

C-Tb: a latent tuberculosis skin test for the 21st century?



The UN Sustainable Development Goals have led to global plans to end the tuberculosis epidemic. Individuals with latent tuberculosis infection are at risk of reactivation disease and onward transmission to contacts. Identification of these people before they develop active tuberculosis will, therefore, help to control the epidemic. Unfortunately, there is no gold standard diagnostic test for latent tuberculosis infection, and existing tests have poor ability to predict which individuals will go on to develop active tuberculosis. Those used at present are the tuberculin skin test (TST), which is cheap and simple to administer in the field but can be falsely positive in people who have received BCG vaccination or been exposed to non-tuberculous mycobacteria,¹ and interferon γ release assays (IGRAs), which are more specific but are expensive and need specialist laboratory processing.

In *The Lancet Respiratory Medicine*, Morten Ruhwald and colleagues² report an assessment of C-Tb (Statens Serum Institut, Copenhagen, Denmark), a diagnostic skin test for latent tuberculosis infection. This test is based on the *Mycobacterium tuberculosis*-specific RD1 antigens ESAT-6 and CFP10 that are used in IGRAs. C-Tb combines the simplicity of administering a skin test without the need for laboratory processing and high specificity because of the use of *M tuberculosis*-specific antigens that are not present in the BCG vaccine or most environmental mycobacteria. The authors compared C-Tb with the QuantiFERON-TB Gold In-Tube (QFT) IGRA and the TST in 979 people separated into subgroups of varying degrees of risk of infection with *M tuberculosis*, ranging from people with no known history of exposure to tuberculosis (n=263), to occasional contacts (n=299) and close contacts (n=316) of people with tuberculosis, to patients with culture-confirmed tuberculosis (n=101), as has been used previously to assess IGRAs.³ All participants older than 5 years were tested with QFT. People were then randomised to be tested with the TST in the left arm and C-Tb in the right arm or vice versa or, in a small subgroup of negative controls, C-Tb alone to test for an interaction with the TST. A trend was found towards positivity with increasing risk of infection, with concordant results seen between C-Tb and QFT in 785 (94%) of 834 participants. C-Tb, however, was classified as positive in fewer patients

with active tuberculosis than was QFT (68 [67%] vs 82 [81%], p=0.003). The overall safety profiles of C-Tb and TST were similar, although injection-site haematoma was seen more often with C-Tb than with the TST (14% vs 2%).

WHO encourages testing and treatment of contacts of patients with pulmonary tuberculosis and of individuals with various forms of immunosuppression, including HIV, in low-incidence countries.⁴ Additionally, treatment without testing is an option for children younger than 5 years who are contacts of people with infectious tuberculosis, and for HIV-infected individuals in high-burden countries.⁴ The high degree of concordance between C-Tb and QFT and the ease of administration of C-Tb raises the prospect that the new test for infection with *M tuberculosis* with increased specificity could be used at the point of care, which could lower the number of uninfected people who receive unnecessary treatment and its associated adverse events, such as hepatotoxic effects.⁵

While differences between the TST and IGRAs can be attributed to BCG vaccination and non-tuberculous mycobacteria sensitisation, the reason for, and clinical relevance of, discordant results between the commercial ELISA and the enzyme-linked immunospot versions of IGRAs remain unclear. Similarly, the reasons for discordance between C-Tb and QFT are unclear. The

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different routes of administration—blood for the IGRA and the skin for C-Tb—and, consequently, the different cells recruited or responding to the inoculated antigen, might explain some of the variance. Although further research is needed to understand these differences, the discordance is small and should not affect the practical application of the test. The lower sensitivity of C-Tb than QFT in patients with active tuberculosis could suggest that QFT has better ability to measure the presence of interferon γ . Of note, though, a previously published study of C-Tb by the same investigators showed similar sensitivity for C-Tb (73.9%, 95% CI 67.8–79.3) and QFT (75.1%, 69.3–80.2%) in 273 patients with recently diagnosed active tuberculosis.⁶

Ultimately, an important aim of testing for infection with *M tuberculosis* is to identify individuals at the highest risk of progressing to tuberculosis. A systematic review and meta-analysis reported that the relative risk of developing active tuberculosis among individuals with positive IGRA results compared with those who had negative results was weak to moderate (about 2–3).⁷ That people with a positive C-Tb test will have a higher chance of progressing to active tuberculosis than those with a positive IGRA result seems unlikely because the tests use the same antigens. A further limitation of a skin test is the need for patients to return for the size of induration to be read. Innovative health-care delivery methods using new technologies might allow reading of the skin test immune response without direct contact with health-care workers, which could reduce loss to follow-up and encourage appropriate treatment.

The increased risk of haematoma at the injection site seen with C-Tb compared with the TST found by Ruhwald and colleagues, while not a serious adverse event, should be assessed further. Data from larger

studies as part of postmarketing surveillance are needed to confirm whether the risk of haematoma is truly increased.

C-Tb potentially provides an upgrade to the diagnosis of latent tuberculosis infection by combining the specificity of IGRA with the logistic simplicity of the TST. Fuller assessment of the operational, economic, and predictive aspects of C-Tb, including cost-effectiveness and acceptability, will elucidate its potential in tuberculosis control programmes in different epidemiological settings (eg, those with different burdens of tuberculosis, HIV, and comorbidities). In the meantime, the search for a highly predictive assay for latent tuberculosis infection continues.

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