REVIEW

Close contact investigation of TB in high-burden, low- and middle-income countries

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Abstract

Tuberculosis (TB) remains a very common disease in most of the low- and middle-income countries. As a result of high disease burden, TB control measures in these countries are usually concentrated on intensifying active disease case-finding and early treatment of infectious TB. On the contrary, in countries with low disease burden, the focus is on contact investigation to identify latently infected individuals and prophylactically treating them to prevent disease reactivation and transmission. These two strategies are deemed important for the effective TB control. Nonetheless, WHO cautions that targeted contact investigation and latent TB infection (LTBI) treatment should only be undertaken by countries that have the operational capacity/ resources and have achieved ≥ 85% treatment success rate of active TB. The screening of LTBI is further challenged by the lack of a "gold standard" test to identify and validate individuals with this condition. Tuberculin skin test (TST) is still the preferred investigation as it is cheap, widely available and validated in many trials. The sensitivity and specificity of the newer test—interferon gamma release assay (IGRA) for LTBI screening has been encouraging in low prevalence countries. However, the evidence supporting such usage remains uncertain in high burden settings. Diagnosis of LTBI should adhere to the strict criteria outlined in the guidelines to avoid misdiagnosing active TB as LTBI. The treatment of the latter involved only one or two anti-TB drugs. It has been demonstrated that in the properly conducted contact screening and LTBI treatment, chances of the emergence of multi-drug-resistant TB is very low.

Introduction

Tuberculosis (TB) remains one of the commonest infections in the world. In 2012, it was estimated that 8.6 million people developed active TB and 1.3 million died of the disease[1]. Despite the presence of effective anti-TB treatment over the past 60 years, this "white plague" is still ravaging many parts of the world—Malaysia is certainly not exempted from this menace. In 2011, there were a total of 19,251 TB cases notified.[2]

Historically, the perseverance of TB was linked to overcrowding, poor sanitation and poverty. However, improved socioeconomic status did not necessarily guarantee better disease control. This is in part due to difficulties faced in early detection of active TB. Contrary to the common belief, the early manifestation of TB is generally quite subtle and hence do not normally alert the affected individuals to seek medical advice—this gap often allows bacilli to spread and infect many contacts before they are contained. Besides, *Mycobacterium tuberculosis* possesses a unique ability to remain in a state of dormancy in human body for years and can be reactivated when the immune system of the host turns weak.

In countries with low burdens of TB, most active cases have occurred among persons who were once infected, contained and then later develop the active disease. The identification and treatment of these individuals have been shown to be effective for the prevention of TB reactivation and transmission.[3,4] In United States, this strategy has been estimated to have prevented 44% of active TB cases from 1993 to 2004.[5]

In low- and middle-income countries, where the burdens of TB are often high, the strategy is mainly concentrated on intensifying active case finding. Nonetheless, WHO currently recommends contact investigation (especially for household and close contacts) to be performed for at least 3 high-risk populations in these settings: children aged < 5 years, people living with/or have high-risk of HIV infection and contacts of index cases with multidrug-resistant-TB (MDR-TB) or extensively drug-resistant-TB (XDR-TB).[6–7]

Contact investigation

Contact investigation involves the systematic evaluation of the contacts of known TB patients to identify active disease or LTBI. In a recent systematic review and meta-analysis of

contact investigation for TB, where 95 studies had come from the low- and middle-income settings, the prevalence of active TB among all contacts was 3.1% (95% CI 2.2–4.4%, I^2 = 99.4%), and LTBI was 51.5% (95% CI 47.1–55.8%, I^2 = 98.9%)[8]. Early identification of active TB among these contacts means a better chance of cure and a reduction in further transmission. Besides, contact investigation also allows identification of people who are latently infected and at high risk for active TB.

What is LTBI?

When the TB bacilli are in dormant state, individuals who harbour these organisms are said to be having latent infection. Hence, LTBI can be defined as infection with Mycobacterium tuberculosis complex, where the bacteria may be alive but in the state of dormancy and not currently causing any active disease/symptoms.

Criteria for LTBI Diagnosis

The following are the diagnostic criteria recommended for LTBI diagnosis. Items 1–3 are essential criteria, whereas the 4th criterion may be considered if the patient's CXR shows any abnormal findings.

No.	Criteria	Findings
1	Clinical manifestation	No symptom/sign to suggest active disease
2	Tuberculin skin test (TST)/ Interferon gamma release assays (IGRA)	Positive TST or IGRA
3	Chest imaging	Normal CXR *(If it is abnormal, another CXR performed ≥ 6 months before or after this should not show any interval change)*[9]
4	Sputum/bronchoalveolar lavage	Negative AFB direct smear/Mycobacterium culture on induced sputum or bronchoalveolar lavage *(if indicated)*

It is noteworthy that this is not a subtle form of active TB. The patients must not have any symptoms which may otherwise suggest active disease. Their chest radiographs are typically normal—although occasionally some abnormalities may be found. In the latter case, these patients should be further assessed. Healed lesions are often characterised by nodules and fibrotic lesions that are well-demarcated. The calcified nodular lesions as well as apical/basal pleural thickening pose a low risk for future progression to active TB.[10] In any case, if doubts still exist, a sputum induction or bronchoalveolar lavage may be considered.

Challenges in making a diagnosis of LTBI

The diagnosis of LTBI has always been limited by the lack of a "gold standard" test. The tuberculin skin test (TST) has been used for more than a century to diagnose this condition. The TST is based on the principle of delayed-type hypersensitivity reaction towards the intradermal inoculation of tuberculin (also known as purified protein derivative). In subjects who have been infected, their sensitised memory T-cells will react towards the tuberculin to produce a local inflammatory response, manifesting as an indurated and erythematous skin lesion. Measurements of skin induration at the inoculation sites after 48–72 h are used to gauge the likelihood of LTBI/active TB in the suspected patients.[11] In general, a skin induration of ≥ 5 mm is considered as significant. However, various cut-off points (≥ 5 mm, ≥ 10 mm and ≥ 15 mm) have been recommended to predict the likelihood of latent infection in patients with different immune status and exposure risks using a mathematical calculation called "positive predictive value". For immunocompromised patients, lower cut-off points are used to predict positive results. Similarly, for patients with recent close contact or individuals living in high prevalence areas, lower cut-off points are likely to indicate positive tests. On the other hand, a higher cut-off point needs to be used in low prevalence areas to reduce the likelihood of false-positive result. Despite this mathematical adjustment, the sensitivity of TST is still considerably lower in immunocompromised subjects.[12,13]

The other limitation of TST is that the tuberculin contains more than 200 proteins

which are widely shared among mycobacteria other than *M. tuberculosis,* including *M. bovis* and many non-tuberculous mycobacteria (NTM). As a result of this cross-reactivity, it has a lower specificity in population extensively vaccinated with BCG and in tropics where NTM infection is more commonly occurred.

In order to circumvent some of these limitations, a novel technique called interferon-gamma release assay (IGRA) has been developed in recent years. Two IGRAs have so far been approved and commercially available—the T-SPOT.TB test and the QuantiFERON-GIT (Gold In-Tube) test. In the IGRAs, only two or three specific antigens are used. They include the ESAT-6 (early secretory antigenic target-6), CFP-10 (culture-filtrate protein-10) and TB 7.7 peptides (the latter only included in QuantiFERON-GIT test). These antigens are expressed in M. tuberculosis complex *(M. tuberculosis, M. bovis and M. africanum)*, but are absent in all strains of M. bovis BCG and the majority of NTM.[1418,15,16,17]

The IGRA is an ex vivo test in which blood from a suspected individual is collected and tested outside the body. When it is incubated with the specific antigens, the T-cells of the infected/sensitised individuals will be stimulated to secrete interferon-y. In the QuantiFERON-GIT test, the quantity of this chemokine in the test tube supernatant is measured by means of the enzyme-linked immunosorbent assay (ELISA). For the T-SPOT.TB test, mononuclear cells that harbour interferon-y are enumerated by the enzyme-linked immunospot test (ELISPOT).

Comparison between IGRA and TST

Sensitivity and Specificity

The sensitivity and specificity of the IGRAs and TST varied significantly across different studies. In two different recent meta-analysis and systematic review of IGRAs for the diagnosis of LTBI by Menzies et al. and Pai et al., it was found that the pooled sensitivity of QuantiFERON-TB tests were 70% (95% CI, 63–78%) for QuantiFERON-TB GIT test and 78% (CI, 73–82%) for QuantiFERON-TB Gold test. The pooled sensitivity of another IGRA, the T-SPOT.TB was at 90% (CI, 86–93%). When compared to TST with a pooled sensitivity of 0.77 (CI, 0.71–0.82), it was concluded that the IGRAs were as good as the TST in identifying active TB, although the sensitivities were not consistent across tests and populations. It was also indicated that the T-SPOT.TB might be more sensitive than the QuantiFERON tests and the TST.

In addition, both IGRAs were highly specific—the pooled specificities for both QuantiFERON tests were 99% among the non-BCG-vaccinated participants (CI, 98–100%) and 96% (CI, 94–98%) among the BCG-vaccinated participants. The pooled specificity of T-SPOT.TB (including its precommercial ELISpot version) was 93% (CI, 86–100%).

The specificity of TST in non-BCG-vaccinated participants was consistently high (97% [CI, 95–99%]). However, the pooled specificity of TST in the BCG-vaccinated populations was low at 59% (CI, 46–73%) and highly heterogeneous.[18,19]

Advantages of IGRAs compared to TST

When compared with the conventional TST, the IGRAs have the following added advantages:

- Only a single visit is required for the IGRAs.
- Repeat TSTs often result in enhanced reaction towards the tuberculin (the "booster effect"). This may complicate the interpretation of subsequent test results. As IGRAs are performed ex vivo, repeat testing does not lead to booster effect.
- Due to the utilisation of more specific antigens, there are less false-positive cases diagnosed with IGRAs, particularly in countries where BCG vaccination is practiced. Lower false-positive cases translate into a reduction of unnecessary treatment and cost saving. It is also noteworthy that LTBI treatment is not entirely risk free.[20]

Limitations of IGRAs

- Limited data are available for IGRAs in children younger than 5 years of age (particularly those <2 years of age), immunocompromised persons, and on serial testing.[21-25]
- Recently, an expert group commissioned by WHO concluded that the evidence of IGRAs in LTBI screening for healthcare workers, contacts and outbreak investigations in the low- and middle-income countries was very low. This was due to the fact that the study designs in these settings were highly heterogeneous.[25] As a result, no firm recommendation could be made.
- The cost of IGRAs could be prohibitive.
- Like TST, the sensitivity of IGRAs is also affected by the immune status of the subjects.[24,26]

Which diagnostic test should be used—TST or IGRA?

While TST may be imperfect, it remains the most practical, cheap and widely available test to identify individuals with LTBI in low- and middle-income countries. Besides, for children younger than 5 years of age, it should be the preferred tool for screening. The measurements recommended for positive TST in various risk groups are well-established and the treatment effects have been proven in various studies. IGRA may be reserved for situations where repeat testing is required, e.g. healthcare worker screening or conditions where the result of TST is less certain, e.g. TST in the range of 5–9 mm.

Algorithm of investigation in close contact screening

In the context of close contact investigation, the contacts should be interviewed to elicit any symptoms suggestive of active TB, e.g. cough, anorexia, weight loss, night sweats and/or fever which have lasted for more than 2 weeks. If these symptoms are present, they should be investigated as per usual active TB investigations, e.g. sputum acid-fast bacillus (AFB) direct smear, sputum mycobacterial culture and chest radiograph. On the other hand, if they have no symptom to suggest active TB, they could be assumed to have either LTBI or no infection:

a. A TST/IGRA would be a reasonable preliminary test (instead of a CXR).

b. For those who tested positive are considered to have LTBI.

c. For those who tested negative are considered to have no LTBI. However, caution should be exercised for contacts who are immunocompromised as false-negative result may be produced. For the latter, empirical LTBI treatment may be considered despite a negative test.

d. Before latent TB treatment being initiated, a chest radiograph should be performed to rule out active TB.

e. If there is any suspicion of active pulmonary TB, an induced sputum or bronchoalveolar lavage should be sent for AFB direct smear and mycobacterial culture.

Who should be screened for latent TB?

Based on the Malaysian guidelines and other guidelines from low prevalence countries, the following categories of individuals should be considered for screening:

- Contacts who have been recently exposed to an index case of infectious TB.
- Residents and employees of high-risk congregate settings (such as correctional facilities, prisons, nursing homes, homeless shelters, hospitals and other healthcare facilities).
- Immigrants from high endemic countries, particularly the recent immigrants (<2 years).
- Individuals who are at high risk of developing TB reactivation or acquiring active TB, for example, HIV-infected individuals, chronic dialysis patients, transplant recipients, patients who are going to receive immunosuppressive therapy and people who inject drugs.

The advantage of targeted screening is that these individuals are at high risk of acquiring TB as well as developing reactivation. Besides, the rate of false-positive results in this target groups is considerably reduced.[10] In the healthcare environment and other high-risk congregate settings, where continuous and repeated exposure are likely, one must carefully weigh the benefit of treatment against the risk of reinfection. Treatment should only be considered if the long-term infection control can be ensured. For close contacts younger than 5 years, the risk of progression to active disease is high after primary infection—10% to 20% went on to develop TB disease. Hence, this group of patients should be routinely screened and treated.[27,28]

Should contact investigation be performed in high prevalence countries?

Treatment of LTBI has the potential benefit of breaking the chain of transmission before the infection becomes active. In addition, this strategy is particularly valuable in places with high prevalence of HIV/MDR-TB/XDR-TB, where treatment of active disease has a lower success rate.7 Nonetheless, WHO recommends that contact investigation should be determined on the basis of local epidemiology of TB, operational capacity and resources. In general, contact investigation should be assigned a lower priority in countries or areas where treatment success is <85%.

How should LTBI be treated?

LTBI could be treated with one of the following regimens.[2]

Table 1: Recommended regimens for LTBI treatment

Drugs	Duration (months)	Interval	Completion criteria
Isoniazid	6–9	Daily	180 doses in 9 months (6-month regimen) 270 doses in 12 months (9-month regimen)
Isoniazid + rifampicin	3–4	Daily	120 doses within 6 months
Rifampicin	4	Daily	120 doses within 6 months
Isoniazid and rifapentine*	3	Once weekly	12 doses in 3 months

*this regimen is unsuitable for certain subgroups (see remark below)

*Remark: This regimen is not recommended for:
- Children younger than 2 years
- People with HIV/AIDS who are taking antiretroviral treatment
- People presumed to be infected with isoniazid- or rifampicin-resistant *Mycobacterium tuberculosis*
- Pregnant women or women expecting to become pregnant within the 12-week regimen

Note: This recommendation is adapted from "Centers for Disease Control and Prevention. Treatment Options for Latent Tuberculosis Infection". Available at http://www.cdc.gov/tb/publications/factsheets/treatment/LTBItreatmentoptions.htm.

Isoniazid is the preferred choice as it has a long-established efficacy track record to prevent TB reactivation. This regimen is also the preferred option for HIV-infected people taking antiretroviral treatment and children aged 2–11 years. The recommended duration of LTBI treatment for HIV-seropositive patients is similar to those with HIV-seronegative patients. This decision is supported by a meta-analysis which showed no difference in the development of active TB between the 6- and 12-month therapy (RR = 0.6, 95% CI 0.3–1.1).[29]

For immunocompromised patients, the skin induration size may be less important in determining LTBI treatment. Instead, the history of TB exposure (duration and proximity of contact with the index case) often dictates the need for treatment. For instance, in a Cochrane review in HIV infected persons, the isoniazid preventive therapy (IPT) reduces the risk of developing confirmed, probable or possible TB by 33% regardless of their TST status (RR = 0.7, 95% CI 0.5–0.9). However, for those who were TST positive, this reduction improved to 64% (RR = 0.36, (95% CI 0.22–0.61)).[4]

Regimen with "rifampicin and pyrazinamide for 2 months" is no longer recommended due to concerns on severe liver injury and deaths.[30]

Isoniazid and rifapentine[31] are the latest addition to the LTBI treatment regimens. The 12-dose regimen does not replace other recommended LTBI treatment regimens; it is another effective regimen option for otherwise healthy patients aged ≥12 years who have increased risk of developing TB.

How effective is LTBI treatment in preventing TB reactivation?

Most randomised controlled clinical trials of isoniazid for the treatment of LTBI were conducted in the 1950s and 1960s.[32] Many of them compared the 12-month isoniazid treatment to the placebo arm. In one trial, conducted by the International Union Against Tuberculosis (IUAT), various durations (3-, 6- and 12-month) of isoniazid therapy were

studied to evaluate their effectiveness in preventing TB reactivation among persons with fibrotic pulmonary lesions consistent with inactive TB. It was found that TB reactivations were prevented in 69% and 93% of treatment compliant participants who had taken 6 and 12 months of therapy.[33] An analysis performed by Comstock shows that protection conferred by a 9-month isoniazid therapy is greater than that of a 6-month therapy. However, it is unlikely that further protection is conferred by extending the duration of treatment from 9 to 12 months.[34]

Why treatment of LTBI in high prevalence countries may not be as effective as that in the low prevalence countries?

BCG vaccinations are generally implemented in high prevalence countries. This may result in higher false-positive cases. Treatment of LTBI is most effective if it is given to individuals with recent contacts. In a study of British schoolchildren, 2550 unvaccinated participants had TST converted during the study. Of these, 121 (4.7%) developed clinical TB within 15 years of entry into the study but most of them (82%) developed active disease within 2 years of conversion.[35]

In high prevalence countries, some of the positive cases identified in close contact screening may be due to remote infection rather than recent infection. As a result, the treatment effect (prevention of TB reactivation) will be diluted. Reinfection may occur in the same individuals who have completed LTBI treatment upon re-exposure to an infectious individual. This risk is obviously greater in high prevalence countries.

Is there any risk of inducing drug-resistant *Mycobacterium tuberculosis*?

Emergence of drug-resistant Mycobacterium tuberculosis during treatment is a function of the TB bacillus population size. In patients with genuine LTBI, the number of actively multiplying bacteria is so small that this risk is virtually non-existent. However, concerns still exist if some active TB cases are being treated accidentally as LTBI. Thus, all patients with LTBI should be thoroughly investigated before treatment initiation. The minimal standard of screening, as outlined above, should be observed.

Future direction

It has been shown that improved socioeconomic status does not automatically translate into significant reduction in TB incidence. Hence, policy-makers and healthcare providers in the low- and middle-income countries will now have to find a more innovative way to improve TB control. No doubt, traditional strategies such as intensifying case detection, early treatment of infectious TB, improving treatment adherence and completion rate should still remain the core approaches to battle this menace. However, it is perhaps time for us to take stock from strategy adopted by the advanced countries in teasing out the hidden pool of TB.

Although it is desirable to have large-scale prospective randomised longitudinal studies to compare the efficacy of LTBI treatment versus standard care in high burdens, low- or middle-income countries, this is a feat that is difficult to come by due to the requirement of enormous funding and manpower. Perhaps, a smaller scale, proof-of-concept cluster randomised control study may be more attainable[7]. If this proved efficacious, a mathematical modelling to estimate the cost-effectiveness of such approach could be undertaken before the incorporation of LTBI screening and treatment in the national TB programme of these settings.

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