PROGRAMMATIC MANAGEMENT OF LATENT TUBERCULOSIS INFECTION

EXECUTIVE SUMMARY
(Adapted from the report by ERNI ZURINA ROMLI)

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2020

Background

In accordance with WHO's recommendations, ending tuberculosis requires maintaining and strengthening current tuberculosis control priorities while increasing efforts to identify and treat latent tuberculosis infection among high-risk populations. Malaysia is a middle-income country with intermediate tuberculosis prevalence. To date, there is no prevalence data for latent tuberculosis infection in the general Malaysian population. There is no national system that collects data for LTBI. There also has not yet been a routine screening programme for LTBI among at risk populations in Malaysia. World Health Organization recommends that individual countries determine their own LTBI diagnostic criteria and tests based on local tuberculosis burden and country capacity. A national policy for LTBI management is currently under development and a tailored programmatic management that best suited our local tuberculosis epidemiology could be the key element to strengthen the effort for local tuberculosis control. This technology review was requested by Disease Control Division (TB/Leprosy Sector), Ministry of Health Malaysia to assess the evidence on programmatic management of LTBI in order to identify the optimal approach of its implementation into the national tuberculosis programme given the heterogenous spectrum of national determinants that will influence the decision making process.

Technical Features

Programmatic management of LTBI is defined as management of latent tuberculosis with input from different components responsible for tuberculosis prevention and control involving specific risk groups based on the underlying epidemiology and burden of tuberculosis and the availability of resources. These components include detection of individuals with LTBI, treatment, surveillance as well as monitoring and evaluation of the programme's performance.

Objective:

The objective of this technology review was to evaluate the effectiveness, safety, cost-effectiveness, organisational, ethical and social implications of the programmatic management of LTBI.

Methods

Electronic databases were searched through the Ovid interface: Ovid MEDLINE® In-process and other Non-indexed citations and Ovid MEDLINE® 1946 to December 15, 2019, EBM Reviews - Cochrane Central Register of Controlled Trials – November 2019, EBM Reviews - Cochrane Database of Systematic Reviews – 2005 to December 2019, EBM Reviews - Health Technology Assessment – 4th Quarter 2016, EBM Reviews – NHS Economic Evaluation Database 1st Quarter 2016. Searches were also run in PubMed. Google was used to search for additional web-based materials and information. Grey literature and published guidelines and reports at the US Centres for Disease Control and Prevention (CDC), ECDC, WHO, and the International Union Against Tuberculosis and Lung Disease (IUATLD) were also searched. Additional articles were identified from reviewing the references of retrieved articles. The searches were undertaken on 11 July 2019 and were updated on 17 December 2019 using the same strategies. Last search was conducted on 17 December 2019.

Results and conclusion:
A total of 3751 records were identified through the Ovid interface and PubMed. Additional 13 articles were identified from references of retrieved articles. After removal of irrelevant and duplicate articles, 835 tittles were screened. After reading, appraising and applying the inclusion and exclusion criteria, 33 full text articles were included for qualitative synthesis, which one HTA, 25 systematic reviews (including four systematic reviews of economic evaluation studies), two economic evaluation studies, one cohort and four cross-sectional studies.

Efficacy/Effectiveness
Diagnostic tests for programmatic management of LTBI
There was good level of retrievable evidence to suggest that both TST and IGRA poorly predict the development of active TB (low PPV). Limited evidence had shown that neither test was preferred above the other when assessing progression to TB disease. Among non-BCG vaccinated population, both had similar sensitivity and high specificity to detect LTBI. However, TST displayed lower specificity compared to IGRA in BCG-vaccinated population.

1.Children
The predictive performance of TST 5mm and IGRA for progression to active TB were similar. Interferon gamma release assays performed better than TST 10mm in predicting the development of active TB. In detection of LTBI, IGRA appeared to outperform TST in low TB burden settings but not high TB burden settings, Interferon gamma release assays had reduced sensitivity and specificity in high TB burden settings. This type of effect modification could be explained by higher frequency of exposure to M. tuberculosis, different transmission dynamics, malnutrition, comorbidity, coinfection with HIV or helminthic infection.

2.Immunocompromised people
There was large variation in the performance of IGRAs compared with TST across different clinical subgroups. QFT-GIT and T-SPOT.TB performed better than TST 5 mm/10 mm in those undergoing haemodialysis and those with hepatitis C. In contrast, QFT-GIT performed significantly worse than TST 10mm in people with HIV/AIDS. Among transplant candidates, IGRAs were shown to be more sensitive and specific. For other clinical subgroups of immunocompromised people the evidence was inconclusive because of the high level of uncertainty around the statistically non-significant effect estimates.

3.Migrants
Among recently arrived people from countries with a high TB burden, there was no significant difference between the performance of IGRAs and the performance of TST in identifying LTBI.

Preventive Therapy
There was good level of retrievable evidence to suggest that in comparison to placebo, isoniazid (INH) regimen of six months or 12 to 72 months, rifampicin (RMP) regimen, RMP-INH regimen of 3 to 4 months, RMP-INH-pyrazinamide (PZA) regimen and RMP-PZA regimen were shown to be efficacious in preventing the development active TB. A well tolerated, lesser side effects and shorter duration

regimen was associated with better adherence and higher completion rate.

Safety

There was good level of retrievable evidence to suggest that regimens containing PZA had higher hepatotoxicity compared with six months of INH or 12 weeks of RPT-INH [pooled RR 4.59 (95%CI 2.14, 9.85)]. Serious adverse events were documented to be rare. However, RMP-PZA regimens were reported to have the highest risk for gastrointestinal adverse events, and RMP regimens were reported to have the highest risk for central nervous system adverse events.

Cost-effectiveness

1. *Diagnostic test*

Evidence on screening of high risk populations identified the influence of TST and IGRA sensitivity and specificity, TB and LTBI prevalence, treatment effectiveness, duration and treatment costs on cost-effectiveness.

Based on WTP threshold of USD100,000, from US and Canadian healthcare perspective;

Migrants

The IGRA was found moderately cost-effective in adult migrants, while the TST was dominated by no screening.

Immunocompromised people

- Screening of people with HIV was strongly cost effective with a TST and moderately cost effective with an IGRA
- Neither TST nor IGRA was cost effective for screening of LTBI in renal diseases and diabetic patients, however, the IGRA was found to be the most cost-effective test more often than the TST, if screening had to be performed for renal diseases patients and TST was found to be most cost effective for diabetic patients if screening was done.
- All ICERs for other immunocompromising conditions were cost prohibitive, although the TST was found to be the most cost-effective test if screening had to occur.

The economic model for diagnostic tests showed that the best-available options (the most cost-effective strategies) from NHS UK perspective were:

- In children: TST (≥5 mm) followed by IGRAs if negative
- In immunocompromised people: IGRAs followed by TST (≥5 mm) if negative
- In the recently arrived population from high TB burden countries: TST alone (≥5 mm)

2.*Preventive therapy*

- Three months of weekly RPT-INH was more cost-effective than other WHO-recommended regimens or serial radiographic surveillance, from US and other comparable health system perspective at a WTP threshold of USD50,000 per QALY gained.
- Since RPT-INH-DOT prevented more incident cases of active TB, it was found to be more cost-effective than the same regimen when self-administered (RPT-INH -SAT). The cost-effectiveness of RPT-INH-DOT was strongly driven by treatment completion rates.

Organisational

1. *Identification of target risk groups*

There was fair level of retrievable evidence to suggest that clinical risk groups had no increased risk of LTBI in comparison to general population except for candidates of anti-TNF alpha therapy. However, there was evidence of increased risk of progression to active TB in people with LTBI belonging to clinical risk groups.

Based on limited evidence, it was found that migrants and close contacts of TB cases had an increased risk of being infected and progressing to active TB disease, depending on socioeconomic and epidemiological determinants.

For healthcare workers, there was no increased risk of LTBI, but an increased risk of active TB of LTBI positive healthcare workers compared to the general population.

Based on local published studies, the prevalence of LTBI among healthcare workers and prison employees were 10.6-46% and 81%, respectively. The risk factors for LTBI among healthcare workers were working in clinical areas, duration of employment more than five years, aged ≥ 35, close contacts, having chronic disease, working as a nurse and being male. While the increased risk among prison employees was associated with having worked in the correctional system for 12 months or more and smoking tobacco.

2.*Determinants of LTBI treatment initiation, adherence and completion*

The progressive losses at all stages of the care cascade resulted in low completion rate of LTBI treatment.

Factors associated with higher compliance rate were people with immune-compromising medical indications, female gender, being part of contact investigations, immigrant or refugee status and shorter LTBI treatment regimens with DOTS.

Barriers from patients, providers and within the health system exacerbated nonadherence. The main patient-level barriers included fear or experience of adverse effects, the treatment regimen, lack of transportation to clinics, and lack of knowledge of LTBI. Provider-level barriers included insufficient prioritization of and resources for LTBI control in their setting and lack of coordination of LTBI care, while system-level barriers included a lack of prioritization of LTBI control by governments.

3.*Interventions to improve LTBI treatment initiation, adherence and completion*

Incentives may have positive effects on adherence in the short term, particularly for marginalized populations such as drug users, recently released prisoners, and the homeless

Cultural case management which included targeted and culturally appropriate programming that was focused on specific population was also found to be effective.

Education approaches with innovative strategies for both LTBI patients and health care workers may improve adherence.

4.*Training*
The administration and interpretation of the LTBI diagnostic tests requires adequate training for healthcare workers to guarantee the reliability of the results.

Education and training of healthcare workers designed to increase the knowledge of TB/LTBI and raise awareness of the disease are important. It will help in informing and effectively treating TB patients, thereby contributing to the control of LTBI.

Ethical considerations
LTBI management is a preventive, rather than a curative measure, hence benefits for otherwise healthy people need to outweigh risks. In programmatic management of LTBI, both individual aspects and TB control through prevention of transmission should be considered. The policy development should address three distinctive characteristics of LTBI management; potentiality (the risk of future development of active disease and not the current risk), uncertainty (current limitations imposed by scientific and technological methodology, both diagnosis and treatment of LTBI) and vulnerability (poverty and social marginalisation). Testing for LTBI should be done with the intention of offering treatment when the screening is positive. Screening strategies must be accompanied by appropriate individual and community education to avoid unintended harm for tested individuals.

Social implication
Health-related quality of life
There was no meaningful change in HRQOL among subjects treated for LTBI between time of diagnosis and treatment completion in comparison to subjects treated for TB disease or general population (no decrement detactable by either SF-36 or EQ-5D scores).

However, three themes emerged for the mental health concerns; ambiguous threat, fear of being contagious and future uncertainties.

Recommendation
The tuberculin skin test (TST) and interferon gamma release assays (IGRA) or a combination of both tests may be used to diagnose LTBI. The choice of test should be based on target risk group and available resource. Screening of LTBI should consider availability of and accessibility to diagnostic tests, the intention to provide LTBI treatment (if appropriate), the implementation of interventions promoting the uptake and completion of LTBI screening procedures.

Provision of LTBI treatment should be using treatment regimens that are of shorter duration and lesser toxicity in order to promote adherence and enhance completion by different target groups. The selection of LTBI treatment regimen may be based on an individual risk assessment. The following regimens can be considered: isoniazid alone (for 6–9 months), rifampicin alone (for 3–4 months), isoniazid and rifapentine (for 3 months), isoniazid and rifampicin (for 3–4 months).