

# Use of Tuberculin Skin Test and Isoniazid Prophylaxis among Healthcare Workers in Developing Countries: An Un-Resolved Controversy

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## ABSTRACT

Tuberculosis is one of the most significant causes of infectious morbidity and mortality worldwide and has been an important threat for healthcare workers (HCW) for decades. Although the tuberculin skin test (TST) is less expensive, available and a preferred diagnostic tool for latent tuberculosis infection in most TB-prevalent settings, limitations inclusive of false positivity, cross reactivity with non-tuberculous mycobacteria, interpretative and administrative errors have been described. The acceptance rate of TST-guided chemoprophylaxis among HCW in resource-limited settings has remained low given these recognizable limitations. Isoniazid (INH) has generally been recommended as chemoprophylaxis after a reactive TST. However, the INH treatment in these settings may be complicated by local drug-resistant TB and unavailable infection-control resources and TB control program. Herein we discuss the advantages and disadvantages of utilizing TST and chemoprophylaxis among HCW and unresolved issues that require future research in TB-prevalent settings. (*J Infect Dis Antimicrob Agents* 2010;27:1-9.)

## INTRODUCTION

Tuberculosis (TB) is one of the most common infectious diseases to cause significant morbidity and mortality worldwide. Given an airborne route of transmission, TB becomes an occupational threat to healthcare workers (HCW) who inevitably work in settings with congregated TB patients. The annual rates

of TB reactivation is about 3 percent and 0.1 percent in the first year and after 10 years of acquiring TB infection.<sup>1-4</sup> Thus, most of HCW in TB-prevalent countries, such as Thailand develop TB diseases with the annual rate of 0.1 percent given that they have acquired primary TB early in their lives. To mitigate the adverse effects of TB among HCW, the World

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Health Organization (WHO) has recommended a TB control program be established in all healthcare settings.<sup>5</sup> A 2-step tuberculin skin test (TST) is a part of administrative TB controls and is recommended for use as a TB screening tool by the Centers for Disease Control and Prevention.<sup>6</sup> Although TST has been used in HCW for several decades, evidence of limitations exist for controversy over whether it is still an appropriate screening test. Chemoprophylaxis with isoniazid (INH) is generally recommended after a reactive TST. However, the treatment may be complicated by local TB drug resistance and inappropriate in some settings. In addition, infection-control resources may be limited or not exist to facilitate a TB control program. We will here discuss controversial issues and the need for future research on TST and INH chemoprophylaxis among HCW in middle-income and developing countries.

#### **ADVANTAGES OF TST AND INH PROPHYLAXIS ADMINISTRATION AMONG HEALTHCARE WORKERS**

The TST has been generally used to identify HCW at risk for active TB, especially those with exposure to active TB patients. The TST is inexpensive, readily available, and can be performed by trained personnel. The tuberculins, which are antigenic culture extracts of *Mycobacterium tuberculosis* used, for delayed hypersensitivity reaction induction, are generally safe. The common reactions are injection site related such as bleeding, bruising, discomfort, erythematous reaction, pain, and pruritus. Severe skin reactions, including rashes, blisters, hematoma, necrosis, and regional lymphadenitis are not common and generally self-limited. Anaphylaxis to the tuberculins is extremely rare.<sup>7,8</sup>

Studies from developed countries have shown the benefit of TST-incorporated TB control programs in

the reduction of the annual rate of TST conversion in HCW (Table).<sup>9,10</sup> In addition, TB control measures have been associated with decreased TB nosocomial patient-to-patient and HCW-to-patient transmission in healthcare settings.<sup>11,12</sup> Although limited data exists in developing countries, a study from Thailand revealed similar reduction in the annual HCW TST conversion rate (Table).<sup>13</sup> Although the impact of TST implementation may not be substantial compared to other recommended control measures, HCW remain important sources of TB transmission and require appropriate screening, early diagnostic evaluation, and treatment for TB.<sup>14,15</sup>

Evidence from developed countries exists to suggest that INH prophylaxis reduces the incidence of active TB by 60-93 percent and by 85-93 percent in persons who complete a full 6-month course.<sup>16-18</sup> Among HCW, the prophylaxis was shown to be cost-effective in a decision-analytic model study (Table).<sup>19</sup> There is no data from clinical trials regarding INH prophylaxis for HCW in developing countries. However, the findings from a study of immigrants in the United States (US) may be extrapolated for use in developing countries.<sup>20</sup> In said study, combined TST and INH prophylaxis were shown to be effective and reduced costs.

#### **DISADVANTAGES OF TST AND INH PROPHYLAXIS ADMINISTRATION AMONG HEALTHCARE WORKERS**

TST is not a useful test for differentiation between past TB, acute TB or re-infection. The positive TST results in persons living in TB-prevalent countries usually indicate past TB infection or post Bacillus Calmette-Guérin (BCG) vaccination (V) while the positive tests in those living in low TB prevalence countries mostly indicates acute or recent TB infection.<sup>21</sup> Interpretation of reactive TST has been the major concern in persons

**Table. Evidence from studies of *Mycobacterium tuberculosis* (TB) for the use of tuberculin skin test (TST) and isoniazid prophylaxis (INH-P) in healthcare workers (HCW).**

Test/Treatment	Setting	Evidence	Study findings	Reference
TST	Developed country	Support	Annual rate of TST conversion was lower in a hospital with a TST-incorporated (TB) control programa than the national average rate (0.6% vs 1.2%).	9
	Developed country	Support	TST-incorporated TB control programa decreased the TST conversion rates among HCW from 28 percent to 0 percent over 3-year period.	10
	Developed country	Support	TST-incorporated TB control programa decreased the annual rates of TST conversion among HCW from 9 percent to 2 percent.	13
INH-P	Developed country	Against	Acceptance rate of INH-P among HCW was 0 percent when using TST as a TB screening test.	26
	Developed and developing countries	Against	When compared to IGRA, TST reactivity was affected by several factors including prior BCGV, number of BCGV scars, prior serial TST, and being foreign born or born in TB endemic areas. Mean concordance rate between IGRA and TST was 62 percent.	32-43
	Developed country	Against	TST was less cost-effective than QuantiFERON <sup>®</sup> -TB Gold and QuantiFERON <sup>®</sup> -TB Gold in tube test regardless of BCGV status in a decision-analytic model.	45
	Developed country	Support	INH-P in HCW with reactive TST was cost-effective in a decision-analytic model	19

**NOTE:** <sup>a</sup>A TB control program consisted of implementation of several measures in a three-tier hierarchy; administrative controls (rapid identification, diagnostic evaluation, and isolation of persons with active TB), engineering controls (institution of adequate ventilation and air cleaning) and personal respiratory protection (N95 mask).<sup>5</sup> The individual benefit of TST was difficult to ascertain given that several other measures were implemented at the same time.

<sup>b</sup>Including Denmark, Germany, Israel, Italy, Japan, Singapore, Spain, Taiwan and the United States.

BCGV = Bacillus Calmette-Guérin vaccination; IGRA = interferon-gamma release assay.

from middle-income and developing countries where BCGV has been standard of care. Persons who received BCGV in the neonatal period are less influenced by BCGV than those who received the vaccine later in life, given that the BCGV effect wanes over time.<sup>22,23</sup> However, there is no consensus or data from clinical trials for the appropriate cut-offs for TST reactivity stratified by age or at-risk populations in these countries, as there is no gold standard for the diagnosis of latent tuberculosis infection (LTBI). This variation of BCGV influence was also evident among HCW from developing countries with high rates of TB and BCGV.<sup>24,25</sup> Additionally, TST can result in 'false-positive' interpretations among persons with non-tuberculous mycobacteria, especially *M. avium* complex infection.<sup>26</sup> In contrast, false-negative TST is not uncommon in immunosuppressed persons and persons with severe TB. Furthermore, the 2-visit requirement for TST may affect compliance of returning for result reading. Errors in methods of administration, amount of tuberculins used, and measurement bias can also be potential disadvantages of TST.

In a meta-analysis using self-report of history of active TB contact as a reference for LTBI diagnosis, TST was less sensitive and specific than interferon-gamma release assays (IGRA) in the general population.<sup>27</sup> Studies from developed countries demonstrated that TST was less effective in diagnosis of LTBI in persons post BCGV and less cost-effective among BCGV close TB contact population and foreign-born immigrants compared with QuantiFERON<sup>®</sup>-TB Gold.<sup>28-31</sup> Among HCW, IGRA and TST results were significantly discordant, especially among HCW in developed countries, largely due to BCGV, prior TST, and being foreign born (Table).<sup>32-43</sup> Data from developing countries is limited. However, a study from India demonstrated that the two tests had a high (81%) concordance rate.<sup>44</sup> In a decision-analytic model study

from the US, TST was less cost-effective than IGRA for LTBI screening in both non-BCGV and BCGV HCW (Table).<sup>45</sup>

The acceptance and completion rates of INH prophylaxis among TST-reactive HCW are usually low in developing countries and is attributed to HCW knowledge of TST insensitivity and BCGV influence (Table).<sup>26</sup> A study from a developed country suggested that use of QuantiFERON<sup>®</sup>-TB Gold instead of TST can improve the acceptance and adherence to the prophylactic regimen.<sup>46</sup> Other important factors that affect INH adherence include duration of therapy and potential adverse drug reactions. Although asymptomatic transaminitis is more common, significant hepatotoxicity from INH has occurred in 1 per 1,000 persons on INH.<sup>47</sup> In addition, previous studies suggested that INH monotherapy resulted in more frequent hepatotoxicity and treatment discontinuation than rifampicin monotherapy.<sup>48-51</sup> INH-induced fatal hepatotoxicity rate was reported to be 0.001 percent in persons aged  $\leq 35$  years old while the rate was 0.002 percent in persons aged  $>35$  years old.<sup>18</sup>

Chemoprophylaxis for TB has become challenging given the increase in INH resistance in many countries. Further investigation to rule out active TB, such as chest radiograph or sputum examination, is not always performed adequately or carefully evaluated, especially in resource-limited settings. Presumptive treatment can inevitably result in prescribing INH monotherapy to asymptomatic persons with active TB and promote INH resistance and subsequent treatment failure. In addition, LTBI therapy is not as highly prioritized as the management of higher-burden active TB.<sup>52</sup> Definitive TB prophylaxis guidelines have not been established due to the concern of the inappropriate use of

INH prophylaxis that may promote more INH resistance in these countries.<sup>52</sup> Given the low rate of INH prophylaxis prescription in middle-income and developing countries, all reports of INH resistance with subsequent therapeutic failure associated with INH prophylaxis have exclusively been from developed countries.<sup>53,54</sup> The causes associated with failure were unclear, however, were possibly due to unrecognized INH-resistant LTBI, development of INH resistance after the prophylaxis, or undiagnosed active TB at initiation of prophylaxis.

## **OCCUPATIONAL HEALTH AND TB PREVENTIVE THERAPY**

Occupational health programs are essential and have been associated with improved TB chemoprophylaxis acceptance and completion rates.<sup>55</sup> However, limited budgets and personnel remain obstacles to such program implementation in middle-income and developing countries.<sup>5,26</sup> The important components that are usually included in these programs are evidence-based counseling regarding risks and benefits of TB prophylaxis, monitoring compliance and side effects of the prophylactic regimen, and follow-up and serial testing plans for HCW who are and are not on LTBI therapy. Adoption and modification of these components per available resources should be considered in countries without occupational health and safety programs. Simplified measures that are feasible in resource-limited settings include pre- and post- test counseling by designated healthcare personnel, self-evaluation procedures and peer-support groups to promote chemoprophylaxis, available on-call physicians or assigned personnel for questions and concerns, and self-observation or spontaneous reporting of symptoms of active TB

in HCW who are not on or are declining TB chemoprophylaxis.

## **Unresolved Issues for Future Research**

Although occupational risks of TB acquisition have been recognized for several decades, research revolving around TB screening and preventive therapy has primarily occurred in developed countries. Questions of relevance for improved HCW health and safety in middle-income and developing countries include:

### **TST-related questions**

1. What should be the appropriate cut-offs for TST reactivity in regards to age, TB risk factors, history of BCGV, prior TST and prevalence of TB in the settings where TST is the only available screening test?
2. What should be the optimal interval of TB screening tests?
3. Could yearly TB surveillance by TST detect more recent TB infection among HCW in developing countries and be cost-effective?

### **INH prophylaxis-related questions**

1. What are the efficacy, adverse reactions, and cost-effectiveness of INH prophylaxis in comparison to other prophylactic regimens?
2. What should be the optimal duration of INH prophylaxis in a TB-prevalent setting like Thailand given that it is mostly implemented in the stage of past TB infection rather than recent TB infection?
3. Is INH prophylaxis still effective in the settings where INH resistance rates are high and what should be the best alternative regimens?
4. What is the risk of nosocomial transmission among HCW with LTBI who decline TB

chemoprophylaxis?

### CONCLUSION

TST remains the first-line LTBI screening tool in most TB-prevalent settings and could potentially be implemented for HCW in Thailand. Nonetheless, research is needed to resolve unanswered questions. TB prevention among HCW in middle-income and developing countries is largely neglected in national healthcare preparedness priorities and by the international organizations that fund healthcare initiatives. However, these countries should not delay the implementation of effective preventive strategies while awaiting additional data. These strategies should be practical, less costly, simple and based on the three-level hierarchy recommended by WHO, including administrative controls, environmental controls, and personal respiratory protection.<sup>5</sup>

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