From latent to patent: rethinking prediction of tuberculosis

Tuberculosis remains a major global health problem. It is estimated that more than 2 billion people around the world are latently infected with Mycobacterium tuberculosis, with a lifetime risk of progression to tuberculosis disease of 5–15%. The WHO End Tuberculosis strategy, which aims to end tuberculosis as a major health problem by 2035, calls for reducing this huge reservoir for transmission by scaling up preventive therapy of individuals with latent tuberculosis infection. Preventive therapy with daily isoniazid offers 60–90% protection and combination therapies (daily isoniazid-rifampicin, weekly isoniazid-rifapentine) are effective alternatives. However, preventive therapy is not without cost and toxic effects.

Currently available tests for latent tuberculosis infection—the tuberculin skin test and interferon gamma release assays (IGRAs)—detect an immune memory response to M tuberculosis rather than presence of viable organisms. They have low specificity for predicting disease progression, translating into low positive predictive value (PPV) for incident tuberculosis, and a high number of individuals needed to treat to prevent one case of tuberculosis disease; the tuberculin skin test has a pooled PPV for tuberculosis disease occurring in the next 2 years of only 1·5%, leading to a number needed to treat of 67. Although IGRAs are more specific than tuberculin skin test, their pooled PPV for predicting tuberculosis disease does not exceed 2·7%, which corresponds to a number needed to treat of 37. PPV of IGRAs differs across settings and populations, and is relatively low in individuals living in or immigrating from high tuberculosis incidence countries.

Tests with much greater PPV are needed to allow for targeted and feasible scale-up of preventive therapy to people most at risk for progression to tuberculosis disease, and research to identify relevant biomarkers is ongoing. Here, we present an alternative perspective on latent tuberculosis infection tests, and argue that high PPVs can only be attained for tests that detect early tuberculosis disease, with important implications for how they should be designed and used.

There is increasing recognition that the binary view of tuberculosis, with a clear division between active disease (a symptomatic and potentially infectious state with evidence of pathology resulting from ineffective control of bacillary replication) and latent tuberculosis infection (an asymptomatic state in which bacillary replication is controlled) is an oversimplification. Recent research postulates the existence of a spectrum from spontaneous clearance to quiescent infection and disease. Patient’s position on this spectrum will be defined by their capacity to control bacillary replication. The tuberculin skin test does not distinguish between these states (appendix [1A]).

Several factors are known to increase the risk of progression to tuberculosis disease, including young age, low body-mass index, diabetes, tobacco smoking, HIV infection and treatment with tumour necrosis factor-α antagonists. However, with the exception of the latter two, relative risks for such conditions are too low to be sufficient drivers of the transition towards disease. These risk factors should be considered as predisposing factors. However, it is other, still unidentified, factors which trigger failure of host control of infection, leading to reactivation or rapid progression to disease.

Therefore, a test that indicates persistent M tuberculosis infection capable of progressing to tuberculosis disease can only have a low PPV (appendix [1B]). A high PPV can nevertheless be attained if one or more precipitating events have occurred and disease progression is evolving asymptptomatically (appendix [1C]). It is becoming clear that before clinical presentation with active disease there might be a prolonged asymptomatic phase of early disease during which pathology evolves, a state known as subclinical, or incipient tuberculosis. Data from community surveys suggest that bacilli might be shed in the sputum for approximately a year before clinical presentation. Incipient tuberculosis might involve periods of healing and disease regression as evidenced by radiographic and pathological findings of inactive fibrotic scarring, and some individuals with incipient tuberculosis might not progress to active disease until 12 months or more.

Tests to predict tuberculosis disease should thus be categorised conceptually as persistent infection tests (PIT) versus incipient tuberculosis tests (ITT). This distinction is important, as test performance, use, and design requirements will be different.

PITs would probably measure persistent antigenic stimulation. As persistent infection is a necessary condition for any tuberculosis disease, PITs will have high

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sensitivity for tuberculosis disease developing in the near future. However, their PPV will be low to moderate and population-dependent. It will be lower if more infected individuals remain with persistent infection over time or have acquired their infection remotely rather than recently (appendix [1B]). Consequently, the PPV for markers of persistent infection will be lower in high-incidence populations than in low-incidence populations. This has been observed for IGRAs.\(^4\) Even though it is unclear to what extent IGRAs respond to infections that have been cleared, we suggest that IGRAs are PITs rather than ITTs. PITs have the characteristics of rule-out tests: whereas a positive result might not be very informative, a negative result provides confidence that the individual is unlikely to develop tuberculosis disease in the near future.

ITTs would probably detect mycobacterial replication or the resulting inflammatory response. Provided that analytical performance is adequate, the specificity and PPV of an ITT will be high, population-independent, and determined primarily by the probability that asymptomatic progression is halted spontaneously. However, its sensitivity will be variable and depend on whether the test is done before or after the precipitating event has taken effect (appendix [1C–D]). Therefore, both sensitivity and specificity (and thus PPV) of an ITT will improve if performed closer to the point of clinical presentation of tuberculosis. These assumptions were observed for a 16-transcript blood signature identified recently by Zak and colleagues,\(^4\) suggesting that this signature detects incipient tuberculosis rather than persistent infection. ITTs should be considered rule-in tests: a negative result provides limited information but a positive result indicates that tuberculosis disease will probably develop.

We propose that PITs, as rule-out tests, be primarily used in individuals at high risk of developing severe tuberculosis disease irrespective of when they were infected, such as those with HIV infection or starting anti-tumour necrosis factor-α treatment. Improvement over IGRAs would be PITs that turn negative when M tuberculosis infection has been cleared or treated successfully. ITTs as rule-in tests would be primarily used for screening of all who have been recently exposed to M tuberculosis, such as contacts of infectious tuberculosis patients. ITTs might need to be repeated until becoming positive, and indicate presence of actively multiplying bacilli. They should therefore be inexpensive and easy to perform, and ideally have a semi-quantitative readout reflecting the bacterial burden to allow informed decisions about preventive versus full-course treatment.

The changing paradigm of latent tuberculosis infection as a spectrum leading to disease progression implies that two complementary types of test are needed to detect persistent infection and incipient tuberculosis, with different characteristics used for different purposes. Improved PITs would be important for clinical use, and ITTs for use in public health programmes. If designed as such and available at low cost, ITTs would allow scale-up of contact tracing strategies and mass test-and-treat campaigns in high-transmission settings that could have substantial impact on tuberculosis incidences.

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