

# Tuberculosis: An Epidemic Perpetuated by Health Inequalities

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## ABSTRACT

Tuberculosis (TB) is the leading single-agent infectious disease killer worldwide. The World Health Organization (WHO)'s End TB Strategy aims to achieve tuberculosis (TB) elimination by 2030, and in September 2018, the United Nations General Assembly held a High-Level Meeting on TB to address the urgency of the TB epidemic and the health inequalities that continue to propel it. The meeting endorsed an ambitious, comprehensive approach to the TB epidemic that incorporates universal health coverage and tackles the social determinants of this disease. In this article, we provide an overview of the key strategies promoted in this meeting and introduce work by five Rhode Island-based physicians that align with these goals.

**KEYWORDS:** Tuberculosis, End TB Strategy

## INTRODUCTION

The World Health Organization (WHO)'s End TB Strategy aims to achieve tuberculosis (TB) elimination by 2030 – a formidable goal given that *Mycobacterium tuberculosis* is the leading single-agent infectious disease killer worldwide.<sup>1</sup> In 2017, approximately 10 million people fell sick with TB, and 1.6 million people died from the disease.<sup>2</sup> Multidrug-resistant TB (MDR-TB), which accounted for 558,000 incident TB cases in 2017, further complicates the fight against TB. MDR-TB treatment requires a longer regimen with more toxic drugs. Globally, the treatment success rate for MDR-TB is only 55% compared to 83% for drug-susceptible TB.<sup>2,3</sup>

Drug-susceptible TB treatment was developed >50 years ago and costs less than 10 USD/course. Why, then, has so little progress been made in the fight against a curable, preventable disease, when significant reductions in mortality have been achieved against more difficult-to-treat conditions? In the past century, high-income countries (HICs) have achieved drastic reductions in TB incidence through a combination of improved living standards and dedicated public health infrastructure/resources. Yet, the disease continues to devastate impoverished, marginalized populations in low- and middle-income countries (LMICs), for whom optimal TB care is often deemed “impractical” and not “cost-effective.” Although progress has been made towards

improving TB care in LMICs, technologies and interventions considered essential for combating TB in HICs – such as universal drug susceptibility testing (DST) and treatment of latent TB infection (LTBI) – have only been recently recommended for widespread implementation.

In September 2018, the United Nations (U.N.) General Assembly held a High-Level Meeting on TB (HLM-TB) to address the urgency of the TB epidemic and the health inequalities that continue to propel it. This meeting marked the third time in history that the U.N. has convened to discuss a specific disease. The priority actions for Heads of State and Governments adopted by the 1000 HLM-TB delegates reflected five key points: (1) reach all people by closing the gaps on TB diagnosis and prevention; (2) transform the TB response to be equitable, rights-based, and people-centric; (3) accelerate development of new diagnostic and treatment tools; (4) invest the necessary funds to fight the epidemic; and (5) commit to decisive and accountable global leadership, including regular reporting and programmatic review.<sup>4</sup> These goals convey that an effective, comprehensive response to the TB epidemic must incorporate universal health coverage and tackle the social determinants of this disease.<sup>5</sup> In this article, we provide an overview of the key strategies promoted in this meeting and introduce work by five Rhode Island-based physicians that align with these goals.

## REACHING ALL PEOPLE: FINALLY PRIORITIZING CHILDREN

For decades, pediatric TB has been ignored as health officials prioritized contagious adult cases as the drivers of the epidemic. Therefore, children represent a higher proportion among estimated missing, unregistered TB cases. Children, particularly those < two years of age, are at highest risk for rapid progression to severe TB disease.<sup>6</sup> Additionally, diagnosing TB in children is challenging due to its paucibacillary nature and the inability for most children to produce sputum.<sup>7</sup> Rapid, prompt diagnosis is required in young children, but our current testing strategies are limited. Dr. Silvia Chiang and her colleagues at Partners In Health-Peru and Harvard Medical School have conducted studies in Peru to identify the barriers to childhood TB diagnosis and to develop strategies to improve this process.<sup>8</sup>

Detecting childhood TB is further complicated by its non-specific clinical presentation; the signs and symptoms usually are much more subtle than those of adult TB. Kenya's National TB Program recommends that healthcare workers in all pediatric outpatient settings screen children for TB symptoms, but the high patient-to-healthcare worker ratio is a formidable barrier to this goal. Dr. Daria Szkwarko is leading a study on how to increase screening for childhood TB through the use of a mobile health intervention, which is being piloted in waiting areas at a large county hospital in western Kenya. A community health volunteer (CHV) uses a tablet-based screening application to conduct a symptom screen with parents/caregivers. If the application notifies the CHV that the child has presumptive TB based on two or more symptoms, the CHV gives the parent/caregiver a notification card, which informs healthcare workers that this child is at risk and requires further evaluation. This novel intervention also aligns with the emphasis placed at the HLM-TB on developing digital technologies for TB prevention, treatment, and care.

### INCREASING CASE DETECTION: FIND THE MISSING

Globally, only 64% of estimated drug-susceptible TB cases and 25% of MDR-TB cases were registered and reported in 2017.<sup>2</sup> Finding and treating missing TB cases is key to TB elimination. Every global TB treatment site has a method of reporting TB cases to its national Ministry of Health. These data have been used for tracking the epidemic, but not for evaluating the quality of care. Dr. E. Jane Carter is working with her colleagues at The International Union Against TB and Lung Disease to institute TBData4Action, a new method to examine locally derived TB data to improve finding missing cases and the quality of care. After eighteen months, the project has retrained all county and sub-country TB coordinators in Kenya and increased case detection.

Work by Dr. Chiang and Dr. Natasha Rybak found that the number of children receiving treatment for MDR-TB in Kyiv City, Ukraine, was much lower than the projected number of pediatric MDR-TB cases.<sup>9</sup> This finding is unsurprising since Ukraine is among ten countries with the largest gaps between the number of patients started on MDR-TB therapy and estimates of MDR-TB incidence.<sup>10</sup> To find missing childhood TB cases (both drug-susceptible and MDR) in Ukraine, Dr. Rybak is leading a pilot study to estimate the number of missed pediatric TB cases that end in death. Ukraine's Ministry of Health mandates autopsies in all individuals who die before age eighteen. Dr. Rybak, Dr. Chiang, and their collaborators at Boston University are reviewing pediatric autopsy data to identify possible TB-related deaths. The medical records of these children will then be reviewed to further evaluate the possibility that their deaths were caused by TB. This work will generate preliminary data that

will lead to a more comprehensive effort to identify missed TB cases in Ukraine.

### CLOSING THE GAP ON PREVENTION

LTBI represents the time period between initial infection with *M. tuberculosis* and development of symptomatic disease. LTBI can last for years or decades in immunocompetent individuals, or may be as short as weeks in people living with HIV (PLWHIV) or young children. Highly effective preventive therapy that significantly reduces the risk of progression from LTBI to TB disease has been available since the 1960s; however, its use has been limited to HICs. More recently, preventive therapy has been extended globally to PLWHIV and to children <5 years of age who have been in contact with contagious TB patients. As previously mentioned, young children are particularly vulnerable to TB: compared to non-household contacts, child contacts have a 70% increased risk of TB infection,<sup>11</sup> and a 66% increased risk of mortality.<sup>12</sup> Yet, implementation of preventive therapy for young children has been slow - the rate of preventive therapy initiation in child contacts < 5 years was estimated to be 23% of those eligible in 2017 globally.<sup>2</sup> Drs. Carter and Szkwarko have been working to improve the child contact management care cascade (identification, screening, treatment initiation, treatment completion) since 2011.<sup>13,14</sup> Most recently, Drs. Carter and Szkwarko collaborated with colleagues at Center for Health Solutions to implement a clinic-based child contact management strategy across 100 facilities in Kenya. Of 2022 child contacts < 5 years exposed to contagious TB identified, 149 (7%) were diagnosed with TB disease, and 1613 (80%) initiated preventive therapy.

### ADOPTING A PATIENT-CENTERED APPROACH

Adolescents – defined by the WHO as persons aged between 10–19 years – make up a large proportion of LMICs populations. They have an increased risk of progression from TB infection to disease, have poor adherence to TB therapy, and tend to congregate in group settings – all factors that lead to adolescents comprising a significant proportion of the global TB burden.<sup>6,15-17</sup> Adolescence is a critical time for physical, psychosocial, and cognitive development – all of which may be jeopardized by TB disease and treatment. However, adolescents have been neglected in TB research and policy, mostly because standard TB reporting practices group 10- to 14-year-olds with children and 15- to 19-year-olds with adults.<sup>2</sup> Many knowledge gaps remain with respect to adolescent TB, such as risk factors for poor treatment outcomes, and the impact of adolescent TB disease and treatment on long-term health and wellbeing.

To address these gaps, Drs. Chiang and Rybak are conducting two studies in Ukraine. The first is an analysis of >5000 cases of adolescent TB disease to identify risk factors

for loss to follow-up, death, and drug resistance. The second is a qualitative study to characterize the impact of TB disease and treatment on quality of life in adolescent TB survivors. In Peru, Dr. Chiang and her collaborators at Partners In Health-Peru are interviewing >100 adolescent TB survivors, parents/guardians of these adolescents, and healthcare providers to evaluate TB treatment adherence facilitators and barriers. Informed by these interviews, Dr. Chiang and her collaborators will then enroll 400 adolescents at the start of TB treatment and develop a clinical prediction tool of poor treatment adherence for adolescent TB. Through this study, the investigators will also be able to answer other questions, such as the prevalence of depression among adolescents with TB disease.

### COMBATING DRUG RESISTANCE THROUGH ACCESS TO DIAGNOSTICS AND TREATMENT

In the 1990s, many LMICs relied on loans from international financial institutions to support public health programs; as a result, these programs prioritized interventions that provided high return on investment.<sup>18</sup> Therefore, TB control guidelines focused on diagnosis by sputum microscopy instead of the more expensive culture, and empirical use of first-line drugs for drug-susceptible TB rather than conducting DST to construct regimens based on these results. In the United States and other HICs, combating MDR-TB outbreaks by tailoring individualized regimens based on DST results became the standard of care. However, in most LMICs, the management of MDR-TB remained the same. As TB treatment policy diverged between HICs and LMICs, the MDR-TB epidemic in LMICs worsened and became the most common form of antimicrobial resistance globally.<sup>5</sup>

Today, the creation of rapid molecular TB diagnostics that require less laboratory expertise have facilitated the diagnosis and prompt treatment of MDR-TB worldwide. The roll-out of Xpert MTB/RIF (Cepheid, California) in 122 high TB-burden countries led to an eight-fold increase in MDR-TB case detection by the end of 2015.<sup>19</sup> However, major disparities continue, and only 39% of patients who are diagnosed with MDR-TB receive the recommended panel of DST for second-line drugs.<sup>10</sup> Dr. Tara Bouton and colleagues, with support from the Brown University Global Health Initiative, have shown in Ghana that even at international academic centers, meeting DST guidelines remains a challenge.

Traditional MDR-TB regimens include  $\geq 5$  drugs administered for 18-24 months. Toxicity for second-line regimens is high, with up to 62% of patients developing hearing loss with second-line injectable therapy.<sup>20</sup> In most TB-prevalent settings, patients are infrequently monitored for adverse events. Approval of the first new MDR-TB drugs in 50 years has made possible all-oral and shorter therapies. Dr. Bouton, through collaborations at Boston University and in South Africa, is examining the roll-out of new drugs and the impact of their empirical use on drug resistance.

### CONCLUSIONS

The HLM-TB has focused the world's attention – and more importantly garnered political commitment at government levels – on ending TB by 2030. The attendees' commitment to address TB by focusing on the health inequalities that propel the epidemic is a major step forward. By reaching vulnerable populations, increasing case detection, adopting a patient-centered approach, and combatting drug resistance through improved access to diagnostics and treatment, local Rhode Island physicians are helping to lead the way to ensure that ending TB is no longer a dream but a possible reality.

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