



Commentary

Ringing the alarm bell: Time to scale up drug-resistant tuberculosis preventive treatment

Amy A. Malik^{a,b,*}, Mercedes C. Becerra^c, Hamidah Hussain^d

^a Yale Institute for Global Health, 1 Church Street, Suite 340, New Haven, CT 06510, USA

^b Global Health Directorate, Indus Health Network, Karachi, Pakistan

^c Harvard Medical School, Boston, MA, USA

^d Interactive Research and Development (IRD) Global, Singapore

ARTICLE INFO

Article History:

Received 17 March 2021

Revised 18 March 2021

Accepted 18 March 2021

Preventing tuberculosis (TB) infection from progressing to TB disease is essential for a comprehensive strategy for TB elimination. Recent updates to international guidance underscore the benefits of TB preventive treatment for household contacts of all ages [1]. However, data shows that approximately 80% of children under 5 years and 99% of other household contacts eligible for preventive treatment did not receive it in 2019 [2]. The COVID-19 pandemic has also severely affected the delivery of TB services including decrease in case finding and treatment disruption leading to a potential increase in transmission. This further highlights the importance of preventive treatment. Significant efforts are required globally to improve TB care in line with this year's World TB Day's theme, which is "The Clock is Ticking."

One high-stakes area that requires urgent attention is to expand the delivery of TB preventive treatment for persons exposed at home to drug-resistant tuberculosis (DR-TB) [3]. TB preventive treatment is both effective and cost-effective in protecting these individuals from avoidable illness and death [4]. DR-TB preventive treatment using a fluoroquinolone-based regimen is estimated to afford about 65% protection [5]. Work from Pakistan and elsewhere has shown that DR-TB preventive treatment is safe and can be successfully implemented in a programmatic context [4–6]. However, the current standard of treatment for many TB programs is close programmatic surveillance of contacts of DR-TB patients without the use of preventive treatment. Such surveillance may lead to earlier detection of those developing active TB disease. Still, it does not reduce the risk of becoming sick with active TB disease. Failure to offer preventive treatment can result in economic loss to individuals and the country if these contacts develop TB, as many of them will.

The currently recommended regimen for DR-TB preventive treatment is a fluoroquinolone-based regimen, with evidence of effectiveness [1,3–5]. However, hesitancy remains with regards to the use of this regimen. One reason for this hesitancy is concern regarding the safety of fluoroquinolone to children. The concerns stem from earlier studies in animals and children showing musculoskeletal defects in those exposed to the drug. However, a significant body of evidence has shown fluoroquinolone use to be safe [7]. Still, these concerns need to be addressed through continuing education for clinicians. The institution of a robust pharmacovigilance framework and follow-up for those starting TB preventive treatment can alleviate some of these fears and build trust. On the research side, there is a need to evaluate other regimens for TB preventive treatment, especially those containing newer drugs such as bedaquiline and delamanid. There is also a need for a shorter duration for DR-TB preventive treatment coupled with evaluating other agents for disease treatment. Preventive treatment for drug-susceptible TB with once-weekly isoniazid-rifapentine regimen (3HP) shortened the duration and number of doses dramatically— compared to six-month daily isoniazid— and showed increased completion rates [8]. A one-month course of isoniazid-rifapentine (1HP) shows equal promise [9].

Another important area to consider is contacts initiating and completing treatment. The majority of the contacts are symptom-free and generally well and hence do not wish to begin treatment, especially with a six-month daily regimen [5]. This is also a major factor for discontinuation of treatment once started. It requires an enhanced treatment-literacy campaign and psychosocial support and counseling for the contacts, which better communicates the benefits of preventive treatment [3].

The increasing evidence and WHO recommendation on the effectiveness of DR-TB preventive treatment provides an opportunity for policymakers at the national and international level to incorporate DR-TB preventive treatment into all TB programs. Most TB programs already contact trace the household contacts of DR-TB patients. Now what is needed is the scale up of preventive treatment for contacts free of TB disease. The first step towards this would be for national programs to update their policies and guidelines to incorporate TB preventive treatment for DR-TB. Currently only 20% (7/35) have DR-TB preventive treatment options in their national policies [10]. Other steps required to get programs ready to scale up DR-TB preventive

E-mail address: amyn.malik@yale.edu (A.A. Malik).

treatment include updating existing recording and reporting tools, estimating and providing the necessary human resources to the program, synchronizing procurement and supply chain for preventive treatment with DR-TB treatment supply management, and a robust pharmacovigilance and treatment monitoring including adherence monitoring infrastructure. High-quality interventions for the care of persons exposed to TB, including DR-TB, need to be scaled up quickly if we are to achieve the goal of TB elimination. 'The clock is ticking,' and we are on notice. It is time for the global TB community to up our game to prevent lives lost from this preventable and curable disease.

Declaration of Competing Interest

All authors declare no conflict of interest.

Authors' contribution

AAM wrote the initial draft of the manuscript. All authors contributed to revision, editing and finalization of this manuscript. All authors have approved the final version of the manuscript.

Funding

We did not receive any funding for this work.

References

- [1] World Health Organization. WHO operational handbook on tuberculosis: module 1: prevention: tuberculosis preventive treatment. Geneva, Switzerland: World Health Organization; 2020.
- [2] World Health Organization. Global tuberculosis control report 2020. Geneva, Switzerland: World Health Organization; 2020.
- [3] Brooks M NE, Hussain H, Malik A, Jaswal M, Siddiqui S, Barry Z, Fuad J, Becerra MC, Seddon J, Furin J. How to care for people exposed to drug-resistant tuberculosis: a practical guide. Boston, USA: The Sentinel Project for Pediatric Drug-Resistant Tuberculosis; 2018.
- [4] Marks SM, Mase SR, Morris SB. Systematic review, meta-analysis, and cost-effectiveness of treatment of latent tuberculosis to reduce progression to multidrug-resistant tuberculosis. *Clin Infect Dis* 2017;64(12):1670–7.
- [5] Malik AA, Gandhi NR, Lash TL, et al. Effectiveness of preventive therapy for persons exposed at home to drug-resistant tuberculosis, Karachi, Pakistan. *Emerg Infect Dis* 2021;27(3):805–12.
- [6] Malik AA, Fuad J, Abbass W, et al. Preventive treatment of drug-resistant TB in a rural setting. *Int J Tuberc Lung Dis* 2021;25(3):231–3.
- [7] Goldman JA, Kearns G. Fluoroquinolone use in paediatrics: focus on safety and place in therapy. Geneva, Switzerland: World Health Organization; 2011.
- [8] Sterling TR, Njie G, Zenner D, et al. Guidelines for the treatment of latent tuberculosis infection: recommendations from the National Tuberculosis Controllers Association and CDC, 2020. *MMWR Recomm Rep* 2020;69(1):1–11.
- [9] Malik AA, Farooq S, Jaswal M, et al. Safety and feasibility of one month of rifapentine plus isoniazid (1HP) to prevent tuberculosis in children and adolescents: a prospective cohort study. *Lancet Child Adolesc Health* 2021 (**in press**).
- [10] Médecins Sans Frontières, Stop TB partnership. Step up for TB 2020. Tuberculosis policies in 37 countries. A survey of prevention, testing, and treatment policies and practices. Geneva, Switzerland.