

## Screening for Latent Tuberculosis: Between Too Little and Too Much

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### Abstract

Elimination of tuberculosis from low-incidence countries is slow and not to be reached within a near future with the current strategies and diagnostic and therapeutic tools available. Screening for latent tuberculosis infection (LTBI) and offering a preventive treatment to the persons who have the highest risk of developing tuberculosis in the future, if infected, is now considered as one of the components of the global management of TB, included in the new End TB strategy of the World Health Organization, and could contribute to the acceleration of the decline of TB. Current tests for the detection of LTBI are indirect and have a low positive predictive value but a high negative predictive value. The new Interferon Gamma Release Assays (IGRA) offers several advantages over the tuberculin skin tests and are therefore preferred in settings where they are available and affordable. There is a risk of overuse of the tests, particularly in groups with a very low risk of infection (for instance health-care workers in low-incidence countries) and for the diagnosis of TB, where other tests still have the priority, but they can be of great help to the clinicians in unclear situations, particularly in children and in cases of extrapulmonary TB.

**Keywords:** *Tuberculosis; Latent Tuberculosis Infection; Screening; Interferon Gamma Release Assays*

Latent tuberculosis infection is characterized by an immune reaction in a person who has been contaminated by a patient with a transmissible form of tuberculosis (TB) but who has not (yet) developed the disease. In some persons, the mycobacteria are still alive within granulomas in lymph nodes, under the control of defense mechanisms but may start to develop again at a later time, usually within one to two years after the contamination. In others, the mycobacteria have probably disappeared but the memory of the immune reaction following the first meeting between them and the cell-mediated immune system persists. Therefore, the latent tuberculosis infection is also defined as a Lasting immune response to M.tb [1].

There is currently no way to detect the persistence of living mycobacteria in the organism, as long as they stay quiescent, but there are some indications that they may demonstrate signs of metabolic activity long before the emergence of clinical disease [2]. The detection of latent infection relies on indirect procedures aiming at detecting the release of cytokines (usually Interferon Gamma) from sensitized lymphocytes following the contact with mycobacterial antigens, by an in-vivo test (the time-honoured tuberculin skin test [TST]) or by an in-vitro procedure (one of the Interferon Gamma Release Assays or IGRA: T-SPOT.TB (Oxfordimmunotec, Abingdon, UK) or Quantiferon (Qiagen, Hilden, Germany). All three tests detect an immunologic reaction but cannot distinguish between latent and active TB, and are therefore not diagnostic tests for the active disease.

Until recently, the screening for latent infection was not considered as part of the global strategy for the control of TB. Investigations among the contacts of a case of contagious TB was mainly aimed at detecting secondary cases (i.e. cases already presenting signs of active disease, probably related to the initial or index case). Protection of small children and immunodepressed persons exposed to TB was also considered as useful, but screening asymptomatic contacts without risk factors was not considered as a priority [3]. This has changed in the recent years, under the recognition that the current strategy will not be sufficient to obtain the elimination of TB in a foreseeable future, even in low-incidence countries [4]. Screening all persons who have been exposed to contagion (contacts of a case of active TB)

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and persons with a high risk of progression to TB if infected (small children, immunodepressed patients) and, if resources permit, further risk groups like health-care workers exposed to TB, is now considered as part of the global End TB strategy defined by the World Health Organization [5]. New Guidelines on the screening and management of latent TB infection have also been issued [6]. The choice of the test procedure (TST or IGRAs) is left open, due to differences in local availability and considerations of costs. Cases with recent exposure and patients with immune depression should receive a preventive treatment to decrease the risk of future TB, after careful exclusion of an incipient active disease [7-10].

The main indications of the screening for latent TB are [11]:

- a) The detection of latent infection among persons who have been exposed to TB
- b) The detection of latent infection among persons who have a high risk of development of TB, if infected, whatever the history of previous exposure (patients with natural, viral or drug-induced immunodepression)
- c) In some settings, screening migrants from high-incidence countries for latent TB
- d) In some cases, as an aid to diagnosis of TB in patients with high suspicion of disease but in whom the bacteriological documentation is difficult or impossible (small children, extrapulmonary TB).

In contact investigations, the aim is to detect the contacts who have been infected and have a risk of developing TB in the future. Only a minority of those infected will do so, even without preventive treatment (between 5 and 10% on average), but the risk is nevertheless much higher than for the general population, being for instance of 678/100'000 on average in a study performed in British Columbia [12], but may be much higher for small children, recent contacts with a positive TST and infected contacts who do not receive a preventive treatment [13]. One of the key issues is therefore to identify those persons at highest risk of TB but to limit the number of contacts who are supposed to receive a preventive treatment. The predictive value for TB of all three tests available is not very satisfactory, being estimated at 2.58% for the TST and 4.94 for the IGRAs [6]. The predictive value seems to be higher for infected persons with an increased risk due to immunodepression, particularly in persons with HIV co-infection who do not receive an antiretroviral treatment [14,15]. The number of persons with a positive test result who need to receive a preventive treatment in order to prevent one future case of TB may be as high as 250 if the tuberculin skin test is used for defining latent infection [16] but may be reduced to 30 to 37 if the infection is defined by an IGRAs [17-20], due to the better specificity of IGRAs compared with the TST (no false positives due to prior BCG vaccination or contact with non-tuberculous mycobacteria). In practice, immunocompetent contacts with a negative IGRAs test result had a much lower risk of TB than those with a positive test result, even if they have a positive TST [18].

Screening migrants from high-incidence countries for latent TB and offering a preventive treatment to those with the highest risk of developing TB is now implemented in many countries experiencing a high influx of migrants [21]. This is justified by the fact that the majority of TB cases reported in migrants will be detected after entry, usually by reactivation from latent infection [22]. As the majority of migrants are young adults or children, a policy of screening and preventive treatment for those with the highest risk of infection (estimated according to the origin and incidence rate in the country of origin) is considered as a cost-effective contribution to the control of TB in low-prevalence countries, in addition to the screening for active disease, usually performed at entry [21,23].

Screening health-care workers (HCW) for latent TB has long been considered as necessary, under the assumption that HCW are more exposed to TB than the local population and may be at high risk of infection and TB. This may still be the case in regions with a high prevalence of TB [24]. In low-incidence countries, this does not seem to be the case any more and the risk of infection and TB among HCW is hardly different from the general population [25]. Therefore, systematic screening of all HCW is no more considered as cost-effective, but individual screening is justified if there was a documented exposure to a case of TB.

The use of IGRAs for the detection of latent TB in children has long been regarded as problematic, as the first studies demonstrated a high proportion of indeterminate results, particularly among infants [26]. On the other side, it was obvious that the higher specificity of IGRAs compared with TST, particularly among children vaccinated with BCG, helped to distinguish between reactivity due to vaccina-

tion or contact with non-tuberculous mycobacteria and true TB infection [27]. Recent studies have also demonstrated that the accuracy of IGRAs in young children is satisfactory [28,29] and that there is some correlation between the magnitude of the test response and the risk of TB [30].

Finally, the use of IGRAs as an aid for the diagnosis of TB is controversial, as the IGRA (like the TST) only indicate the presence of an immune reaction but not of living mycobacteria. IGRAs are therefore not recommended as a diagnostic test for active disease. In practice however, they can contribute to the clinical decision in cases where the detection of mycobacteria is difficult or impossible, for instance in small children or in some cases of extrapulmonary TB, but the possibility of a false negative test reaction in active disease, particularly in advanced cases or in immunocompromized hosts, must be kept in mind. A negative test result in a case with high clinical suspicion of TB may also be a clue to the presence of a non-tuberculous mycobacteria as a possible cause of disease [31].

One of the obstacles to the use of IGRA is the high costs of the test compared with the TST, and the need for a laboratory infrastructure. On the other side, considering the potential savings in unnecessary examination and treatment of persons with a false positive TST, re-testing all contacts with a positive TST or testing them directly with an IGRA may have a net saving effect [32]. The same may apply to health-care workers exposed to TB [33].

Latent TB is no more considered as a stable condition [34]. The mycobacterial population may fluctuate, with periods of temporary growth followed by regression. The progression between latent infection and active disease is slow, and there is a period of subclinical growth before the disease is symptomatic and detectable by radiology and bacteriological examination [35]. IGRAs are not the ideal tool for the detection of persons with a risk of progression to TB, but they represent a progress compared with the TST. They have been both underused (in children) and overused (for the diagnosis of active TB) but they may contribute to the reduction of the pool of future cases.

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