Title:

Latent Tuberculosis Infection – diagnostic tests and deciding when to treat

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Latent *Mycobacterium tuberculosis* (*M.tb*) infection (LTBI) is defined by the World Health Organization (WHO) as 'a state of persistent immune response to *M.tb* antigens with no evidence of clinically active TB disease' (WHO, 2018).[1] An estimated 1.7 billion people worldwide have LTBI, of which upto 10% are at risk of re-activating into active TB during their lifetime.[2] LTBI can be effectively treated and this can prevent progression to active TB, benefitting both the individual and the community. Current treatment regimens for LTBI[1] reduce the risk of developing active TB by at least 60%.[1,3] Achieving the 2035 and 2050 End TB Strategy goals will require addressing the very challenging and arduous task of screening and treating this huge LTBI reservoir.

The latest 2018 WHO LTBI guidelines (WHO, 2018) recommend LTBI screening and treatment should focus on people at a high risk of LTBI re-activation regardless of background epidemiology, particularly people living with HIV and children under 5 years of age who are household contacts of pulmonary TB patients in all settings. Others include anyone initiating anti-TNF treatment, receiving dialysis, preparing for organ or haematological transplantation and those with silicosis. In low-TB prevalence countries like the USA, a large proportion of people who are diagnosed with active TB appear to have developed the disease from untreated LTBI.[4] Thus, all western countries now have proactive LTBI screening and treatment programs for all new migrants and refugees.

Despite two decades of research there are no gold standard diagnostic tests for LTBI. Currently three LTBI tests are recommended by WHO[1]: the tuberculin skin test (TST) and two interferon gamma release assays (IGRAs), QuantiFERON®-TB Gold In-Tube and T-SPOT®TB. False negative IGRA tests have been reported in 12% of active TB cases[5] and in 28.8% of patients with extrapulmonary TB.[6] The impact of LTBI tests on patient management outcomes or on TB control programs in high TB endemic countries remains to be defined. Recent cohort studies in low TB endemic countries indicate that IGRAs may predict progression of LTBI to active TB disease[7,8] although they raise more questions than they answer. In contacts of active TB cases who progressed to developing active TB, 39% had a negative QuantiFERON®-TB Gold test, 32% a negative T-SPOT®TB test, and a positive predictive value below 5% and negative predictive value above 99% for IGRAs.[7]

It is important to note that TST nor IGRAs cannot differentiate between LTBI and active TB disease and they should not be used as diagnostic tests for active TB. In those apparently healthy individuals with a positive IGRA or TST, the decision to treat LTBI using one of several LTBI treatment regimens recommended by WHO[1] should not be taken lightly. Before LTBI treatment is commenced on basis of a

positive IGRA or TST test, it is crucial that active TB disease is ruled out by taking a thorough history, conducting physical examination and relevant investigations. Those with weight loss, night sweats, elevated ESR or CRP and abnormal imaging should be investigated further. These persons suspected of having active TB disease should receive the recommended quadruple therapy, and not LTBI treatment regimens. This is particularly important in cases of extra-pulmonary TB (EPTB)[6] and children[9] where the lack of access to clinical samples makes it difficult to accurately exclude active TB. Another vexed issue is that in individuals with LBTI who have been exposed to multidrug-resistant TB (MDR TB) or extensively drug-resistant TB (XDR TB)[10], the preventive treatment regimens may not be suitable options.

Recent studies focused on host gene expression and blood RNA signatures symmetry during progression from LTBI to active TB disease show promise.[11,12] For consistency of comparison of existing IGRAs and TST with newer tests, it would be prudent to use the evaluation framework[13] for new tests which predict progression from LTBI to active clinical disease. There is an urgent need for more specific LTBI screening tests that reliably identify LTBI and predict the likelihood of LTBI progressing to active TB disease. That would be the most important contribution to programmatic management of LTBI, allowing accurate identification of LTBI, distinguish LTBI from active TB disease, and enable LTBI specific treatment.

World leaders at the unprecedented United Nations General Assembly (UNGA) High Level meeting on TB[14] in September 2018 unanimously adopted a political declaration in which they committed to identify and treat 30 million people with LTBI, highlighting the importance of proactive screening of contacts of active TB cases. For all their imperfections, the IGRAs and TST currently are the only WHO-approved LTBI screening tests that we have at present, and they must be used prudently and optimally following the latest WHO programmatic guidelines on LTBI.

References

1. WHO 2018. Latent tuberculosis infection – updated consolidated guidelines for programmatic management. https://www.who.int/tb/publications/latent-tuberculosis-infection/en/ (Accesses 7 Dec 2018)

2. Houben RM, Dodd PJ. The Global Burden of Latent Tuberculosis Infection: A Re-estimation Using Mathematical Modelling. PLoS Med. 2016 Oct 25;13(10):e1002152. doi: 10.1371/journal.pmed.1002152. eCollection

3. Erkens CG, Slump E, Verhagen M, Schimmel H, Cobelens F, van den Hof S. Risk of developing tuberculosis disease among persons diagnosed with latent tuberculosis infection in the Netherlands. Eur Respir J. 2016 Nov;48(5):1420-1428.

4. France AM, Grant J, Kammerer JS, Navin TR. A field-validated approach using surveillance and genotyping data to estimate tuberculosis attributable to recent transmission in the United States. Am J Epidemiol. 2015;182:799–807.

5. Nguyen DT, Teeter LD, Graves J, Graviss EA. Characteristics Associated with Negative Interferon-γ Release Assay Results in Culture-Confirmed Tuberculosis Patients, Texas, USA, 2013-2015. Emerg Infect Dis. 2018 Mar;24(3):534-40.

6. Kim YJ, Kang JY, Kim SI, Chang MS, Kim YR, Park YJ. Predictors for false-negative QuantiFERON-TB Gold assay results in patients with extrapulmonary tuberculosis. BMC Infect Dis. 2018 Sep 10;18(1):457

7. 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.

8. Winje BA, White R, Syre H, Skutlaberg DH, Oftung F, Mengshoel AT, et al. Stratification by interferon-γ release assay level predicts risk of incident TB. Thorax. 2018 Apr 5. pii: thoraxjnl-2017-211147. doi: 10.1136/thoraxjnl-2017-211147.

9. Egere U, Togun T, Sillah A, Mendy F, Otu J, Hoelscher M, et al. Identifying children with tuberculosis among household contacts in The Gambia. Int J Tuberc Lung Dis. 2017 Jan 1;21(1):46-52.

10. van der Werf MJ, Sandgren A, Manissero D. Management of contacts of multidrug-resistant tuberculosis patients in the European Union and European Economic Area. Int J Tuberc Lung Dis. 2012 Mar;16(3):426.

11. Thompson EG, Du Y, Malherbe ST, Shankar S, Braun J, Valvo J, et al; Catalysis TB–Biomarker Consortium. Host blood RNA signatures predict the outcome of tuberculosis treatment. Tuberculosis (Edinb). 2017 Dec; 107:48-58.

12. Suliman S, Thompson E, Sutherland J, Weiner Rd J, Ota MOC, Shankar S, et al. Four-gene Pan-African Blood Signature Predicts Progression to Tuberculosis. Am J Respir Crit Care Med. 2018 Apr 6. doi: 10.1164/rccm.201711-2340OC. [Epub ahead of print]

13. Kik SV, Schumacher S, Cirillo DM, Churchyard G, Boehme C, Goletti D, et al. An evaluation framework for new tests that predict progression from tuberculosis infection to clinical disease. Eur Respir J. 2018 Oct 25;52(4). pii: 1800946.

14. UN GA 2018. GA/12067 26 September, 2018. World Leaders Reaffirm Commitment to End Tuberculosis by 2030, as General Assembly Adopts Declaration Outlining Actions for Increased Financing, Treatment Access https://www.un.org/press/en/2018/ga12067.doc.htm