A novel blood test for tuberculosis prevention and treatment

Almost 1 in every 100 South Africans is diagnosed with active tuberculosis (TB) disease every year, an incidence that ranks among the highest of the world’s 22 high-TB-burden countries; TB accounted for an astounding 14.6% of deaths among 15 - 44-year-olds in South Africa (SA) in 2014.3,4 Globally, TB is recognised as the leading cause of mortality by an infectious agent, with 1.4 million deaths and 10.4 million new TB cases in 2015.5,6 Although most forms of TB are treatable, prompt diagnosis is challenging and passive case-finding approaches have failed to control the epidemic. The estimated 80% of SA adults who are latently infected with Mycobacterium tuberculosis form a massive reservoir for future reactivation cases.7,8 Indeed, even if all new M. tuberculosis infections were prevented, the incidence of TB stemming from the global reservoir of 1.7 billion latently infected people (23% of the world population) would be 16.5 per 100 000 person-years in 2035, falling short of the 2050 target for eradicating TB.9

As preventive therapy at this scale is not feasible, no single current diagnostic has been qualified, in prognostic specificity of 84% and sensitivity of 71% (area under the curve = 0.76) 1 year before the onset of TB disease (A Penn-Nicholson – unpublished data). The PCR assay has been qualified, and engagement is underway with commercial partners to translate this test technology to a smaller, simpler, faster and cheaper point-of-care test. Prevention of TB disease arising from latent infection significantly elevates the risk of TB disease.13 Performance of the RNA signature will also be tested in an observational study of SA adults living with HIV, in parallel with CORTIS. The PCR assay has been translated into a polymerase chain reaction (PCR) test and was independently validated in cohorts from The Gambia and SA. The 16-gene PCR test predicted incident TB in adolescents, with a specificity of 82% and sensitivity of 70% within a year of testing – in the combined training and test sets.10 To improve throughput of the test, we have refined the RNA signature to 11 genes, resulting in prognostic specificity of 84% and sensitivity of 71% (area under the curve = 0.76) 1 year before the onset of TB disease (A Penn-Nicholson – unpublished data). The PCR assay has been qualified, and engagement is underway with commercial partners to translate this treat-and-treat strategy that may in future replace chronic IPT.14

Should the CORTIS screen-and-treat strategy prove efficacious in predicting and reducing the incidence of TB disease by targeted preventive therapy, the critical question is whether implementation would be feasible for the SA healthcare system. Key considerations are: (i) test performance; (ii) population level impact; (iii) cost/benefit ratio; (iv) operational feasibility; and (v) political commitment. RNA signature performance is being tested prospectively in CORTIS, but preliminary models predict that a TB screen-and-treat strategy that reached 30% of HIV-negative SA adults annually could reduce the incidence of TB disease than low-risk signature-negative individuals (COR−); and that 3HP will reduce the incidence of TB disease in COR+ participants compared with COR+ participants under active surveillance.

The RNA signature might also have diagnostic utility for undiagnosed, sub-clinical TB disease when deployed as a triage tool to trigger investigation in otherwise healthy, RNA signature-positive individuals. We have provisionally demonstrated 93% specificity and 92% sensitivity to discriminate healthy South Africans with latent M. tuberculosis infection from those with active TB disease (F Darboe et al. – unpublished data). Within CORTIS, we will further assess the use of the RNA signature to diagnose prevalent TB in HIV-negative adults. If successful, this would enable targeted investigation of RNA signature-positive individuals for sub-clinical TB disease, allowing early curative treatment; RNA signature-positive individuals found not to have active disease would be offered preventive therapy; and those found to be RNA signature negative would be spared unnecessary intervention (Fig. 1).

It is estimated that 11% of South Africans live with HIV; yet, 57% of the burden of all TB in SA is borne by those living with HIV.15 HIV infection significantly elevates the risk of TB disease.16 Performance of the RNA signature will also be tested in an observational study of SA adults living with HIV, in parallel with CORTIS. If the prognostic RNA signature performs as expected, it might also be used to identify HIV-positive individuals at highest risk of TB disease within a year of testing, and thus trigger initiation of targeted, short-course preventive therapy regimens that may in future replace chronic IPT.17

Fig. 1. Proposed RNA signature screen-and-treat algorithm.
national TB incidence by 14% (95% confidence interval (CI) 11 - 18%) over 5 years. If extended to both HIV-negative and HIV-positive people, estimations suggest a reduction in TB incidence of 29% (95% CI 24 - 32%), and in TB mortality of 35% (95% CI 29 - 37%), within 5 years (R G Sumner and T White – unpublished data). In the face of the potential impact, the cost/benefit assessment of such a strategy needs to be compared with that of untargeted IPT for all latently infected South Africans, which is clearly not feasible. SA already has an established health infrastructure for large-scale HIV test-and-treat programmes, which could be augmented to enable annual community-based screening for TB, using an affordable near-point-of-care device. Finally, with nearly 100 000 South Africans dying from TB in 2015, scientific, pharmaceutical and governmental stakeholders have a collective responsibility to act promptly on new TB research findings and implement novel strategies to save lives. The current inadequate tools for screening, diagnosing, treating and preventing TB must be urgently and significantly improved if we are to end TB in our lifetime.

Adam Penn-Nicholson, Thomas J Scriba, Mark Hatherill
South African Tuberculosis Vaccine Initiative, Institute of Infectious Disease and Molecular Medicine, and Division of Immunology, Department of Pathology, Faculty of Health Sciences, University of Cape Town, South Africa
adam.penn-nicholson@uct.ac.za

Richard G White, Tom Sumner
TB Modelling Group, TB Centre, Faculty of Epidemiology and Public Health, London School of Hygiene and Tropical Medicine, UK
