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Review

Preventive therapy for latent tuberculosis infection—the promise and the challenges

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SUMMARY

Around one third of the world's population may harbour latent tuberculosis infection (LTBI), an asymptomatic immunological state that confers a heightened risk of subsequently developing tuberculosis (TB). Effectively treating LTBI will be essential if the End TB Strategy is to be realized. This review evaluates the evidence in relation to the effectiveness of preventive antibiotic therapy to treat LTBI due to both drug-susceptible and drug-resistant bacteria. Current national and international preventive therapy guidelines are summarized, as well as ongoing randomized trials evaluating regimens to prevent drug-resistant TB. Populations that may benefit most from screening and treatment for LTBI include close contacts of patients with TB (particularly children under 5 years of age) and individuals with substantial immunological impairment. The risks and benefits of treatment must be carefully balanced for each individual. Electronic decision support tools offer one way in which clinicians can help patients to make informed decisions. Modelling studies indicate that the expanded use of preventive therapy will be essential to achieving substantial reductions in the global TB burden. However, the widespread scale-up of screening and treatment will require careful consideration of cost-effectiveness, while ensuring the drivers of ongoing disease transmission are also addressed.

1. The global significance of latent tuberculosis infection

Tuberculosis (TB) is a leading infectious cause of death and affects nearly ten million people each year.[1] In addition, around one third of the world population – over two billion people – may harbour latent tuberculosis infection (LTBI), as indicated by an immunological reaction to *Mycobacterium tuberculosis*.[2] Asymptomatic individuals with *M. tuberculosis* infection may develop active disease at any time during their lives, representing a substantial hidden reservoir for future disease – independent of global TB control activities focused on limiting transmission.[3]

The antibiotic treatment of high-risk individuals with LTBI to prevent active disease has been a core strategy of TB control programmes in high-income countries for half a century.[4] In these settings, the delivery of preventive therapy has contributed to very low rates of disease, accompanied by early detection and effective treatment of infectious TB cases.[5] Although the treatment of active TB remains a top priority in endemic settings, this approach alone will not be sufficient to achieve the steep annual reductions in incidence necessary to reach the End TB Strategy targets or TB elimination by 2050 (defined as less than one case per million population).[6] This strategy builds upon the Sustainable Development Goals, and forms the centrepiece of the World Health Organization (WHO) approach to global TB control. Addressing the substantial reservoir of latent infection will ultimately be required.[7] This review explores the rationale for TB preventive therapy and describes the evidence for antibiotic regimens to prevent drug-susceptible and drug-resistant TB. New opportunities for scaling up LTBI therapy as a potential turning point in the battle against TB are highlighted.

2. The natural history of tuberculosis infection

M. tuberculosis infection was previously considered to lead to one of two binary states (infection versus clinical disease). However, advanced imaging now suggests that TB infection

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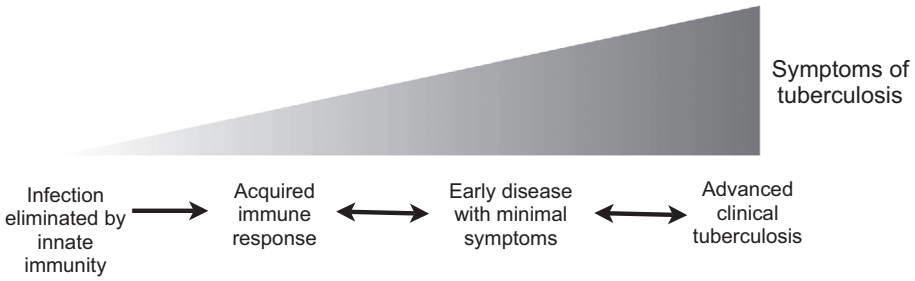

Figure 1. The spectrum from latent tuberculosis infection to disease.

outcomes represent a spectrum of immunological responses to the infecting mycobacteria.[8] At one end of the spectrum, an individual may completely clear all viable bacteria. At the other end, bacterial replication may result in fulminant active TB (sepsis) (Figure 1). Animal studies have shown that tuberculous lesions may develop, then disappear, without necessarily causing symptoms or progressing to disease.[9] This suggests that disease may arise when the host immune system is no longer able to contain the pathogenic bacteria. In immunocompetent individuals, only a small minority of those with LTBI will develop symptomatic disease. Cohort studies from low-transmission settings indicate that between 5% and 15% of recently infected individuals will suffer from TB during their lifetimes, with the highest risk being among those with recent primary infection (during the past 2 years), demonstrated by tuberculin skin test (TST) conversion.[3,10] Individuals with marked immunological impairment have a particularly high risk of both early disease progression and disease reactivation at a later stage. Such individuals include people living with HIV, patients with poorly controlled diabetes, and those taking immunosuppressive therapies.[11] Recognized risk factors associated with disease progression are shown in Table 1.

Table 1
Predisposing factors associated with progression to active tuberculosis among individuals with latent tuberculosis infection

Risk factor	Risk of developing TB disease compared to those without the risk factor	References
Based on TB exposure		
Close contact with an infectious TB case	16–46	11
Recent migration from a high-prevalence setting	15	3
Chest X-ray with fibronodular abnormalities	6–19	64–66
Based on comorbidities		
High risk		
HIV infection	80–110	67,68
Age <2–3 years[a]	>10	69,70
TNF-α inhibitors	10	71,72
Chronic kidney disease, on dialysis	8	73
Organ transplantation	70–300	74–76
Stem cell transplant	20	76
Intermediate risk		
Age 3–4 years[a]	>3	69,70
Silicosis	1.4–2.5	77,78
Glucocorticoid therapy (oral)	3–8	38,79
Severe underweight	3	80
Poorly controlled diabetes mellitus	1.5–5	81–84
Cigarette smoking[b]	2[c]	85,86
Low risk		
Glucocorticoid therapy (inhaled)	2.5	87
Diabetes[d]	2	88
Very low risk		
Normal healthy individual with positive TST and no recent TB exposure	1	N/A

TB, tuberculosis; TNF-α, tumour necrosis factor alpha; TST, tuberculin skin test; N/A, not applicable (reference category).
[a] The risk of TB is particularly increased in children <3 years of age.[69]
[b] Data are from settings where community transmission is substantial.
[c] The risk of death due to TB among smokers was 3.0 in a case–control study in India.[89]
[d] Poorly controlled diabetes is associated with a higher risk of disease.[88]

3. Testing for LTBI

The diagnosis of LTBI may only be made once active TB has been excluded. For adults, this typically involves symptom screening and chest radiography, followed by bacteriological testing (such as sputum smear, culture, or nucleic acid amplification testing). For children at risk of infection, symptom-based screening alone is generally sufficient to rule out active disease, given the practicality and sensitivity of this approach, as well as the poor specificity and unavailability of chest radiography in many settings.[12]

The two available methods of diagnosing LTBI measure immune sensitization to *M. tuberculosis* proteins. The TST (or 'Mantoux test') is an in vivo method of measuring delayed type hypersensitivity to purified protein derivative (PPD) that is injected subcutaneously. This test has been used to diagnose LTBI for more than a century, but is difficult to standardize and is highly operator-dependent. A false-negative test result may occur with inadequate PPD storage, poor administration technique, overwhelming TB disease (e.g., miliary disease in young children), and other causes of immunosuppression such as severe malnutrition, HIV, or following measles infection in children. False-positive results may occur due to bacille Calmette–Guérin (BCG) vaccination, which is most problematic in the first 2 years following vaccination at birth,[13] or following exposure (and especially disease) caused by environmental (non-tuberculous) mycobacteria.[14]

Interferon-gamma release assays (IGRAs) (including the commercially available Quantiferon Gold In-Tube Assay (Cellestis) and T-SPOT.TB (Oxford)) are in vitro diagnostic tests that present TB antigen to whole blood, quantifying interferon-gamma production by sensitized T-cells.[15] The interpretation of IGRAs is based on a calculation that includes subtracting the reading of the negative control tube from that of the TB antigen tube. Test results should always be interpreted in the context of clinical and epidemiological history of potential infection. IGRAs offer increased specificity compared to the TST, as they include antigens rarely found in environmental mycobacteria. However, this method is more costly and technically challenging to implement, particularly in resource-limited settings.

A skin test employing the same antigenic targets as Quantiferon (Culture Filtrate Protein 10 (CFP-10) and Early Secretory Antigenic Target 6 (ESAT-6)) is under development. Early studies suggest sensitivity and specificity similar to the in vitro Quantiferon assay,[16] but without the requirement for expensive laboratory infrastructure. However, it has no internal quality controls and will suffer from the same operator dependency as the TST.