The uncertain science of predicting tuberculosis

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Around a quarter of the world's population is infected with *Mycobacterium tuberculosis*.[1] Unfortunately, currently available immunodiagnostic methods are unable to discriminate the stages within the spectrum of tuberculosis infection.[2,3] Neither the tuberculin skin test (TST) nor interferon-gamma release assays (IGRAs) meet the need for a highly predictive test that can identify latently infected people who are at increased risk of developing tuberculosis disease and would therefore benefit most from preventive therapy.[4] This, as well as the high prevalence of latent tuberculosis infection, makes it daunting for high-burden countries to address latent tuberculosis in their control programmes.[5]

While the search for new predictive biomarkers and biosignatures is starting to show promise,[6] are there ways to squeeze more predictive value out of existing tests? One way to do this is to make sure that people at low risk for tuberculosis infection are not screened. While this recommendation is already a part of guidelines,[7] many low-risk people still get screened in practice. A good example is the widespread annual screening of low-risk health-care workers in north America, a practice that is already posing challenges.[8]

Another approach to enhance predictive value is to use multivariable risk prediction models that incorporate clinical and epidemiological risk factors—eg, age, history of contact, HIV infection, immunosuppressive medications—with test results.[9] Online risk calculators (eg, the Online TST/IGRA Interpreter) have made this feasible.

A third approach is to use serial (repeated) testing rather than cross-sectional testing.[9] It is well known that people with recent TST conversions are at high risk of progression. Using the same logic, individuals with IGRA conversions should be at a higher risk of developing tuberculosis disease. Although limited, there is some evidence to support this hypothesis.[10]

In *The Lancet Respiratory Medicine*, Jason R Andrews and colleagues[11] analysed longitudinal data from a cohort of 2512 Bacille Calmette-Guerin-vaccinated, Quantiferon-TB Gold In-Tube (QFT)-negative and HIV-uninfected South African infants recruited into a tuberculosis vaccine trial. They investigated the association between IGRA conversion (ie, increase in interferon-γ values determined by serial QFT testing) and the risk of subsequent development of active tuberculosis disease. The results showed that QFT converters at interferon-γ values higher than 4·00 IU/mL had a significantly higher disease incidence compared with both non-converters (incidence rate ratio [IRR] 42·5; p<0·0001), and converters at interferon-γ values between 0·35 IU/mL and 4·00 IU/mL (IRR 11·4; p<0·00047).

So, the results suggest that a big spike in interferon-γ levels is strongly associated with risk of tuberculosis. But does the spike predict future risk of tuberculosis disease, or is it a consequence of subclinical or incipient disease? While ten of 63 children with QFT conversion (threshold of interferon-γ >4·00 IU/mL) were diagnosed with tuberculosis disease (28·0 cases per 100 person-years), the median time to diagnosis among these QFT converters from the time of QFT testing was merely 44 days. Thus, one can make a case that the interferon-γ levels spiked as these children were developing active tuberculosis. Therefore, an increase in interferon-γ levels is not really predictive of future risk progression to active tuberculosis, but could be due to imminent development of subclinical or incipient tuberculosis disease.

Another recent study suggested that a 16-transcript whole-blood RNA signature might prospectively identify adolescents at risk of developing tuberculosis disease.[6]

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The predictive potential of the tuberculosis risk signature was highest in the 6-month period immediately before diagnosis, and less predictive over longer periods. Together, both biomarker studies seem to identify those with subclinical or incipient disease over the short-term, rather than truly predict future tuberculosis development. We agree with Cobelens and colleagues[12] who call these incipient tuberculosis tests compared with persistent infection tests.

This distinction is crucial because it is hard to see how preventive therapy can be given to children who might already have subclinical disease, or who are on the verge of developing active tuberculosis; preventive therapy might be inadequate or dangerous in this context. As such, instead of isoniazid preventive therapy, health-care workers could use a spike in interferon-γ levels to aggressively investigate and treat tuberculosis disease. However, the cost-effectiveness and real world applicability of serial IGRA testing or blood gene signature assays in high burden countries is doubtful. Major translational work is required to develop simple, affordable, predictive assays that can be used by tuberculosis control programmes in low-resource settings, and target product profiles for such tests have been drafted.[13]

While the science of tuberculosis prediction remains uncertain, there is no uncertainty about the high burden of tuberculosis in South Africa, even in young children. In Andrews and colleagues' study,[11] about 7% of infants had QFT conversions after a year, suggesting a very high annual risk of tuberculosis infection in this community. This suggests poor control of tuberculosis among adults, and ongoing transmission in the community. Clearly, much more needs to be done to protect children from tuberculosis in South Africa and globally.

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