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Towards optimal treatment for LTBI in low and high TB endemic settings

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Tuberculosis is the commonest infectious disease cause of death worldwide.¹ To achieve the ambitious WHO End TB strategy goal of eliminating TB by 2050 the current global incidence of TB must decrease by 20% per year² - a seemingly impossible task. Achieving this target will not be possible without the identification and treatment of 2 billion people with Latent TB infection (LTBI) who have viable *Mycobacterium tuberculosis* (*M.tb*) bacilli within their tissues but show no signs or symptoms of TB disease.³ This delicate balance between host and pathogen⁴ can be perturbed by underlying risk factors which compromise protective immunity. Between 5% to 10% of people re-activate their LTBI into active TB disease over the course of their lifetime, thus constantly adding to the large pool of infectious TB cases. Preventing this future risk of LTBI re-activation is a priority agenda in the historic 2018 United Nations General Assembly High-Level Meeting declaration with a target set at treatment of 30 million people with LTBI by 2030.⁵

To take forward this mammoth task, both high and low TB endemic countries are expected to utilize and implement the latest WHO 2018 updated guidelines for programmatic management of LTBI.⁶ These 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. Since not all persons with LTBI go on to developing active disease, WHO guidelines recommend that only people at the highest risk for progression should be considered for LTBI treatment.⁶ However, the majority of active TB 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 TB endemic settings, the decision to treat an individual with LTBI should weigh the benefits against the risks of drug side effects, exclusion of active TB and the likelihood of drug resistant *M.tb* strains.⁷ The conventional 6 to 9 months of isoniazid regimen has 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 rifampin or 12 dose weekly rifapentine and isoniazid are recommended, albeit based on weaker evidence.⁶

The natural history of *M.tb* infection and underlying immune mechanisms governing LTBI remains poorly understood.^{4,8} Eradicating *M.tb* with LTBI drug treatment may remove the antigenic stimulation required to sustain protective immunity to re-infection. Furthermore, the prevailing TB incidence correlates with *M.tb* re-infection rates, and in high TB endemic countries persons treated for LTBI are more likely to become re-infected due to the high prevailing load of infectious cases.⁹ Thus long-term benefits of LTBI treatment for the individual and the community may not be substantial.¹⁰ In contrast, in low TB burden countries where *M.tb* transmission rates are low, most cases of active TB are due to

reactivation of LTBI, the protection given by LTBI treatment to the individual from progressing to active TB is more pronounced given the low re-infection risk.¹¹

The current WHO LTBI management guidelines,⁶ focused on eradicating the pathogen *M.tb* with TB drugs, do not address important underlying host factors which cause an increased risk of LTBI progressing to active TB disease in the majority of people worldwide. These include the poor, homeless, migrants, refugees, prisoners, elderly, children, people living with HIV, alcoholics, diabetics, substance abusers, amongst others. There is an urgent need for developing more optimal treatment regimens for LTBI which should target underlying host-factors. Technological advances now provide unique opportunities to gain new insights into understanding host-pathogen interactions operating in LTBI, defining protective immune responses, identifying presence of drug resistant *M.tb* isolates within lesions, and for evaluating effects of HDTs on mycobacterial replication and local immune responses. For example, imaging studies using position emission tomography (PET) with [18F]fluoro-2-deoxy-D-glucose (FDG) combined with CT scan have shown *M.tb* granulomas lesions evolving over time.¹² *M.tb* mRNA can be detected in non-resolving lesions on PET/CT images suggesting that even apparently curative treatment for TB may not eradicate all *M.tb* bacilli. Recent integrated analyses of 3 heterogeneous longitudinal cohorts at different stages of *M.tb* infection to identify stage-specific host responses to *M.tb* infection provide novel insights into the pathophysiology of LTBI and show promise for identifying potential peripheral blood biomarkers.¹³ Further studies are required to identify specific factors across all geographical regions which influence and determine outcomes of *M.tb* infection.

More specific diagnostic tools which could reliably predict the risk for progression of LTBI to active disease, will allow for more targeted, safer LTBI management universally, and would greatly enhance the prospect of aligning TB 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 TB prevention and would complement current pre-exposure TB vaccine pipeline to prevent *M. tb* infection at population level. LTBI treatment is currently based on treatment with TB drugs. This needs to be complemented with host-directed therapies to address underlying immune factors which drive progression of LTBI to active TB disease. The current management of LTBI remains sub-optimal and requires more investments into research to address host and pathogen factors. A major step-up change in research and investment, at the level that led to progress in the control of HIV in the last 3 decades, is required to address these challenges. Meanwhile, current WHO LTBI management guidelines must be adhered to and implemented widely and effectively.

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