of additional resistance to both fluoroquinolones and injectables in MDR *Mycobacterium tuberculosis* strains) have been adopted (and make sense) if they identify cases requiring different clinical management. Future studies involving new drugs (such as delamanid, bedaquiline, and pretomanid) need to be designed to help detect patient subgroups who are at the highest risk of negative outcomes (failure and death), with the final goal of understanding whether existing definitions are adequate to guide routine clinical management or new ones are needed.

Rosella Centis, Giovanni Sotgiu, Giovanni Battista Migliori
Istituti Clinic Scientifici Maugeri IRCCS, Tradate 21049, Italy (RC, GBM) and Clinical Epidemiology and Medical Statistics Unit, Department of Medical, Surgical and Experimental Sciences, University of Sassari, Sassari, Italy (GS)
rosella.centis@icsmaugeri.it

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1 von Groote-Bidlingmaier F, Patientia R, Sanchez E, et al. Efficacy and safety of delamanid in combination with an optimised background regimen for treatment of multidrug-resistant tuberculosis: a multicentre, randomised, double-blind, placebo-controlled, parallel group phase 3 trial. *Lancet Respir Med* 2019; **7:** 249–59.

2 WHO. WHO best-practice statement on the off-label use of bedaquiline and delamanid for the treatment of multidrugresistant Tuberculosis. WHO/HTM/TB/2017.20. 2017. http://apps.who.int/iris/bitstream/handle/10665/258941/WHO-HTM-TB-2017.20-eng.pdf?sequence=1&isAllowed=y (accessed Oct 12, 2018).

3 Pontali E, D'Ambrosio L, Centis R, Sotgiu G, Migliori GB. Multidrug-resistant tuberculosis and beyond: an updated analysis of the current evidence on bedaquiline. *Eur Respir J* 2017; **49:** 1700146.

4 Pontali E, Sotgiu G, Tiberi S, D'Ambrosio L, Centis R, Migliori GB. Cardiac safety of bedaquiline: a systematic and critical analysis of the evidence. *Eur Respir J* 2017; **50:** 1701462.

5 Diacon AH, Pym A, Grobusch MP, et al. Multidrug-resistant tuberculosis and culture conversion with bedaquiline. *N Engl J Med* 2014; **371:** 723–32.

6 Pontali E, Sotgiu G, Tiberi S, et al. Combined treatment of drug-resistant tuberculosis with bedaquiline and delamanid: a systematic review. *Eur Respir J* 2018; **52:** 1800934.

7 Borisov SE, Dheda K, Enwerem M, et al. Effectiveness and safety of bedaquiline-containing regimens in the treatment of multidrug and extensively drug-resistant tuberculosis: a multicentre study. *Eur Respir J* 2017; **49:** 1700387.

8 Hafkin J, Hittel N, Martin A, Gupta R. Early outcomes in MDR-TB and XDR-TB patients treated with delamanid under compassionate use. *Eur Respir J* 2017; **50:** 1700311.

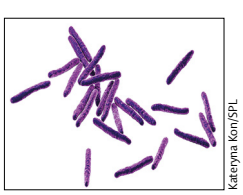
9 Hafkin J, Hittel N, Martin A, Gupta R. Compassionate use of delamanid in combination with bedaquiline for the treatment of MDR-TB. *Eur Respir J* 2018; published onine Oct 25. DOI:10.1183/13993003.01154-2018.

10 WHO. Rapid communication: key changes to treatment of multidrug- and rifampicin-resistant tuberculosis. WHO/CDS/TB/2018.18. 2018. http://www.who.int/tb/publications/2018/rapid_communications_MDR/en/ (accessed Oct 12, 2018).

11 Migliori GB, Global Tuberculosis Network (GTN). Evolution of programmatic definitions used in tuberculosis prevention and care. *Clin Infect Dis* 2018; published online Nov 20. DOI:10.1093/cid/ciy990.

Towards optimal treatment for latent *Mycobacterium tuberculosis* infection

Tuberculosis is the most common infectious disease cause of death worldwide.[1] To achieve the ambitious WHO End TB strategy goal of eliminating tuberculosis by 2050, the current global incidence of tuberculosis must decrease by 20% per year,[2] a seemingly impossible task. Achieving this target will not be possible without the identification and treatment of an estimated 2 billion people with latent *Mycobacterium tuberculosis* infection (LTBI), who have viable *M tuberculosis* bacilli in their tissues but show no signs or symptoms of tuberculosis disease.[3] This delicate balance between host and pathogen[4] can be perturbed by underlying risk factors that compromise protective immunity. Between 5% and 10% of people have reactivation of their LTBI into active tuberculosis disease over the course of their lifetime, thus constantly adding to the large pool of people with infectious tuberculosis. Preventing this future risk of LTBI reactivation is a priority in the historic 2018 UN General Assembly High Level meeting declaration, with a target set at treatment of 30 million people with LTBI by 2030.[5]


Kateryna Kon/SPL

To take forward this mammoth task, both high and low tuberculosis endemic countries are expected to use and implement the latest WHO 2018 updated guidelines for programmatic management of LTBI.[6] These guidelines are based on the strengths and weaknesses of scientific and operational research evidence, benefits and risk, cost, acceptability, and feasibility of implementation. It is impossible to detect and treat all 2 billion people with LTBI. As not all people with LTBI go on to develop active disease, WHO guidelines recommend that only people at the highest risk for progression should be considered for LTBI treatment.[6] However, most cases of active tuberculosis will develop in individuals who are not known to be in the risk groups currently recommended to be treated for LTBI.

In both high and low tuberculosis endemic settings, the decision to treat an individual with LTBI should weigh the benefits against the risks of potential side effects of drugs, and the risk of failing to identify active tuberculosis and the likehood of drug-resistant *M tuberculosis* strains.[7] The conventional 6–9-month isoniazid regimen is supported by strong evidence of clinical efficacy, but has a small risk of hepatotoxicity and death. The shorter course regimens such as 3 months of isoniazid plus rifampicin or 1 dose per week of rifapentine plus isoniazid for 12 weeks duration are recommended, albeit based on weaker evidence.[6]

The natural history of *M tuberculosis* infection and the underlying immune mechanisms governing LTBI remain poorly understood.[4,8] Eradicating *M tuberculosis* with LTBI drug treatment could remove the antigenic stimulation required to sustain protective immunity to reinfection. Furthermore, the prevailing tuberculosis incidence correlates with *M tuberculosis* reinfection rates, thus in high tuberculosis endemic countries, people treated for LTBI are more likely to become reinfected because of the high prevailing load of infectious individuals.[9] Therefore, the long-term benefits of LTBI treatment for the individual and the community might not be substantial.[10] By contrast, in low tuberculosis burden countries where *M tuberculosis* transmission rates are low, most cases of active tuberculosis are due to reactivation of LTBI. The protection given by LTBI treatment to the individual from progressing to active tuberculosis is more pronounced given the low reinfection risk.[11]

The current WHO LTBI management guidelines,[6] which focus on eradicating the pathogen with tuberculosis drugs, do not address important underlying host factors that cause an increased risk of LTBI progressing to active tuberculosis disease in most people worldwide. These include people living in poverty, homeless people, migrants, refugees, prisoners, older people, children, people with HIV, alcoholics, patients with diabetes, and substance users, among others. LTBI treatment needs to be complemented with interventions that tackle the underlying host social and immune factors, which drive progression of LTBI to active tuberculosis disease.[12] Technological advances now provide unique opportunities to gain insights into host–pathogen interactions in LTBI, defining protective immune responses, identifying the presence of drug-resistant *M tuberculosis* isolates within lesions, and for evaluating effects of host-directed therapies on mycobacterial replication and local immune responses.[12] For example, imaging studies with use of PET with [^{18}F]-fluorodeoxyglucose combined with CT scans have shown *M tuberculosis* granuloma lesions evolving over time.[13] *M tuberculosis* mRNA can be detected in non-resolving lesions on PET or CT images, suggesting that even apparently curative treatment for tuberculosis might not eradicate all *M tuberculosis* bacilli. Recent integrated analyses of three heterogeneous longitudinal cohorts at different stages of *M tuberculosis* infection to identify stage-specific host responses to *M tuberculosis* infection provide novel insights into the pathophysiology of LTBI and show promise for identifying potential peripheral blood biomarkers.[14] Further studies are required to identify specific factors across all geographical regions that influence and establish outcomes of *M tuberculosis* infection.

More specific diagnostic tools that can reliably predict the risk for progression of LTBI to active disease will allow for more targeted, safer LTBI management universally. Such tools would greatly enhance the prospect of aligning tuberculosis case detection and LTBI preventive therapy. A new, effective, post-exposure vaccine to prevent the disease in individuals with LTBI could change the landscape of tuberculosis prevention and would complement the current pre-exposure tuberculosis vaccine pipeline to prevent *M tuberculosis* infection at the population level. The current management of LTBI remains sub-optimal and requires more investment into research to address both host and pathogen factors. A major step change in research and investment, at the level that led to progress in the control of HIV in the last three decades, is required to address these challenges. Meanwhile, current WHO LTBI management guidelines must be adhered to and implemented widely and effectively.

*Ibrahim Abubakar, Jeremiah Chakaya, Markus Maeurer, *Alimuddin Zumla*

University College London Institute for Global Health, University College London, London, UK (IA); Union Headquarters, International Union Against Tuberculosis and Lung Disease, Paris, France (JC); Department of Medicine, Kenyatta University, Nairobi, Kenya (JC); Champalimaud Foundation, Centre for the Unknown, Avenida Brasília, Lisbon, Portugal (MM); Division of Infection and

Immunity, Center for Clinical Microbiology, University College London, London, UK (AZ); and National Institute of Health Research Biomedical Research Centre, University College London Hospitals, London NW1 2PG, UK (AZ)
a.zumla@ucl.ac.uk

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1 WHO. Global Tuberculosis Report 2018. 2018. https://www.who.int/tb/publications/global_report/en/ (accessed Dec 25, 2018).
2 Menzies NA, Wolf E, Connors D, et al. Progression from latent infection to active disease in dynamic tuberculosis transmission models: a systematic review of the validity of modelling assumptions. *Lancet Infect Dis* 2018; **18:** e228–38.
3 Houben R, Menzies NA, Sumner T, et al. Feasibility of achieving the 2025 WHO global tuberculosis targets in South Africa, China, and India: a combined analysis of 11 mathematical models. *Lancet Glob Health* 2016; **4:** e806–15.
4 Pai M, Behr MA, Dowdy D, et al. Tuberculosis. *Nat Rev Dis Primers* 2016; **2:** 16076.
5 WHO. World leaders commit to bold targets and urgent action to end TB. 2018. http://www.who.int/news-room/detail/26-09-2018-world-leaders-commit-to-bold-targets--and-urgent-action-to-end-tb (accessed Dec 21, 2018).
6 WHO. Latent tuberculosis infection–updated consolidated guidelines for programmatic management. 2018. https://www.who.int/tb/publications/latent-tuberculosis-infection/en/ (accessed Dec 27, 2018).
7 Fox GJ, Dobler CC, Marais BJ, Denholm JT. Preventive therapy for latent tuberculosis infection- the promise and challenges. *Int J I Dis* 2017; **56:** 68–76.
8 Zumla A, Atun R, Maeurer M, et al. Viewpoint: Scientific dogmas, paradoxes and mysteries of latent *Mycobacterium tuberculosis* infection. *Trop Med Int Health* 2011; **16:** 79–83.
9 Ragonnet R, Trauer JM, McBryde ES, et al. Is IPT more effective in high-burden settings? Modelling the effect of tuberculosis incidence on IPT impact. *Int J Tuberc Lung Dis* 2017; **21:** 60–66.
10 Kim HW, Kim JS. Treatment of latent tuberculosis infection and its clinical efficacy. *Tuberc Respir Dis* 2018; **81:** 6–12.
11 Abubakar I, Drobniewski F, Southern J, et al. Prognostic value of interferon-γ gamma release assays and tuberculin skin test in predicting the development of active tuberculosis: the UK PREDICT tuberculosis cohort study. *Lancet Infect Dis* 2018; published online Aug 30. http://dx.doi.org/10.1016/S1473-3099(18)30355-4.
12 Kaufmann SH, Lange C, Rao M,et al. Progress in tuberculosis vaccine development and host-directed therapies–a state of the art review. *Lancet Respir Med* 2014; **2:** 301–20.
13 Martin C, Castaigne C, Vierasu I, Garcia C, Wyndham-Thomas C, de Wit S. Prospective serial FDG PET/CT during treatment of extrapulmonary tuberculosis in HIV-infected patients: an exploratory study. *Clin Nucl Med* 2018; **43:** 635–40.
14 Chowdhury R, Vallania F, Yang Q, et al. A multi-cohort study of the immune factors associated with *M. tuberculosis* infection outcomes. *Nature* 2018; **560:** 644–48.

Isoniazid preventive therapy for children in sub-Saharan Africa

In 2017, an estimated 1 million children aged 15 years and under developed active tuberculosis disease and 239 000 children died from the disease.[1] In sub-Saharan Africa, tuberculosis in children remains a neglected issue and many children remain undiagnosed and untreated.[2] An estimated 1·7 billion adults and children worldwide have latent *Mycobacterium tuberculosis* infection (LTBI),[3] which can reactivate into active clinical disease during their lifetime. In children, risk factors for progression of existing LTBI to active tuberculosis disease or acquisition of new *M tuberculosis* infection include living with an adult with recently diagnosed sputum-smear pulmonary tuberculosis, malnutrition, HIV infection or other causes of immunocompromise, and being younger than 5 years old.[4]

It is well established that isoniazid preventive therapy (IPT) can reduce the overall risk of progression of LTBI to active tuberculosis disease in children by up to 59%.[5] IPT can also reduce the risk of active tuberculosis and death in children with newly diagnosed HIV not receiving antiretrovirals.[6] Therefore, testing and treatment of LTBI in child contacts to prevent progression of LTBI to active symptomatic disease is one of the ten priority indicators for monitoring the implementation of the WHO End TB Strategy, which has set targets at 90% or more LTBI contact investigation coverage and treatment.[7] Although several national and international guidelines for screening of LTBI and administering IPT have been developed, effective programmatic implementation of these by countries with high endemic tuberculosis has not been optimal. Disappointingly, in sub-Saharan Africa, 16% of children eligible for IPT were identified and given IPT in 2017,[1] and worldwide only 13% of eligible children are estimated to receive IPT.[8,9]

Despite the known effectiveness of IPT and its potential to contribute to reducing tuberculosis morbidity and mortality in children, uptake continues to remain at unacceptably low levels. A major step change in scaling up the implementation of IPT in sub-Saharan Africa is needed and will entail overcoming several obstacles (panel).[9–11]

These multifactorial, programmatic, community, and clinical limitations of implementing WHO LTBI IPT management recommendations require immediate, short, medium, and long-term plans. The plans should be supported with budgetary commitment to drastically change the current status quo and narrow the major gaps in IPT delivery, implementation, community acceptance, and treatment completion rates. Recent