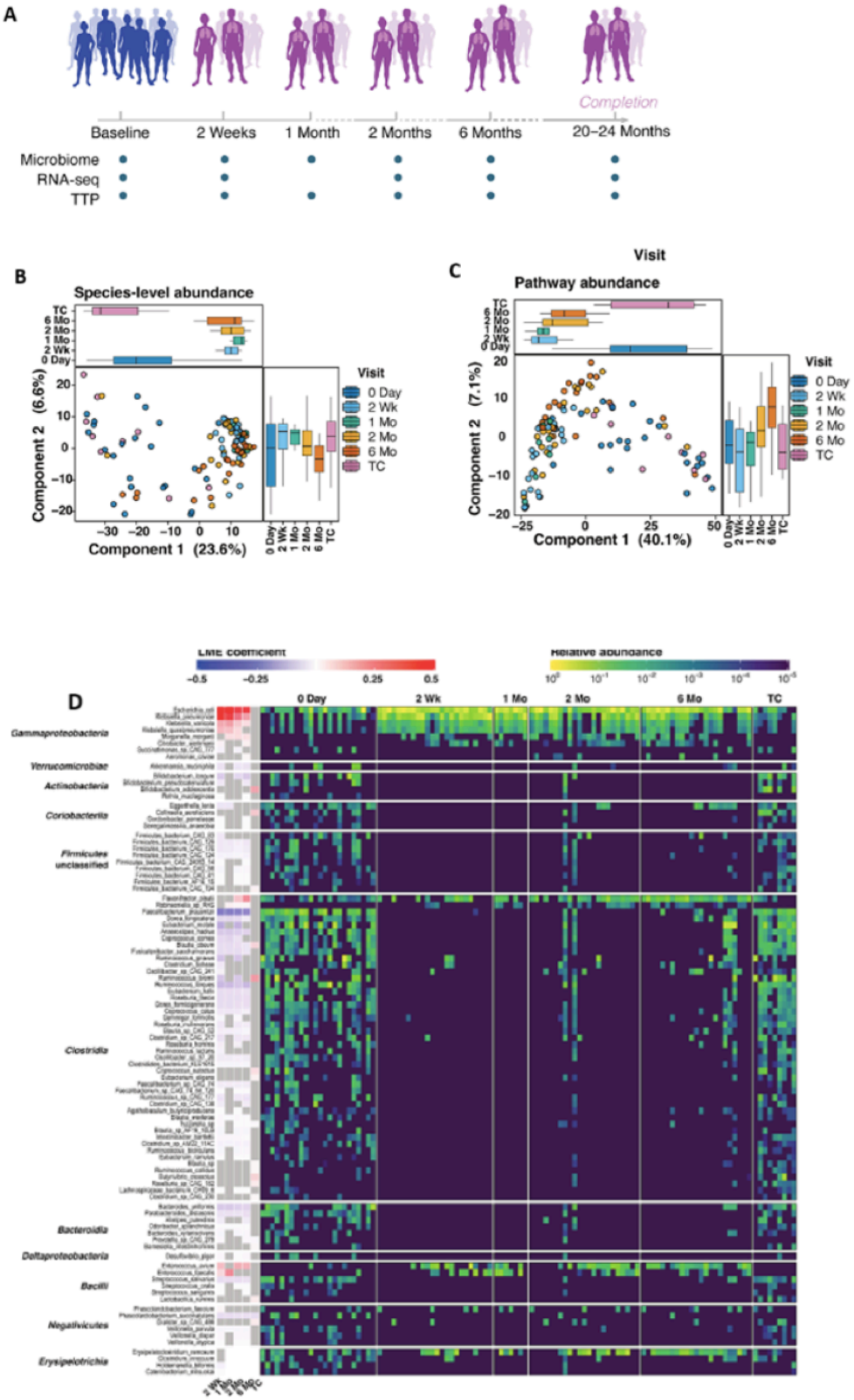

Figure 1: MDR TB treatment induces Mtb lung sterilization and causes a temporary perturbation in the microbiome, which recovers by treatment cessation. Schematic of the MDR TB treatment observational cohort. (B and C) Principal coordinate analysis on center-log-ratio transformed data for species abundances (B) and functional pathway abundance (C)from metagenomic sequencing. (D)Taxonomic abundance of the microbiome during MDR treatment. Bhattarai et al., Sci. Transl. Med. 16, eadi9711 (2024)

Emerging MDR TB strains have invigorated the need of finding novel mechanisms of adaptation of the pathogen in order to suggest strategies of intervention against it. Two component signaling system (TCS), comprising of a sensing component known as histidine kinase (HK) and a downstream responsive component named as response regulator (RR), is a predominant toolbox used by bacteria and lower eukaryotes for sensing and adaptation [5]. Phosphorylation at histidine residue of HK (hence the name) upon incoming signal and physical transfer of the phosphoryl group to aspartate residue of RR thereafter, forms the atypical "talk" to inform and respond towards the incoming signal. HK and RR are present on the same operon in the bacterial genome like a couple made in heaven and hence termed as a cognate pair. Mtb TCSs are recently shown to have non-cognate interactions as well informally known as "crosstalk" [6]. TCSs are a playground for mathematicians and theoreticians for identifying various signaling landscapes and unveiling their unique and vivid output features. In another recent study, sequestration of HK by other non-cognate RRs establishes a signal detection threshold below which all incoming signals for the HK get diffused and ignored [5]. The pathogen uses this simple design principle to define the quantum of signal versus noise thereby distinguishing what to ignore and what to respond. This sequestration phenomenon where non cognate RR tightly binds to a signal-active HK could be imagined similar to our close friend acting like a sequester by hugging us tightly in the middle of an altercation posed by a bully so that we don't respond to it and lose our mind over it. This power of ignorance is blissful for Mtb allowing it to avoid mounting disproportionately large and biologically costly responses against frivolous signals. Since incoming signals or ligands for many HKs in Mtb are unknown, without employing mathematical framework and statistical tools, it would have been an arduous task to achieve both (a) visualize and formalize this underlying phenomenon and (b) proving it quantitatively and robustly. Considering a theoretical signal of various strengths (Concentration and time) as input and expression levels of the downstream genes for the signaling cascade as output, the input-output profiles with and without sequestration were mathematically modeled using all phosphorylation and other chemical reactions leading to the expression events. Most of the kinetic parameters of the reactions were obtained by biochemical and biophysical techniques in vitro (in test tubes) and others were obtained through literature. The enthralling moment in the study is witnessing the mathematical model employing invitro kinetic parameters predicting the extent decrease in expression of downstream genes due to sequestration given the relative increase in the sequester amount in vivo (in mycobacterial cell) overlapped robustly with the expression levels of the downstream genes in vivo obtained by qRT PCR. Phosphohistidine and phosphoaspartate in signal activated HKs and RRs respectively, being unique and rare in humans, make TCSs potent drug targets. Targeting such a sequestration interaction can render the bug to get bugged even with small stress signals posed by host immunity and or drug regimens. Exploiting this finding to pin a sequestration interaction, in principle, can exhaust the pathogen enough to succumb to host-immune pressures. Pinning down various protein complexes using molecular scaffolds has been a tried and tested hack by pharma companies which could be easily extended in this case. Here, we again observe that mathematics and statistics rendered envisioning a phenomenon of HK sequestration by non-cognate RRs, thus providing a potential target against the tuberculosis pathogen.

Mathematics and statistics have been savior to simulate clinical trials for various potent vaccine candidates during the COVID-19 pandemic in order to proceed with the expensive and exhaustive multiple phase clinical trial of the best candidate thereby accelerating vaccine development when it was most required (Trial simulator software by Certara Inc, USA), Further to compute optimal dosage amount and regimen for the vaccine mathematical models defining immunological mechanisms are extensively used [7]. Mathematical modeling has also helped elucidate and provide the possible mechanistic insights of natural and post-treatment control and quantified effects of antiretroviral therapy used against HIV [8]. Given the extensive utilization of mathematics and statistics in not only in TB research but also to other infectious diseases, I honestly feel that having some level of training in mathematics from high school till graduation is imperative and should be ensured through government policies. The western world has realized this in its full glory where a former British PM recently enforced mathematics as a compulsory subject in its high school curriculum rather than being optional. Indeed, generative AI tools like Bard, ChatGPT, Perplexity AI will exist to assist us for the future, yet, they won't help in developing the underlying logic and rationale, essential for building algorithms. Better learn a subject for a few productive years than to be a lifetime slave or subscriber of AI, right?

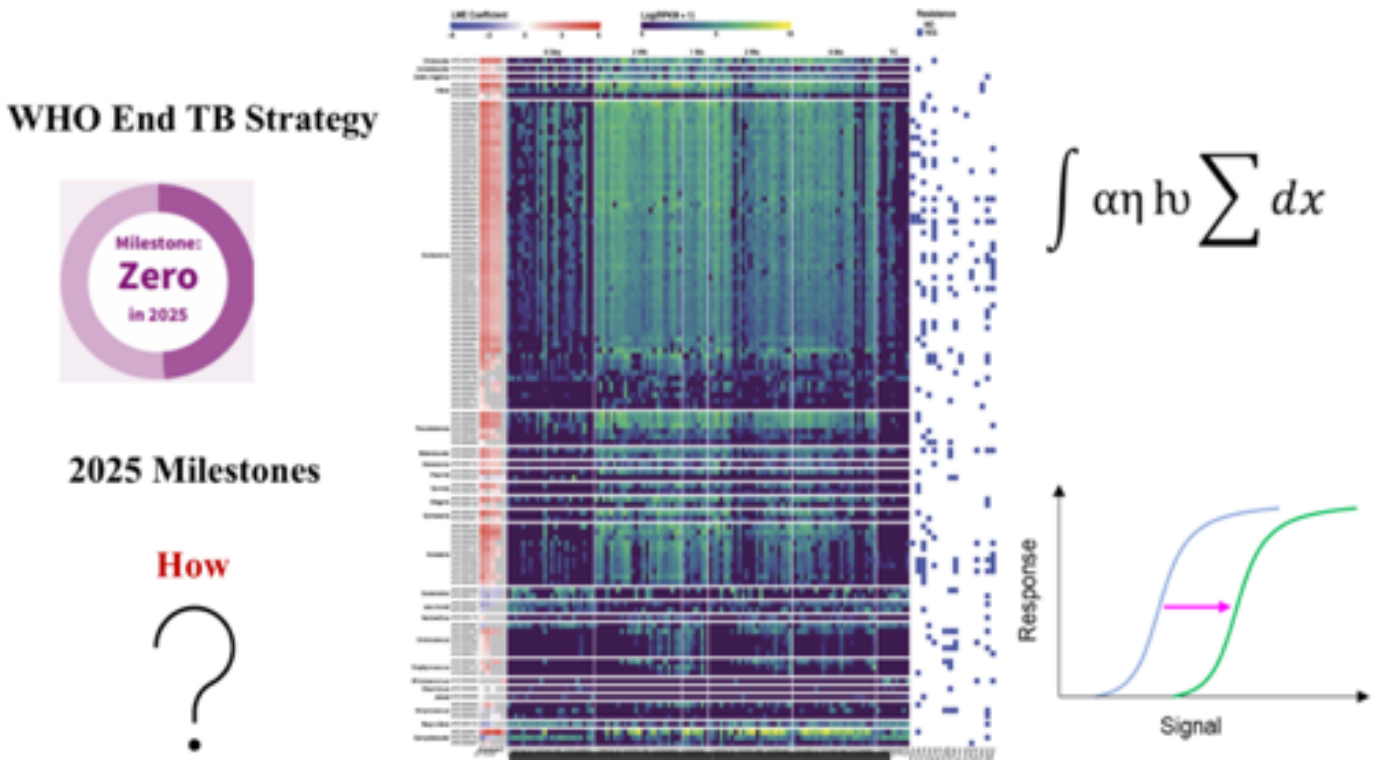

Figure 2: Abstract art highlighting ambitious WHO End TB Strategy target (left), a possible method to reach that goal could be utilization of mathematics and statistics in TB research as showcased in a representative heat map relative abundance of various bacterial families in gut microbiome [2] (center) and elucidative equation with graphical representation of Stimulus-Response profile with sequestration.

References

1. Global tuberculosis report 2023: Geneva: World Health Organization: 2023. https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2023.
2. Bhattarai, S. K., Du, M., Zeamer, A. L., M Morzfeld, B., Kellogg, T. D., Firat, K., Benjamin, A., Bean, J. M., Zimmerman, M., Mardi, G., Vilbrun, S. C., Walsh, K. F., Fitzgerald, D. W., Glickman, M. S., & Bucci, V. (2024). Commensal antimicrobial resistance mediates microbiome resilience to antibiotic disruption. Science translational medicine, 16(730), eadi9711. https://doi.org/10.1126/scitranslmed.adi9711.
3. Lloyd-Price, J., Arze, C., Ananthakrishnan, A. N., Schirmer, M., Avila-Pacheco, J., Poon, T. W., Andrews, E., Ajami, N. J., Bonham, K. S., Brislawn, C. J., Casero, D., Courtney, H., Gonzalez, A., Graeber, T. G., Hall, A. B., Lake, K., Landers, C. J., Mallick, H., Plichta, D. R., Prasad, M., ... Huttenhower, C. (2019). Multi-omics of the gut microbial ecosystem in inflammatory bowel diseases. Nature, 569(7758), 655–662. https://doi.org/10.1038/s41586-019-1237-9.
4. Sankhe, G. D., Dixit, N. M., & Saini, D. K. (2018). Activation of Bacterial Histidine Kinases: Insights into the Kinetics of the cis Autophosphorylation Mechanism. mSphere, 3(3), e00111-18. https://doi.org/10.1128/mSphere.00111-18.
5. Sankhe, G. D., Raja, R., Singh, D. P., Bheemireddy, S., Rana, S., Athira, P. J., Dixit, N. M., & Saini, D. K. (2023). Sequestration of histidine kinases by non-cognate response regulators establishes a threshold level of stimulation for bacterial two-component signaling. Nature communications, 14(1), 4483. https://doi.org/10.1038/s41467-023-40095-2.
6. Agrawal, R., Sahoo, B., & Saini, D.K. (2016). Cross-talk and specificity in two-component signal transduction pathways. Future microbiology, 11, 685-97, https://doi.org/10.2217/fmb-2016-0001.
7. Giorgi, M., Desikan, R., van der Graaf, P. H., & Kierzek, A. M. (2021). Application of quantitative systems pharmacology to guide the optimal dosing of COVID-19 vaccines. CPT: pharmacometrics & systems pharmacology, 10(10), 1130–1133. https://doi.org/10.1002/psp4.12700.
8. Vemparala, B., Chowdhury, S., Guedj, J., & Dixit, N. M. (2024). Modelling HIV-1 control and remission. NPJ systems biology and applications, 10(1), 84. https://doi.org/10.1038/s41540-024-00407-8.

Diagnosing the Missing Millions: Connecting TB Patients to Care

Dr. Radha Munje, Prof and Head, Respiratory Medicine, IGGMC, Nagpur

Dr. Neha Pachbhai, Asst Prof, Respiratory Medicine, IGGMC, Nagpur

Abstract

Tuberculosis (TB) continues to be a major global health challenge, with approximately one-third of cases going undiagnosed despite significant efforts. This article explores the factors leading to missed diagnoses, including barriers to healthcare access, stigma, and underreporting from private healthcare providers. Additionally, the financial burden on TB patients, particularly in high-burden countries, is examined. Social protection programs and the involvement of private practitioners are highlighted as key components in addressing TB control. The article also underscores the importance of new diagnostic innovations and multisectoral approaches to combat the growing threat of multidrug-resistant TB (MDR-TB) and achieve TB elimination by 2025.

Introduction

Despite global initiatives aimed at eliminating tuberculosis (TB), millions of cases remain undiagnosed, particularly in high-burden countries. In 2014, the World Health Organization (WHO) launched the "Reach the 3 Million" campaign to address the 3 million TB cases being missed annually. However, even with substantial efforts, the goal remains unfulfilled for many countries. By 2022, although 10.6 million people were diagnosed with TB globally, nearly one-third of cases continued to go undiagnosed [1, 2].

This article focuses on the various factors that contribute to undiagnosed TB cases, the financial burden on patients, and the role of private healthcare sectors. It also highlights the growing burden of multidrug-resistant TB (MDR-TB) and emphasizes the need for a comprehensive, multisectoral approach and innovative diagnostic technologies to achieve TB elimination by 2025.

Barriers to TB Diagnosis

Missed Diagnoses and Contributing Factors

Several factors contribute to the high number of missed TB diagnoses, especially in countries with a heavy TB burden. Key factors include:

- Limited Access to Healthcare: Many patients, particularly in rural areas, lack access to healthcare services for diagnosis and treatment.
- Stigma: The social stigma associated with TB often discourages individuals from seeking medical care.
- Misdiagnosis: Inaccurate diagnosis by healthcare providers can result in patients receiving inappropriate treatment.
- Private Sector Underreporting: In many high-burden countries, a significant portion of TB cases are managed outside the formal healthcare system. These cases, treated in private settings, are frequently not reported to national TB programs (3).
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Approximately 75% of the missing TB cases are concentrated in 13 priority countries, including India, Indonesia, Bangladesh, South Africa, and Nigeria [3].

Impact of Delayed Diagnosis

Delayed TB diagnosis has far-reaching consequences, including increased transmission rates, higher mortality, and the stagnation of TB case notifications. Furthermore, delays in diagnosis and treatment significantly contribute to the spread of multidrug-resistant TB (MDR-TB), which poses a severe challenge to global TB control efforts [3]. Many high-burden countries have failed to integrate traditional healers and private medical practitioners into national TB programs, thereby reducing the effectiveness of TB detection and treatment [2].

Financial Burden on TB Patients

Despite free treatment being available under national TB programs, TB patients and their households face catastrophic financial costs in many countries. These costs include transportation, income loss, and diagnostic expenses. For example, TB patients in India incur an average cost of ₹50,000 INR (~$600 USD), even with free treatment available. This financial burden is shared by patients in other countries, as detailed in Table 1 [4].

Country	Catastrophic Costs per TB Patient	Key Drivers of Cost	Reference
India	₹50,000 INR (~$600 USD)	Income loss, transportation, diagnostics	Chatterjee et al., 2024 [4]
Kenya	$396 USD	Medical expenses, income loss	Barasa et al., 2021 [5]
Nigeria	$285 USD	Income loss, transportation	Ukwaja et al., 2013 [6]
Peru	$350 USD	Diagnostics, income loss	Rocha et al., 2016 (7)
Global Estimate	$100–$500 USD	Transportation, income loss, medical expenses	WHO Report, 2021 [8]

Table 1: Catastrophic Costs Incurred by TB Patients Across Different Countries

Social Protection Measures

Social protection programs can significantly alleviate the financial burden on TB patients and improve treatment adherence. Notable examples include:

1. Brazil's Bolsa Família Program: This conditional cash transfer program has improved access to healthcare services, including TB care, by providing financial support to low-income families. It has been shown to increase TB cure rates and improve overall TB control [9].
2. India's Nikshay Poshan Yojana: Launched in 2018, this program provides financial support for nutritional needs to TB patients. It has been credited with enhancing treatment adherence and reducing the economic burden on TB patients in India [10].
3. South Africa's TB Care and Control Program: Social protection measures, including transportation subsidies and cash transfers, have helped to reduce catastrophic costs for TB patients, leading to improved treatment adherence [11].

Multidrug-Resistant TB (MDR-TB)

MDR-TB is a growing global concern, with some countries reporting MDR-TB rates exceeding 18%. In India, estimates indicate that between 1.8% and 2.8% of new TB cases are MDR-TB, while 15% to 20% of retreatment cases are MDR-TB [12].

Diagnosing MDR-TB requires advanced laboratory capacity, including culture and drug susceptibility testing (DST). However, many high-burden countries lack the necessary infrastructure to conduct these tests. Even when MDR-TB is diagnosed, second-line TB drugs are often expensive and difficult to procure, which poses a significant challenge to MDR-TB treatment [12].

The Role of Private Healthcare Providers

Efforts to involve private healthcare providers in TB control have yielded positive outcomes in some countries. For example, in India, private practitioners have been incentivized to notify TB cases and provide free diagnostic services and treatment. This strategy has led to a significant increase in case notification rates, with some districts reporting that over 30% of TB cases are now being reported from the private sector. The 2023 India Tuberculosis Report recorded a notification of 2.42 million cases, a 13% increase compared to 2021 [13].

Image Credit: MedIndia

Innovations in TB Diagnostics

To achieve TB elimination by 2025, it is critical to implement advanced diagnostic technologies. Rapid diagnostic tools, such as AI-based chest X-rays and PCR tests, have the potential to identify TB cases earlier, preventing delays in treatment. While these technologies are promising, their adoption remains limited due to high costs and the need for significant laboratory infrastructure in resource-poor settings [14].

Innovative diagnostic methods, combined with comprehensive public-private partnerships and social support systems, are essential to achieving the goal of TB elimination.

Conclusion

The fight against TB, especially in high-burden countries, requires more than just medical interventions. A multisectoral approach that includes innovative diagnostics, integration of private healthcare providers, and strong social protection measures is essential. The rise of MDR-TB further complicates the global effort to eliminate TB by 2025. To overcome these challenges, we must focus on early detection, ensuring access to quality diagnostics and treatments, and reducing the financial burden on TB patients through expanded social support programs.

References

1. WHO. Global Tuberculosis Report 2014. Geneva: World Health Organization; 2014. Available from: https://www.who.int/tb/3million/en.
2. World Health Organization. Global Tuberculosis Report 2022. Geneva: WHO; 2022. Available from: https://www.who.int/teams/global-tuberculosis-programme/tb-reports.
3. Mishra GP. Public-private mix in tuberculosis. Lancet Infect Dis. 2012;12(12):908-9. doi: 10.1016/S1473-3099(12)70257-8.
4. Chatterjee S, Das P, Stallworthy G, Bhambure G, Munje R, Vassall A. Catastrophic costs for tuberculosis patients in India: Impact of methodological choices. PLOS Glob Public Health. 2024 Apr;4(4). doi: 10.1371/journal.pgph.0003078.
5. Barasa E, Ayieko P, Cleary S, English M. Determinants of household catastrophic costs for drug-sensitive tuberculosis patients in Kenya. Infect Dis Poverty. 2021;10:95. doi: 10.1186/s40249-021-00879-4.
6. Ukwaja KN, Alobu I, Abimbola S, Hopewell PC. Household catastrophic payments for tuberculosis care in Nigeria. Infect Dis Poverty. 2013;2:21. doi: 10.1186/2049-9957-2-21.
7. Rocha C, Montoya R, Zevallos K, Curatola A, Yataco R, Franco J, et al. Beyond pills and tests: addressing the social determinants of tuberculosis. Clin Med (Lond). 2016 Dec;16(Suppl 6). doi: 10.7861/clinmedicine.16-6s-s79.
8. World Health Organization. Global Tuberculosis Report 2021. Geneva: WHO; 2021.
9. Torrens AW, Rasella D, Boccia D, et al. Effectiveness of a conditional cash transfer programme on TB cure rate: a retrospective cohort study in Brazil. Lancet Glob Health. 2016 Sep;4(9). doi: 10.1016/S2214-109X(16)30183-2.
10. Central TB Division, Ministry of Health and Family Welfare, Government of India. India TB Report 2022. Available from: https://tbcindia.gov.in.
11. Mudzengi D, Sweeney S, Hippner P, et al. The patient costs of care for those with tuberculosis and HIV: a cross-sectional study from South Africa. Health Policy Plan. 2021;36(1):78-87. doi:10.1093/heapol/czaa153.
12. Sharma S. Mission End TB: Finding the Missing Millions and Bridging the Gap. J Community Health Manag. 2023;10(3):80-82.
13. Central TB Division. India TB Report 2023. New Delhi, India.
14. Sharma S. Mission End TB: Finding the Missing Millions and Bridging the Gap. J Community Health Manag. 2023;10(3):80-82.

Salvage Regimen for DR TB Treatment

Dr. K. K. Chopra1, Former Director, New Delhi Tuberculosis Centre, Jawaharlal Nehru Marg, New Delhi-110002

Dr. Sanjay Rajpal, Director, New Delhi Tuberculosis Centre, Jawaharlal Nehru Marg, New Delhi-110002

Treating multidrug-resistant tuberculosis (MDR-TB), characterized by Mycobacterium tuberculosis strains resistant to both isoniazid and rifampicin, presents significant challenges, especially in resource-constrained settings. Persistent sputum culture positivity despite the administration of second-line TB medications leaves limited options for patients, particularly when the disease has progressed too far for surgical intervention to be viable. In this context, salvage therapy is employed, which involves formulating a treatment plan that combines new and previously used medications in a last effort to achieve sputum conversion before declaring the treatment unsuccessful.

Image Credit: AidsMap

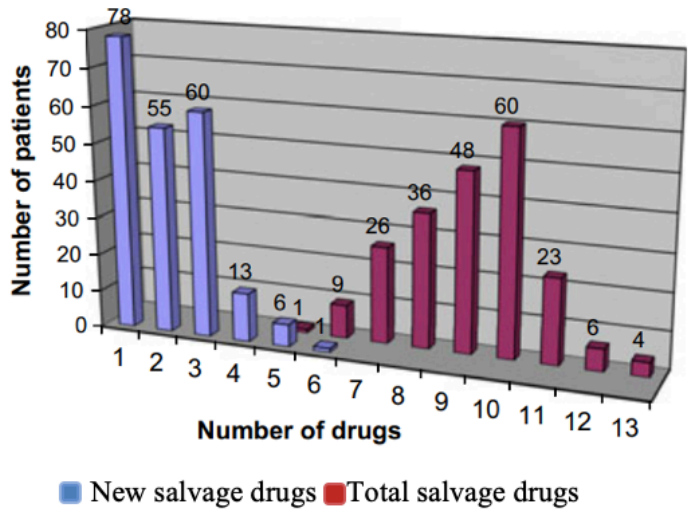
Tuberculosis is still a major problem in India and the world. As per data from 2021 there were 450,000 new DRTB cases. Treatment success rate among these cases remains at 59%. [1]. A retrospective study assessed [2] the effectiveness of salvage therapy in 213 patients in Peru. The salvage regimens included a median of two new drugs (ranging from 1 to 6) and nine total drugs (new and previously used combined, ranging from 5 to 13). Moxifloxacin was the most commonly used new drug, followed by capreomycin, amoxicillin-clavulanate, kanamycin, and clarithromycin. Of the patients, 65 (30.5%) achieved culture conversion. Notably, salvage regimens containing moxifloxacin had a significantly higher likelihood of resulting in culture conversion (OR 2.2; p = 0.02). This finding indicates that later-generation fluoroquinolones, like moxifloxacin, should be included in salvage therapy and possibly in the initial MDR-TB treatment, to enhance the chances of curing the patient when they are in the best position for a successful outcome.

For patients who remain sputum-culture-positive and are on second line therapy, treatment options are limited. Salvage therapy is a regimen which combines new and previously used drugs for DR TB treatment to attain sputum conversion before treatment outcome is declared as failed. [2] It is needed for patients who receive BDQ (bedaquiline) under conditional access but fail to treatment. Its DST guided approach with a selection of First and second line drugs including group 3 drugs to scientifically design a regimen wherever possible. [1, 10]As per a study, Salvage regimens included a median of two new drugs (range 1-6) and nine (range 5-13) [Fig.1] total (new plus previously used) drugs. Moxifloxacin followed by capreomycin, amoxicillin-clavulanate, kanamycin and clarithromycin were found to be very effective After use of this regimen culture conversion was seen in 30.5% patients [Table 1]. Salvage treatments incorporating moxifloxacin demonstrated a notably higher probability of resulting in culture conversion compared to those without it. This correlation remained statistically significant even among the group of individuals who were treated with a salvage regimen where moxifloxacin was the sole newly introduced medication.

Drug	Received before starting salvage therapy	Received as a part of salvage therapy
Moxifloxacin	9.4% (20)	50.7% (108)
Capreomycin	51.2% (109)	33.8% (72)
Amoxicillin-clavulanate	56.3% (120)	23.4% (50)
Kanamycin	53.5% (114)	20.7% (44)
Clarithromycin	5.6% (12)	20.7% (44)
PAS	89.7% (191)	9.4% (20)
Streptomycin	15.0% (32)	9.4% (20)
Pyrazinamide	43.2% (92)	8.9% (19)
Ethambutol	32.9% (70)	7.5% (16)
Clofazamine	51.6% (110)	6.6% (14)
Rifabutin	1.9% (4)	5.6% (12)
Ethionamide/prothionamide	83.6% (178)	4.7% (10)
Isoniazid	5.2% (11)	3.8% (8)
Cycloserine	96.2% (205)	2.8% (6)
Ciprofloxacin/ofloxacin	90.6% (193)	2.8% (6)
Rifampicin	5.2% (11)	2.8% (6)
Levofloxacin	4.2% (9)	0.5% (1)

PAS, para-aminosalicylic acid.

Table 1: Number of drugs used in the salvage regimen (n = 213)
https://doi.org/10.1111/1469-0691.12335.



https://doi.org/10.1111/1469-0691.12335.

Bedaquilin and Delamanid with other regimens:

Studies quote [3] that use of Bdq and Dlm (delamanid) in combination with the WHO-recommended regimens showed good efficacy and safety. Experience withFluoroquinolone -resistant MDR-TB and XDR-TB have poor treatment outcome, and 95% patients in this study achieved culture conversion duringtreatment with the two new TB drugs .As per the study 82% patients achieved good outcomes at the 12-month interim analysis, despite fluoroquinolone-resistant MDR-TB in all patients and XDR-TB in 64% of patients [4,5]. Another study concluded that in the optimized background regimen (OBR), adding BDQ or DLM, excellent response was achieved with lower death rates. Available studies [6] also concluded that BDQ-DLM-based regimens in drug-resistant TB were effective while managing adverse events.

Linezolid (LZD) and Clofazimine (CLF):

Studies have concluded that LZD when is used for 6 months for DRTB patients it accelerates treatment culture conversion. Clofazimine, has concentration-dependent anti-mycobacterial, pro-oxidative, and anti-inflammatory properties. When it is included to the regimen, studies have shown reduced lung bacterial load and relapse rates in mice, raising the potential for shortening the treatment duration.

BPaL (Bedaquiline, Pretomanid, Linezolid) Regimen:

As per a study [5], TB programmes may consider combining newer drugs with repurposed drugs rather than using them individually with OBR. Various studies have shown the effectiveness of combining Bedaquiline (BDQ) and Delamanid (DLM) as a combination with good culture conversion results after 6 months of therapy. During the therapy no additive / synergistic QTc-prolongation was observed.World Health Organization (WHO) suggests including drugs from both group A and B to have at least 4 effective medicines in a regimen. Pretomanidwhen used in combination with bedaquiline and linezolid are contraindicated in patients for whom bedaquiline and/or linezolid is contraindicated.[2]

BPaL, consists of bedaquiline pretomanid and linezolid. WHO TB guidelines allow for the programmatic implementation of treating almost all forms of drug-resistant TB with pretomanid-containing regimens using six-month, all-oral, three or four drug regimens with reported success rates of approximately 90% in clinical trials. The global treatment success rate has been 63% with 9+ month treatment standards

The Future: BPaL(M)

BPaL/M is a 6 month long DRTB, all-oral treatment regimen compromising of bedaquiline, pretomanid, linezolid, with or without moxifloxacin (M) (DR-TB). This regimen has been suggested by the WHO. The regimen was first studied in South Africa under the Nix-TBm Phase 3 clinical trial with several subsequent clinical and observational studies establishing its applicability in country settings.

Conclusion:

A committee in South Africa in 2011 advised Use of salvage regimens in individual patients with high-grade resistance [7]; Studies have also shown that (7) fully oral, short-course regimen of BDQ and DLM with other drugs gives a favorable outcome of 91% in patients with MDR-TBFQ+/SLI+ and 69% in those with both FQ (fluoroquinolones) and SLI (second-line injectable) resistance. The median time to culture conversion was approximately 8 weeks. Favorable outcome of this regimen is greater than that seen in a South African cohort study whereby Bedaquiline along with Delamanid was used along with moxifloxacin, CFZ, or pyrazinamide [1] with similar results at the end of the study. A study from Mumbai ,India concluded that home-based meropenem therapy using peripherally inserted central catheter is feasible with few adverse effects. This can be a promising strategy in the management of MDR/FQ/SLI/XDR-TB when an effective oral regimen cannot be otherwise constituted [2]. More promising results are also seen in the BPaL (M) regimen. WHO in May 2022, has issued guidance to use BPaL(M) regimen for treatingall forms of DR-TB in patients aged 14 years and above [1]and this hold a promising future.

Current WHO guidelines offer several treatment options for patients with MDR/RR-TB. The choice of treatment regimen is influenced by several factors, including the patient's specific drug-resistance profile, history of previous TB treatment, drug-resistance patterns in close contacts, patient age, extent of pulmonary TB, and the location of any extrapulmonary TB.

For patients who do not qualify for, or did not respond well to, the standard 6-month or 9-month regimens, have extensively drug-resistant TB (XDR-TB), or cannot tolerate essential drugs in these shorter regimens, longer individualized regimens are recommended. These regimens typically last at least 18 months and are tailored according to the patient's drug-resistance profile, medical history, and a hierarchical grouping of secondary TB medications [8].

References:

1. WHO. Tuberculosis Geneva: World Health Organization. World Health Organization 2020; [27.10.2021]. Available from: https://www.who.int/health-topics/tuberculosis#tab=tab_1

2.Seung, K. J., Becerra, M. C., Atwood, S. S., Alcántara, F., Bonilla, C. A., & Mitnick, C. D. (2014). Salvage therapy for multidrug-resistant tuberculosis. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases, 20(5), 441–446. https://doi.org/10.1111/1469-0691.12335.

3.https://www.tballiance.org/access/pretomanid-and-bpal-regimen

4. Kwon Y-S, Jeon D, Kang H, et al. Concurrent use of bedaquiline and delamanid for the treatment of fluoroquinolone-resistant multidrug-resistant tuberculosis: a nationwide cohort study in South Korea. Eur Respir J 2021; 57: 2003026 [https://doi.org/10.1183/13993003.03026-2020].

5. Padmapriyadarsini C, Vohra V, Bhatnagar A, Solanki R, Sridhar R, Anande L, Muthuvijaylakshmi M, Bhatia M, Jeyadeepa B, Taneja G, Balaji S, Shah P, Saravanan N, Chauhan V, Kumar H, Ponnuraja C, Livchits V, Bahl M, Alavadi U, Sachdeva KS, Swaminathan S; for BEAT India Team. Bedaquiline, Delamanid, Linezolid and Clofazimine for Treatment of Pre-extensively Drug-Resistant Tuberculosis. Clin Infect Dis. 2022 Jun 29;76(3):e938–46. doi: 10.1093/cid/ciac528. Epub ahead of print. PMID: 35767251; PMCID: PMC9907500.

6.Mongia, H., Mamnoon, F., Silsarma, A., Mahajan, R., Dalal, A., Galindo, M. A., Iyer, A., Singh, P., Mansoor, H., Das, M., Morales, M., Spencer, H., & Isaakidis, P. (2024). Concomitant bedaquiline and delamanid therapy in patients with drug-resistant extra-pulmonary tuberculosis in Mumbai, India. Journal of clinical tuberculosis and other mycobacterial diseases, 35, 100433. https://doi.org/10.1016/j.jctube.2024.100433.

7.Management of DRTB:Policy Guidelines ,Health Department ,Republic of South Africa,August 2011, https://www.nicd.ac.za/assets/files/MANAGEMENT%20of%20drug%20resistant%20TB%20guidelines.pdf

8.https://www.who.int/news-room/questions-and-answers/item/tuberculosis-multidrug-resistant-tuberculosis-(mdr-tb)

Artificial Intelligence in TB Control

Dr. V K Arora, Chairman, TB Association of India, Gokul Nagar, Sansad Marg Area, New Delhi-110001

Dr. Sanjay Rajpal, Director, New Delhi Tuberculosis Centre, Jawaharlal Nehru Marg, New Delhi-110002

Dr. Kamal Kishore Chopra, Former Director, New Delhi Tuberculosis Centre, Jawaharlal NehruMarg, New Delhi-110002

Dr. Ankita Anand, New Delhi Tuberculosis Centre, Jawaharlal Nehru Marg, New Delhi-110002

Traditional methodsof diagnosing tuberculosis require significant time and resources, particularly in countrieswhere the diseaseis prevalent and healthcare systemsare less developed. Additionally, more and more tuberculosis cases are becomingresistant to drugs, posing a significant hazard to public health. Culture-based TB diagnosis, which has long beenconsidered the most reliable method,faces challenges due to its long testingtimes. To addressthis issue, MTB/RIF assays such as GeneXpert and Truenat were developed. These are rapid molecular tests that detect Mycobacterium tuberculosis DNA and rifampicin resistance [1]. However, as of 2022, their use remains limited, with only 33% of people globally using them as initial diagnostic tests [2].

Image Credit: MedScape

In recent decades, the rapid advancement of computer technology has led to an increased interest in artificial intelligence (AI) across various industries, particularly in the realm of image recognition. The term "Artificial Intelligence" was coinedby John McCarthy[3]. AI involvescreating computer systemscapable of studyingand developing theories, methods, and technologies, as well as performing tasks that simulate and extend human intelligence. Researchers and innovators are utilizing AI to supplement and enhance current diagnostic methods, acknowledging the necessity for improved accessibility, cost-effectiveness, sensitivity, awareness, and infrastructure. Over the past decade, there has been a significant increase in investment in various techniques and technologies for TB treatment. These efforts include precision medicine, improved surveillance, program management, prevention strategies, AI-supported early diagnosis, monitoring, and optimization of patient care. Around 23% of the global population is estimated to have LTBI [4]. In India, the estimate is 35- 40% of the population [5]. Identifying whom to test for latent tuberculosis infection(LTBI) can be challenging since individuals often do not seek care due to the absenceof symptoms. Therefore, testing and treating a large section of the population presents a challenge. AI has the potential to identify areas that are more vulnerable and, require greater interventions. By using a range of input parameters, a potential AI solution can forecast the probability of LTBI progressing into active TB.

Early detection of active TB cases in a community is critical in breaking the chain of transmission. Globally,2.9 million TB cases are unreported (the gap betweenestimated cases and newlydiagnosed cases) due to underreporting of diagnosed cases or underdiagnosis [6]. AI can accelerate medicaldiagnosis by swiftlyand accurately analyzingmedical images like chest X-rays within minutes.For example, AI-basedsoftware called qXR, rapidly classifies X-ray scans, identifies lung abnormalities, and highlights them on the X-ray, enablingthe detection of TB within minutesand linkage to treatment on the same day [7]. Although AI-assisted X-ray reading has the potentialto detect radiological lesions promptly but it has limitations of differential diagnosisand identifying lesionsof other diseases.

There is a hypothesis that the cough sounds produced by individuals with pulmonary tuberculosis (TB) may possess a distinct signature. Therefore, if an AI solution can learn the characteristics of these cough sounds, it could classify individuals in real-time as either healthy or likely to have tuberculosis. An AI-based mobile platform called "Swaasa," currently undergoing validation with support from the India Health Fund & ACT Grants, utilizes a mobile phone's microphone to record cough sounds from a patient. These sounds are analyzed to identify unique cough signatures, enabling the rapid detection of possible TB presence within seconds [8]. But the reliability of AI study of cough sound is being assessed in large cohorts before making it a universal screening tool. Even then, it may become a screening test but not diagnostic of tuberculosis, which we may require complementing it with symptomatic screening.

AI-enabled readingand interpretation of diagnostic tests can help improve the efficiency and accuracy of test results.One such exampleis the AI-enabled reading and interpretation of Line Probe Assay (LPA) strips used for the diagnosis of Drug-resistant tuberculosis. But first we have to ensure the availability of these tests both in public and private sectors.

Adherence to medication posesa significant challenge for patients with TB [9]. Electronic medication monitors, capable of transmitting text messages, have been effectively used in low-resource settings with a high burden of TB. Virtual directly observed treatment via video (VDOT)allows providers to remotely observe patients taking medication through smart phones or tablets. Both of these technologies still require substantial input from healthcare workers to interpret the signals they send. Artificial intelligence holds promise in reliably recognizing patternsand gestures, enhancingthe effectiveness of these tools. For instance,AI-enabled software in VDOT can identify unique features of individuals taking medication, generating a distinct signature transmitted to caregivers. This approach could also benefit other clinical monitoring scenarios beyond TB treatment [10, 11, 12, 13].

Drones can be used as crucialtools to connectprimary healthcare facilities to hospitals by delivering patientinformation and samplesin rural areas [14]. A study highlighted the use of drones for transporting biological specimens with a finding that that time saving was 20–30% less in the urban model but 65–74%in the rural areas using drones at higher speeds. Finally, a study from Ghana [15] proves that an AI-enhanced medical drone application in the healthcare supply chain (HSC) contributes significantly to the host country's HSC and sustainable development goals (SDGs).

The future of AI in healthcare lies in Generative-AI (Gen AI), which provides instant outputs that are often indistinguishable from human-generated content. Gen AI is the new kid on the block as far as the healthcare revolution is concerned, offering solutions from real-time clinical decision support to personalized patient interaction. Number of Gen AI startups in India has more than doubled in the last three years.

AI applications in TB control hold significant promisein various aspectsof prevention, diagnosis, and treatment. AI could make an impact in early detection and assistance in diagnosis where AI algorithms can analyze chest X-rays and CT scans to detect TB lesions with high accuracy, enabling earlier diagnosis and intervention. AI-powered tools can assist healthcare providers in interpreting diagnostic tests such as sputum smear microscopy, molecular tests, and serological assays, improving diagnostic accuracy and speed. AI can be beneficial in the drug discoveryprocess by analyzingvast datasets to identify potentialdrug candidates and predict their efficacy againstTB bacteria, includingdrug-resistant strains. AI can play an important role in epidemiological surveillance by analyzing various epidemiological data and also help in healthcare resource allocation by predicting TB incidence, treatment outcomes, and healthcare utilization, enabling policymakers to allocate resources more efficiently and effectively. PublicAwareness can be improved with the help of AI which can facilitate the development of interactive educational tools, chatbots, and virtual simulations to raise awareness about TB. Other Areas where AI can be advantageous is in treatment Optimization by analyzing patientdata to personalize treatment regimens, Telemedicine and Remote Monitoring. AI-powered predictive modelingcan analyze behavioral data to understand factors influencing TB transmission and develop targeted interventions for behavior change and prevention.

The future of TB control holds great potentialfor improving outcomes,reducing transmission, and ultimately, achievingglobal eradication goals. However, it's essential to address challenges such as data privacy,equity, and implementation barriers to ensure that AI innovations benefitall communities affectedby TB.

Last but not least, while the adoption of AI in healthcare offers numerous potentialbenefits, it also raises significant ethical, legal, and social concerns.The development and deployment of AI-based solutionsmust address issues such as data safety,sharing, and privacy.For instance, while AI can facilitate easy diagnosis and access to healthcare, unsupervised use may pose risks. Therefore, establishing an ethical and regulatory frameworkis essential before integrating AI into health research and healthcare delivery.

Integrating AI into TB diagnosis offers a valuableopportunity to enhanceand automate screeningand detection processes. However, successful adoptionrequires addressing challenges such as establishing standardized reporting guidelines, addressing diagnostic variations, resolving implementation issues,enhancing technical expertise, developing assessment frameworks for AI technology, and securing sufficient financial resources. Collaboration among physicians, researchers, innovators, funders, implementers, and policymakers is crucialfor effectively tacklingthese challenges.

In conclusion, AI has great potential in identifying the areas which are more vulnerable and can help in improving the outcomes through early diagnosis by rapid detection of TB by identifying cough sounds and improvingthe efficiency and accuracy of test resultsby AI-enabled readingand interpretation of diagnostic tests. AI can be favorablein effective treatment optimization and it can help in treatment adherence by telemedicine and remote monitoring. Drones via AI can be useful in bridging the gap between primary healthcare facilities and tertiary care hospitals. It can be effective in transporting biological specimens and can contribute to healthcare supply chain management. AI can be fruitful in reducing transmission and ultimately achieving TB eradication goals.

References:
1. Strategies for advanced personalized tuberculosis diagnosis: Currenttechnologies and clinicalapproaches. Precis. Clin.Med.2021;2:35–44. doi: 10.1093/pcmedi/pbaa041
2.World Health organization. (2021). GLOBAL TUBERCULOSIS REPORT 2021. WHO. Retrieved June 14, 2023, from https://cdn.who.int/media/docs/default-source/hq-tuberculosis/tb-report-2021/factsheet-global-tb-report 2021.pdf?sfvrsn=86011b1e_5&download=true
3. P. J. Hayes and L. Morgenstern, "On John McCarthy's 80th birthday, in honor of his contributions," AI Magazine, vol. 28, no. 4, p. 93, 2007
4.Anthony DH , Ajay MVK 1,3,4, Srinath S , PruthuT, et al.The Growing Importance of Tuberculosis Preventive Therapy and How Research and Innovation Can Enhance Its Implementation on the Ground.Trop. Med. Infect.Dis. 2020, 5(2), 61; https://doi.org/10.3390/tropicalmed5020061
5.Adam C, Victor D M, ThomasS, Christian W. The globalprevalence of latenttuberculosis: a systematic review and meta-analysis. European Respiratory JournalSep 2019, 54 (3) 1900655; DOI: 10.1183/13993003.00655-2019
6. WHO'sGlobal TB Report2022. available at: https://www.who.int/teams/global- tuberculosis-programme/tb-reports/global-tuberculosis-report-2022
7. qXR. (2022, June 11). India Health Fund. https://www.indiahealthfund.org/our- portfolio/qxr/
8. Swaasa.2023. India HealthFund. https://www.indiahealthfund.org/our- portfolio/swaasa/
9. MunroSA, Lewin SA, Smith HJ, et al. Patient adherenceto tuberculosis treatment: asystematic review of qualitative research.PLoS Med 2007;4: e238
10.Liu X, Lewis JJ, ZhangH, et al. Effectiveness of electronic reminders to improve medication adherence in tuberculosis patients:a cluster-randomised trial.PLoS Med 2015;12: e1001876.
11.Garfein RS, CollinsK, Muñoz F, et al. Feasibility of tuberculosis treatmentmonitoring by video directly observedtherapy: a binational pilot study.Int J Tuberc Lung Dis 2015;19: 1057–1064.
12. StoryA, GarfeinRS, HaywardA, et al. Monitoring therapycompliance of tuberculosis patientsby using video-enabled electronic devices. Emerg InfectDis 2016; 22: 538–540.
13.AiCure. Advanced Medication Adherence Solutions. https://aicure.com/wp-content/uploads/2016/12/Shafner_et_al_Vancouver_Feb_2017.pdf Date last accessed: May 26, 2017. Date last updated:2017.
14.Pudasaini, Uttam. (2019). Drones Optimized TherapySystem (DrOTS): Use of Drones for Tuberculosis Diagnosis in Nepal. International Journalof Human and Health Sciences (IJHHS). 14. 10.31344/ijhhs.v0i0.132.
15.Isaac SakyiDamoah, Anthony Ayakwah,Ishmael Tingbani, Artificial intelligence (AI)-enhanced medicaldrones in the healthcare supplychain (HSC) for sustainability development: A case study,Journal of Cleaner Production,Volume 328,2021,129598, ISSN 0959-6526.

Tuberculosis - Recrudescence of Thoracic Surgery

Dr. Nasser Yusuf, MS, MCh, FIAMS, FNCCP, FICC, FUAPM , FIAB, Cardiothoracic Surgeon, Sunrise Hospital, Kochi

Abstract:
From the time of Hippocrates, Tuberculosis was known as phthisis, a term derived from the Greek language which means "decaying". There is no more dangerous disease than pulmonary phthisis; no other is so common. It destroys a very great part of the human race. Antoine Portal, Paris, 1832 The swollen glands of the neck were known as scrofula and the King' s evil. Although Tuberculosis (TB) is essentially a medical disease, a sizeable proportion of patients fall into the realm of surgery, may it be due to the primary disease or its sequelae. TB was the leading cause of death in the 17th century. Patients were nursed in sanatoriums and treated with plenty of sunlight and good food. Surgery then became widely prevalent as a treatment modality, and Pulmonary Tuberculosis (TB) became the history of thoracic surgery.

Image Credit: Practo

Introduction:
The first thoracic surgical procedure, an open drainage of a TB pleural empyema was performed by Hippocrates. During the first half of the last century, the finding that Mycobacterium tuberculosis was an obligate aerobe led to the rapid growth of thoracic surgical operations: thoracoplasty, induced pneumothorax, plombage, and phrenic nerve crushing [1]. Remarkably, Thoracoscopy was first introduced in 1886 by Francis Richard Cruise [2] and popularized by Jacobeus as the approach for pleural biopsy and adhesiolysis in TB patients [3].

In 1944, the discovery of Streptomycin modified the therapeutic protocol leaving little place for surgery. Developed in the 1960 s, Rifampicin and other anti- TB drugs radically transformed the prognosis of the disease and undermined the existence of thoracic surgery as a specialty; however, rapid increase in the incidence of lung cancer meant that thoracic surgeons soon found an important application for skills developed through years of TB' s surgical treatment [4] and more recently in Post COVID 2019 complications of the lung [5]. Presently, the world is witnessing a resurgence of the role of surgery in managing TB due to the overall increase in global incidence and the burgeoning emergence of Multi Drug- Resistant TB (MDR- TB to both Isoniazid and the Rifampicin) or Extensive Drug Resistant TB (XDR TB, resistance to Rifampin and Isoniazid, to fluoroquinolones and at least one of the following injectable anti TB drugs: capreomycin, Kanamycin, or Amikacin) [6]. Moreover, a trend for an increasing incidence of the disease in the western world are due to people migrating from developing countries and a surge in tourism.

Thoracic surgery offers highly effective treatment of TB and its sequelae with less trauma and morbidity than ever before. The advantage of Minimally Invasive Thoracic Surgery allows a wider range of TB patients to be considered for effective surgical management [7]. A thorough preoperative evaluation is essential - routine laboratory work, acid- fast bacilli sputum smears and cultures and accurate localization of TB lesions. Cardiopulmonary function should be assessed and similarly Pulmonary-function tests to ensure adequate pulmonary reserve. Fiber-optic bronchoscopy is used to evaluate endobronchial tuberculosis, contralateral disease and co- existing malignant disease. Echocardiography rules out pulmonary hypertension and congestive heart failure. The value of nutritional assessment with appropriate supplements for malnourished patients cannot be more stressed [8].

TB remains the foremost cause of death from an infectious agent. Current drug regimens achieve a cure rate > 85 %, with poorer outcomes in geographical areas where multi- drug resistant (MDR) strains are prevalent. Presently, the surgical indications in pulmonary TB are TB complications and cases displaying an inappropriate healing response to proper drug regimens.

In this critical global scenario, surgery could be crucial in the treatment of the sequelae of TB as well as for clinically and bacteriologically severe forms of pleuro- pulmonary MDR- TB. The need for surgery is estimated to have increased from 5% to 15 % over the last twenty years [9].

Indications for Surgery:
Referrals for surgery are often made when treatment has been failing for a long time, a large part of the lung parenchyma has already been destroyed and the patient is extremely symptomatic. In this sense, the physician' s awareness should be increased to identify and call for early surgical evaluation before the disease is far too advanced denying the patient the benefits of resection – relief of symptoms and/ or possible cure.
Although specific practical guidelines concerning surgical indications and approaches are currently unavailable, a summary of the evidence is listed [1,4].

Image Credit: BigStock

Emergency indications where without surgery, death is imminent and unavoidable include:

- Profuse lung hemorrhage - massive hemoptysis
- Tension spontaneous pneumothorax

Elective indications are:

A. Complications of Scarring

- Massive hemoptysis
- Cavernoma (cavity)
- Lung cancer
- Tracheoesophageal or bronchoesophageal fistula
- Bronchiectasis
- Extrinsic airway obstruction by tuberculous lymph nodes
- Endobronchial tuberculosis and bronchostenosis
- Middle lobe syndrome
- Aspergilloma

B. Failure of Medical Therapy

Cases displaying an inappropriate healing response to medication, in which clinical and radiological pictures remain unchanged or indicate progression, lung destruction and left bronchus syndrome.

Drug resistance - acid-fast bacilli sputum smears positivity after 3-month treatment period, with a circumscribed radiological lesion or a destroyed lung; and previous relapse(s) in patients with histories of TB and proper drug regimen (e.g., cavity, tuberculoma).

C. Pleural Tuberculosis

- Undiagnosed pleural effusion
- Empyema
- Bronchopleural fistula

D. Surgery for Diagnosis

- Pulmonary lesions of unknown cause
- Mediastinal adenopathy of unknown cause

E. Miscellaneous

- Cold Abscess and Osteomyelitis of the Chest Wall
- Consequences of insufficient surgery
- Thoracoplasty
- Delayed complications of plombage

A multi- disciplinary approach should be adopted when surgery is contemplated. The new evolving role of thoracic surgery in the treatment of pulmonary TB involves infectious disease specialists, respiratory physicians, radiologists, and thoracic surgeons to continue working in partnership to identify TB patients who can benefit from surgery. Surgery is always considered as an adjunct to proper medical therapy. A diagnostic surgical approach is recommended when pleural effusion occurs without any radiologic signs or established cause [10]. VATS or mediastinoscopy with ex-tempore histological examination may be helpful to distinguish between malignant and TB lesions. With proper indications for surgery, sputum conversion rates of more than 90 % can be obtained. In established cases of TB, patients are operated on with proper antibiotic coverage of at least 3 months duration, and surgeries are always followed by complete courses of therapy, the lengths of which are dictated by the resistance of the organisms and the susceptibilities of the hosts.

One of the main indications for surgery is massive hemoptysis along with known destructive pulmonary sequelae such as destroyed lung. It may occur due to infection, cavity, aspergilloma or bronchiectasis. Surgery is also recommended for cases with major residual pleural thickenings. The role of surgery is to remove the burden of mycobacteria in actively infected patients or to treat debilitating consequences caused by the ongoing scarring process that characterizes the healing of TB. It is indeed very difficult to sterilize cavities or destroyed lungs, probably because the medications are unable to penetrate the lesions. Surgery would also benefit patients who have extreme patterns of drug resistance who are left with residual cavities and destroyed lung despite maximum medical treatment. These lesions pose a risk of relapse which are difficult to manage. Excision of such localized pathology can significantly improve the chances of cure in this group. There is also a higher percentage of non-conversion with lobectomy and segmentectomy compared to pneumonectomy, suggesting that a more radical procedure may be more effective than a smaller resection [11]. However maximal parenchymal sparing should be exercised in cases of MDRTB due to the possibility of relapse – a catch-22 situation. The mortality rate after lobectomy is about 2–3%, after pneumonectomy is 7-8% and surgery for empyema has complications of about 8–11% [12]. The post-operative complications of surgeries are 9–26%, the commonest being persistent air leakage (40%) however most get resolved with suitable maneuvers [13].

Thoracotomy, VATS and RATS:

Video-assisted thoracoscopic surgery (VATS) was first reported in 1992. Thoracoscopy has an amplifying action and a deep illumination effect. Further, in addition to the advantage of cosmetic appearance, pain is minimal as there is little injury to the ribs, muscles and subcutaneous tissues. VATS therapeutic resection could be safely performed in selected patients with medically failed pulmonary TB as an effective adjunct with satisfactory results [14]. Similarly, Robotic Assisted Thoracoscopic Surgery (RATS) may be employed. However, there is no clear conclusion whether RATS can achieve an equal or even better surgical effect when compared with VATS [15]. Further a recent paper stated that in the setting of a comprehensive enhanced recovery protocol, patients undergoing VATS versus open lobectomy exhibited similar short-term outcomes [16]. Incompleteness of interlobar fissures and solid pleural symphysis and dense fibro-vascular adhesions, common in tuberculous destroyed lung, are among “technical contraindications” for thoracoscopy [17]. However, there is no role for VATS or RATS in the emergency setting of massive hemoptysis; instead, a thoracotomy is to be performed.

Conclusion:

Most of the available literature is from North America and Europe where the incidence of TB is low in comparison to the developing countries. India has the dubious distinction of having the largest estimated number of MDR-TB cases in the world, responsible for around 26% of the global burden [18]. In our series of over 1,000 patients during the past 25 years, the most common indications for Surgery in TB were the sequelae - Bronchiectasis, Aspergilloma, Empyema, Bronchopleural fistula and Destroyed lung. Emerging indications are resection of localized lesions in patients with persistent sputum AFB positive and MDRTB. A significant number of patients belonged to ASA Class IV. Outcomes were on par with existing literature [19]. Successful treatment of TB depends on prompt diagnosis and proper medical therapy. Sequelae of TB forms the major chunk of patients requiring surgery. The increase in the number of new TB cases and the number of patients with MDRTB are the present challenges for medical providers. When patients fail medical therapy or are at high risk to do so, surgery remains a very effective tool in the management of this difficult problem. Relevant indications, appropriate timing of referrals and proper selection of patients are crucial to the final outcome. The increasing role of surgery in the treatment of TB is incontrovertible.

References:

1. Pomerantz M. Surgery for the management of mycobacterium tuberculosis and nontuberculous mycobacterial infections of the lung. In: Shields TW, Lo Cicero J, Ponn RB, et al. eds. General Thoracic Surgery, 6th ed. Lippincott Williams & Wilkins: Philadelphia, PA; 2005:1251-611.
2. Haksch B, et al.Thoracoscopy before Jacobaeus. The Annals of Thoracic Surgery; Our Surgical heritage: Volume 74, Issue 4, October 2002, Pages 1288-1290.
3. Jacobaeus HC. The Cauterization of Adhesions in Artificial Pneumothorax Treatment of Pulmonary Tuberculosis under Thoracoscopic Control. Proc R Soc Med 1923;16:45-62.
4. Mehran RJ, Deslauriers J. Tuberculosis and atypical mycobacterial diseases. In: Patterson GA, Cooper JD, Deslauriers J, et al. eds. Pearson's thoracic and esophageal surgery. Philadelphia: Churchill Livingstone; 2008:507-27.
5. Raveglia F, Scarci M, Yusuf N, et al: The Role of Surgery in Patients with COVID - 19 related Thoracic Complications. Frontiers in Surgery 24 May, 2022, Volume 9, Article 867252.
6. Sihoe AD, Shiraishi Y, Yew WW. The current role of thoracic surgery in tuberculosis management. Respirology 2009;14:954-68.
7. Takeda S, Maeda H, Hayakawa M, et al. Current surgical intervention for pulmonary tuberculosis. Ann Thorac Surg 2005;79:959-63.
8. Kempker RR, Vashakidze S, Solomonia N, et al. Surgical treatment of drug resistant tuberculosis. Lancet Infect Dis 2012;12:157-66.
9. Moran JF. Surgical treatment of pulmonary tuberculosis. In: Sabiston DC Jr, Spencer FC. editors. Surgery of the chest. 6th ed. Philadelphia: W.B. Saunders Company, 1995:752-72.
10. Mouroux J, et. al.: Surgical management of pleuropulmonary tuberculosis. J Thorac Cardiovasc Surg 1996; 111: pp. 662.
11. Van Leuven M, et al: Pulmonary resection as an adjunct in the treatment of multiple drug-resistant tuberculosis. Ann Thorac Surg 1997; 63: pp. 1368.
12. Zaleskis R. Role of surgical methods in the treatment of tuberculosis. Probl Tuberk. 2001; 9:3–5 (in Russian). Surgery in the treatment of pulmonary TB and M/XDR-TB page 14.
13. Naidoo R. Active pulmonary tuberculosis: experience with resection in 106 cases. Asian Cardiovasc Thorac Ann 2007;15:134-8.
14. Yau-Lin Tseng, et al. "The Role of Video-Assisted Thoracoscopic Therapeutic Resection for Medically Failed Pulmonary Tuberculosis" (Medicine 95(18):e3511).
15. Jianglei M, et al.Robot-assisted thoracic surgery versus video-assisted thoracic surgery for lung lobectomy or segmentectomy in patients with non-small cell lung cancer: a meta-analysis. BMC Cancer 21, Article number: 498 (2021).
16. Elizabeth D, et al. Is less really more? Re-examining video-assisted thoracoscopic versus open lobectomy in the setting of an enhanced recovery protocol. The Journal of Thoracic and Cardiovascular Surgery, Vol 159, Issue 1, January 2020, Pages 284-294.
17. Yen YT, et al. The role of video-assisted thoracoscopic surgery in therapeutic lung resection for pulmonary tuberculosis. Ann Thorac Surg 2013; 95: 257-263.
18. Global tuberculosis report 2015. Geneva: World Health Organization (WHO), 2015.
19. Yusuf N, et al : Surgery in Pleuro-pulmonary Tuberculosis - On the comeback trail. Astrocyte, Vol 4, Issue 2, July-September 2017.

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The World of TB: Advances in Detection, Cure and Outreach

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

Abstract:

Respiratory infections have been haunting humanity for a long time, and Tuberculosis is one such major infection. Skeletal remains show some prehistoric humans had TB. Researchers have found tubercular decay in the spines of Egyptian mummies dating from 3000 to 2400 BC. TB is a global disease found in every country in the world. TB remains one of the world's deadliest infectious killers. TB is present in all countries and age groups. The statistics provided by WHO [1] are startling. In 2022, 1.3 million people died from TB, and ~10.6 million people fell ill with TB. Estimates put infections at ~1% of the population each year. Multidrug-resistant TB (MDR-TB) remains a public health crisis and a health security threat. One-quarter of the world's population is estimated to have a latent TB infection [2]. TB is a curable disease. Research is being pursued, newer methods for early and efficient detection and new drugs and procedures are being developed. Efforts are also being made to reach out to the people to remove the taboo and encourage them to come forward and take the treatment. In this article, a few advances in the research and efforts made in outreach are discussed. No thorough search has been made to identify the developments. Some of them which found a place in the media have been randomly selected and shared the same below.

Development of a New 3D Hydrogen Culture System:

Researchers at the Indian Institute of Science (IISc), Bengaluru, have developed a new 3D hydrogen culture system that closely mimics the human lung environment to study TB [3]. This innovative platform helps track how TB bacteria infect lung cells and test the effectiveness of TB treatments. It provides a platform to track and study how TB infect lung cells and test the efficacy of therapeutics used to treat TB. The team also demonstrated the model's potential for drug testing. They found that a common TB drug, pyrazinamide, was effective at much lower, more clinically relevant doses than typically required in 2D cultures. Researchers indicated that their plans include using the model to study why TB manifests differently among patients and to explore new drug development possibilities. This breakthrough could accelerate TB research and potentially lead to more effective treatments for this persistent global health threat. The research team members are Vijaya V Vaishnavi, Vishal K Gupta, and Rachit Agarwal (Faculty Member) at the Bioengineering Department.

Unravelling an Adaptation Process of the Tuberculosis Pathogen:

The bacterium that causes TB possesses the brilliant ability to sense threats and adapt inside the host. A new study at the IISc, Bengaluru, led to unravelling a mechanism allowing the TB bacterium to ignore small environmental stimulations it senses through these two-component signalling systems (TCSs) [4]. Such sequestration or blocking of signalling by a non-partner is a simple design principle that helps delineate signal from noise. "Targeting such an interaction node can disarm the bacterium, and even weak stresses posed by immunity or drug regimens would generate a strong undesirable response in the bacterium," says Deepak, lead researcher of the work. "Exploiting this finding to pin a sequestration interaction, in principle, can exhaust the pathogen, thereby increasing their susceptibility to immune pressures," adds another team lead researcher, Gaurav. The study elegantly blends experimental and mathematical approaches to extract intricate signalling processes from one of the most dreaded pathogens. The team: Deepak K Saini (Department of Developmental Biology and Genetics) and Narendra M Dixit (Department of Chemical Engineering, IISc).

India Introduces New Treatment Regimen for Multidrug-resistant TB:

Time is of the essence when adopting advanced technology in medical care. Early adoption of the new treatment regimen is welcome. When medical technology arrives, delaying adoption does not lead to transformative effects. WHO regularly evaluates new evidence on the use of specific drug compositions and combinations of regimens of different durations. Most recently, new evidence has resulted in a significant breakthrough in the treatment that can be recommended for people with MDR-TB and pre-XDR-TB. Faster-acting and simplified TB drug regimens are of more urgent need than ever in the fight against TB. The Health Ministry of India's decision to introduce the new treatment regimen for drug-resistance TB hardly a couple of years after WHO introduced it is a step in that direction [5]. Designated as a BPaLM regimen consisting of four drugs-Bedaquiline, Pretomanid, Linezolid and Moxifloxacin), it has proved to be a safe, more effective and quicker treatment option than the previous MDR-TB treatment procedure. The treatment regime has been brought under the "National TB Elimination Program". While traditional treatment can last up to 20 months, the BPaLM regimen can cure drug-resistant TB in six months with a high success rate.

Vaccine for TB:

Since its development a century ago, the BCG vaccine remains the sole licensed TB vaccine. Its efficacy remains limited, preventing only about 20% of infections in children and offering partial protection against disease development. A Phase 3 trial is underway for what could be the first vaccine to help prevent pulmonary TB in adolescents and adults. It is the first new TB vaccine in over a century [6]. Initiated across six provinces in South Africa, the trial aims to combat the progression to active pulmonary TB in adults infected with the TB-causing bacteria. Results from a Phase 2b clinical trial conducted in Kenya, South Africa, and Zambia indicated that administering two doses of M72/AS01E reduced the development of active TB disease with about 50% efficacy. Researchers are excited about the outcome and if such a level of efficacy, if sustained over 25 years, could potentially avert 8.5 million deaths and prevent 76 million new TB cases.

Subclinical TB:

TB is not a binary, latent TB and active TB. People can have TB and yet not display any of the characteristic symptoms associated with TB. It is estimated that about 40% of the Indian population is infected with TB bacteria, the vast majority of whom have latent TB rather than TB disease. Subcritical TB patients can infect others. They may pass on the bacteria not necessarily through cough but by coming out of breath. Subcritical TB prevalence can be high in all high-burden states in India. Subcritical TB can be the reason for the reduction in the incidence of TB coming down, opines Dr Soumya Swaminathan. Convincing people to take the diagnosis and start early treatment will help them recover quickly. Going into the community, screening everybody, and treating all the TB cases you find can significantly reduce the burden of TB in the community. There have been such demonstration studies, says Dr Soumya Swaminathan, referring to agnostic screening adopted by Vietnam. The challenge is bringing people to diagnostic centres. Regarding advanced treatments, Dr Soumya indicated that multiple companies have applied to the ICMR to validate their AI algorithms, and two have received approval [7].

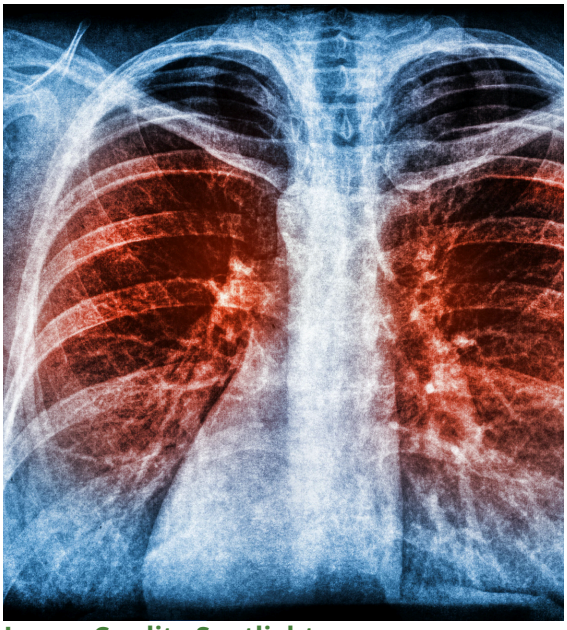

Image Credit: Spotlight

Reaching Out to People : Champions Play a Major Role in Reducing Stigma:

Stigma is attached to TB. The journey of the people with TB is not easy. Scores of TB survivors in Chennai decided that their journey did not end with their recovery. Drawing from their personal experience, be it late or missed diagnosis, lack of family support or stigma, many survivors continue to reach out to people diagnosed with TB. They are helping them in one way or another and playing a crucial role in TB elimination and reducing stigma. REACH, a non-profit organization working on TB has trained TB survivors to be champions in Tamil Nadu. These are narratives of hope and resilience. Creating awareness at the community level is one of the primary roles of a TB champion. It is a survivor-led network in Tamil Nadu. Ramya Ananthakrishnan, Director of REACH, said TB champions provided peer support using their stories to motivate others and played a role in service delivery [8].

Tuberculosis in Prisons:

Societies face another problem with criminals. People housed in prisons have a high risk of developing TB. A UN report has estimated that worldwide, there are 11.7 million people held in prisons (2019 data). That number increased by just over 25% between 2000 and 2019. Region-wise variations are seen. People in prisons bear a much more significant burden of ill health, both physical and mental, than people outside prisons [9]. The situation they are in makes the recovery process delayed and complicated. When they return to society, they carry the burden and the potential to spread the disease. Urgent steps need to be taken to take the treatment regimens to them in prisons.

An XDR-TB patient with his TB medication at MSF's TB clinic in Mumbai. © Atul Loke/Panos Pictures

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References:

1.https://www.who.int/news-room/fact-sheets/detail/tuberculosis.

2.http://tbinfo.org/sites/default/files/202208/World%20Tuberculosis%20Day%20%20%20Invest%20to%20End%20TB%20and%20Save%20Lives_0.pdf

3.https://timesofindia.indiatimes.com/home/science/breakthrough-in-tb-research-iisc-team-develops-3d-system-to-mimic-lung-environment/articleshow/111256394.cms

4.https://iisc.ac.in/unravelling-an-adaptation-process-of-the-tuberculosis-pathogen/

5.Health Ministry approves new treatment regimen for multidrug-resistant TB - The Hindu

6.https://www.nature.com/articles/d44148-024-00101-1

7.Subclinical TB is the reason for slow drop in TB incidence, says Soumya Swaminathan - The Hindu

8.Champions of the battle against TB play a major role in its elimination, and stigma reduction - The Hindu

9.https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2023/featured-topics/tb-in-prisons

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