Diagnosis and treatment of tuberculosis infection: can it contribute to achieving tuberculosis elimination?

Alberto Matteelli[1] and Jan-Willem C. Alffenaar[2,3,4]

[1]Institute of Infectious and Tropical diseases, WHO Collaborating Centre for Tuberculosis/HIV coinfection and for the Tuberculosis Elimination Strategy, University of Brescia, Brescia, Italy. [2]Sydney Institute for Infectious Diseases, The University of Sydney School of Pharmacy Faculty of Medicine and Health, The University of Sydney, Sydney, Australia. [3]School of Pharmacy, Faculty of Medicine and Health, The University of Sydney, Sydney, Australia. [4]Westmead Hospital, Sydney, Australia.

Corresponding author: Alberto Matteelli (alberto.matteelli@unibs.it)

Shareable abstract (@ERSpublications)
Management of tuberculosis infection needs to be strengthened to achieve the goal of tuberculosis elimination https://bit.ly/37iYQfD

Cite this article as: Matteelli A, Alffenaar J-WC. Diagnosis and treatment of tuberculosis infection: can it contribute to achieving tuberculosis elimination? *Eur Respir J* 2022; 60: 2200540 [DOI: 10.1183/13993003.00540-2022].

Received: 15 March 2022
Accepted: 5 April 2022

The END tuberculosis (TB) strategy, launched in 2015, calls for elimination of TB, defined as an incidence of less than one case of the disease per million population [1]. For the first time ever, it broadens the concept of TB control and raises the profile of diagnosis and treatment of the pool of infected individuals from which future TB cases will be generated [2]. Currently, the World Health Organization (WHO) estimates 10 million incident cases per year [3], while the number of persons with the infection is estimated at 1.7 billion [4]. Although not contagious, people with *M. tuberculosis* infection represent the reservoir for future TB cases. To meet the TB elimination goal, it is imperative that such a reservoir will also be extinguished. Models predict that elimination of TB can be reached by 2050 and that diagnosis and treatment of tuberculosis infection (TBI) outperforms other interventions [5].

In 2018, the United Nations High-Level Meeting on TB, recognising that it will not be possible to end the TB epidemic unless we prevent the progression from infection to the disease, committed to rapid expansion of testing for TBI and provision of tuberculosis preventive therapy (TPT) and set the target of 30 million people to be treated by 2022 [6]. The target, in fact, represents only less than 2% of the total reservoir of infections and is a consequence of current WHO recommendations for diagnosis and treatment of TBI that target only 11 populations at risk, a marginal fraction of the global target [7]. There are reasons for being so conservative: first, the available diagnostic test for TBI, the tuberculin skin test and the interferon-γ release assay, have a very low positive predictive value for future progression, estimated at less than 10% [8]. From a public health perspective this means that 10 treatment courses need to be completed to prevent one TB case. From an individual perspective, the benefit of completing treatment may be perceived as small, compared to the risks of adverse events associated to drug intake [9]. Second, treatment of TBI is still based on regimens that are long and potentially associated with side-effects affecting treatment completion [10]. The latter is particularly concerning when considering that the drugs are used on completely asymptomatic subjects. Historically, the treatment of TBI has been based on isoniazid taken daily for 6–9 months, but, in the past two decades, research was directed towards increasing the benefits of TPT through wider adoption of shorter rifamycin-based regimens, for which there is increasing evidence of greater safety, and that could also reduce health resource requirements [11]. Several potential alternatives to isoniazid are now available and recommended, including a 3-month regimen of daily isoniazid and rifampicin, a 12-week regimen of weekly isoniazid and rifapentine, and a 1-month regimen of daily isoniazid and rifampicin [7, 12].

The *European Respiratory Journal* publishes, in this issue, a report from Xin *et al.* [13] on the effectiveness of an additional potential regimen, consisting of 6 weeks of twice weekly rifapentine and isoniazid.

The regimen showed a protective efficacy of 61% over 5 years, compared to no treatment, and demonstrated that preventive treatment based on short-course regimens is applicable to low–intermediate incidence settings like China. This report is significant, as it potentially gives us the second shorter regimen for the treatment of TBI, after the 1-month daily rifapentine/isoniazid regimen [14]. This new intermittent regimen could be innovative, particularly for difficult risk groups, such as drug-users and homeless persons, offering the choice of supervised therapy. However, the regimen is not transformative: it is still too long and comprises drugs with well-known potential for toxicity.

Besides current therapy being too long, there is an urgent need for effective preventive treatment for close contacts of patients with multidrug-resistant (MDR)-TB. Several initiatives are ongoing. Delamanid efficacy and safety is being evaluated by an ongoing study for preventing TB in high-risk household contacts of adults with MDR-TB [15]. Levofloxacin is compared to placebo to prevent TB in household contacts living with patients with bacteriologically confirmed rifampicin-resistant or MDR-TB with a positive tuberculin skin test [16].

The report from Xin *et al.* [13] brings light on the long-term protection of preventive therapy in a country with moderate transmission: the estimated TB incidence rate in China is 59 per 100 000 [3]. This is important, as it provides evidence, as previously shown for Brazil, that preventive therapy can play a role outside low-burden countries. Such evidence is essential to advocate for more attention and funds from national policy makers in these settings. However, the question about the role of preventive therapy in high-burden countries remains: where the burden of the disease is high, the durability of TPT is expected to be short due to the high potential for reinfection. In these settings, it would definitely be worthwhile to provide preventive therapy to very high-risk groups, such as people living with HIV and close contacts of contagious cases, but what about expanding the intervention beyond these groups? Delivering intermittent courses of short course preventive therapy in people living with HIV on antiretroviral therapy was long proposed as a potentially effective approach in high-burden countries. However, in a recently published randomised intervention study, TB incidence was similar (hazard ratio 0.96, 95% CI 0.61 to 1.50) among participants receiving a 12-week weekly rifapentine/isoniazid regimen for 1 or 2 consecutive years [17].

An interesting finding from the study of Xin *et al.* [13] is that protection was higher among participants with higher baseline releasing level of IFN-γ in TBI testing. The authors postulate that individuals with increased IFN-γ levels may have been infected more recently and demonstrate a more active infectious

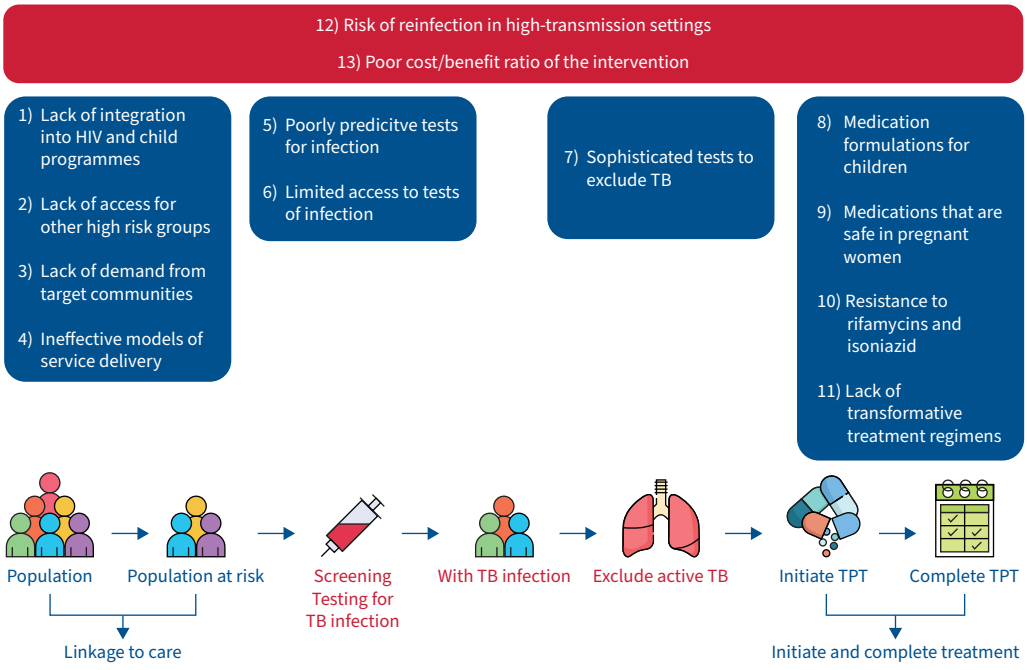

FIGURE 1 Research gaps according to the steps of the cascade of prevention of tuberculosis (TB). TPT: TB preventive therapy.

process as bacteria might be in a replicative state, and preventative treatment is therefore more effective. Rightfully, the authors mentioned that the study was not designed to test this hypothesis. The finding does justify further study as it may help to understand who are more likely at risk for developing TB and who are more likely to respond to preventative therapy. Future studies may have a closer look at actual test values which may help to improve the predictive value of the test [8]. This could have the potential to reduce the number of patients required to be treated to prevent one case of TB.

In conclusion, the way to develop effective tools for the elimination of the infection reservoir is still long. The deadline set more than 5 years ago for TB pre-elimination remains far away, while time elapses. Multiple gaps have been identified at each and every step of the cascade of prevention in high- and low-income countries [18, 19], as reported in figure 1. Research to improve each of the steps of the prevention cascade are strongly needed to erode the infection reservoir globally.

Conflict of interest: The authors have no conflict of interest to be declared.

References

1 Uplekar M, Weil D, Lonnroth K, *et al.* WHO's new end TB strategy. *Lancet* 2015; 385: 1799–1801.
2 Lönnroth K, Migliori GB, Abubakar I, *et al.* Towards tuberculosis elimination: an action framework for low-incidence countries. *Eur Respir J* 2015; 45: 928–952.
3 World Health Organization. Global Tuberculosis Report 2021. Geneva, World Health Organization, 2021.
4 Houben RMGJ, Dodd PJ. The global burden of latent tuberculosis infection: a re-estimation using mathematical modelling. *PLoS Med* 2016; 13: e1002152.
5 Dye C, Glaziou P, Floyd C, *et al.* Prospects for tuberculosis elimination. *Annu Rev Public Health* 2013; 34: 271–286.
6 Marais B, Zumla A. Advancing global tuberculosis control after the UNGA-HLM. *Lancet* 2018; 392: 1096–1097.
7 World Health Organization. WHO Consolidated Guidelines on Tuberculosis. Module 1: Prevention – Tuberculosis Preventive Treatment. Geneva, World Health Organization, 2020.
8 Zhou G, Luo Q, Luo S, *et al.* Interferon-gamma release assays or tuberculin skin test for detection and management of latent tuberculosis infection: a systematic review and meta-analysis. *Lancet Infect Dis* 2020; 20: 1457–1469.
9 Hirsch-Moverman Y, Colson PW, Bethel J, *et al.* Can a peer-based intervention impact adherence to the treatment of latent tuberculous infection? *Int J Tuberc Lung Dis* 2013; 17: 1178–1185.
10 Matteelli A, Rendon A, Tiberi S, *et al.* Tuberculosis elimination: where are we now? *Eur Respir Rev* 2018; 27: 180035.
11 Getahun H, Matteelli A, Abubakar I, *et al.* Management of latent *Mycobacterium tuberculosis* infection: WHO guidelines for low tuberculosis burden countries. *Eur Respir J* 2015; 46: 1563–1576.
12 Migliori GB, Wu SJ, Matteelli A, *et al.* Clinical standards for the diagnosis, treatment and prevention of TB infection. *Int J Tuberc Lung Dis* 2022; 26: 190–205.
13 Xin H, Cao X, Zhang H, *et al.* Protective efficacy of 6-week regimen for latent tuberculosis infection treatment in rural China: 5-year follow-up of a randomised controlled trial. *Eur Respir J* 2022; 60: 2102359.
14 Swindells S, Ramchandani R, Gupta A, *et al.* One month of rifapentine plus isoniazid to prevent HIV-related tuberculosis. *N Engl J Med* 2019; 380: 1001–1011.
15 Clinicaltrials.gov. Protecting Households On Exposure to Newly Diagnosed Index Multidrug-Resistant Tuberculosis Patients (PHOENIx MDR-TB). Identifier NCT03568383. Date last accessed: 9 March 2022. www.clinicaltrials.gov/ct2/show/NCT03568383
16 Fox GJ, Nguyen CB, Nguyen TA, *et al.* Levofloxacin *versus* placebo for the treatment of latent tuberculosis among contacts of patients with multidrug-resistant tuberculosis (the VQUIN MDR trial): a protocol for a randomised controlled trial. *BMJ Open* 2020; 10: e033945.
17 Churchyard G, Cárdenas V, Chihota V, *et al.* Annual tuberculosis preventive therapy for persons with HIV infection: a randomized trial. *Ann Intern Med* 2021; 174: 1367–1376.
18 Alsdurf H, Hill PC, Matteelli A, *et al.* The cascade of care in diagnosis and treatment of latent tuberculosis infection: a systematic review and meta-analysis. *Lancet Infect Dis* 2016; 16: 1269–1278.
19 Oxlade O, den Boon S, Menzies D, *et al.* TB preventive treatment in high- and intermediate-incidence countries: research needs for scale-up. *Int J Tuberc Lung Dis* 2021; 25: 823–831.