The Risk of Tuberculin Skin Test Conversion in Individuals Who Travel to Countries with High Prevalence Rates: A prospective Study

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A. Study Purpose and Rationale

Targeted tuberculin skin testing (tst) for latent tuberculosis infection (LTBI) and treatment of LTBI are essential components of tuberculosis (tb) control and prevention in this country. The Centers for Disease Control and Prevention (CDC) and the American Thoracic Society (ATC) recommend screening only those individuals who are at increased risk of developing active tb, including those with close contact with persons with infectious tb, recent immigrant or individuals who have immigrated within the past 5 years from an endemic country, residents and employees of high-risk congregate settings, and persons with specific clinical conditions placing them at higher risk for developing tb. In addition to the above recommendations, the American Association of Pediatrics (AA) also recommends more frequent screening for children who travel to tb endemic countries, countries that have a high prevalence of tb. While it has been shown repeatedly that foreign birth is associated with tb infection, there have been limited studies assessing the increased risk of tb infection in individuals who travel to and from endemic countries. Two case control studies found that a positive tst in children was associated with travel to an endemic country.[1,2] Their results led the investigators to support the recommendation that children living in areas in the US where tb case rates are higher than the national average should be asked about travel history routinely and screened for tb more frequently if a positive response is elicited. The recommendations for adults who travel to and from endemic countries have not been clearly defined although studies have shown an increase risk of tb in adults who travel to highly endemic regions.[3,4] One recent study used RFLP analysis to demonstrate that cases of tb amongst non-US born persons are more likely due to reactivation of latent tb as opposed to recent infection from known contacts, which underlines the importance of identifying at risk groups for LTBI and treating them.[5] To date, no prospective study has taken place that specifically assesses the risk of travel to endemic regions. In order to answer the question of whether adults who travel to endemic countries should be considered a high-risk group at increased risk of tb infection, I propose a prospective study following individuals with a negative tst at baseline for a two year period with yearly screening using tst, specifically assessing the risk of tb infection associated with travel.

B. Study Design and Statistical Analysis.

The study will be a prospective observational study following adults with a negative tst at baseline for a 2 years period, comparing the tst conversion rates in a cohort that travels to and from a tb endemic region with a cohort that does not travel. In order to arrive at the number of study participants, I first looked at the tst conversion rates for health care personnel, a group considered to be at high enough risk for tb infection that annual screening is warranted. The average annual conversion rate of health care personnel is approximately 1.5%.[6] If the annual conversion rates of the cohort who travel approach that of health care workers this would support a recommendation for more frequent screening of individuals who travel to tb endemic regions for adults. Assuming a conversion rate of .02% in the cohort that does not travel, the annual number of cases of tuberculosis reported to the Department of Health from the Washington Heights area, and a conversion rate in the cohort who travel of 1.5% annually, the approximate conversion rate for health care workers, a total of 1368 study participants would be needed to obtain 80% power, testing at p=.05. Assuming 20% are lost to follow-up, another 274 (= 20%*1368) study participants should be recruited for approximately 1642 participants in total.

For univariate analysis, rates of tst conversion and prevalence of positive tst's will be analyzed using the Mantel Haenzel chi-squared test for dichotomous variables and an analysis of variance for continuous variables. A p value of less than or equal to .05 will be considered significant for all statistical tests. A multivariate logistic regression will be constructed for variables found to be significant in the univariate analysis to assess the independent effects of each variable on tst conversion while controlling for possible confounding variables.

C. Study Procedures

Skin testing will be done on all study participants using the Mantoux technique with the use of .1mL of purified protein derivative containing 5 TU, which will be placed on the volar aspect of the forearm and read 48-72 hours after placement by a nurse or physician. The results will be measured as the diameter of induration transverse to the axis of the forearm and recorded in millimeters (mm). A positive tst will be defined as induration equal to or greater than 10 mm. If the participant has a written documentation of a tst done in the past, only one tst will be performed at baseline. If no previous documentation for tst is found, the 2-step test will be done (i.e. 2 tst's performed 1-3 weeks apart) as part of initial testing to minimize the likelihood of interpreting a boosted reaction as a true conversion due to recent infection. Self-reporting of results will not be permitted. A questionnaire will be administered at the time of initial testing and follow up tst's and questionnaires will be administered at 1 year and 2 years after the initial testing date. The test and the questionnaire will take approximately 15 minutes to administer, which may pose an inconvenience to the subjects. The subject will return in 24-72 hours to have the test read and this should take less than 5 minutes. Some subjects may experience minimal pain or irritation at the site of the ppd placement but this should be temporary.

D. Study Questionnaires

Questionnaires will be administered in either English or the primary language of the parent or guardian before the tst is read to minimize recall bias. Age, sex, country of birth, ethnicity, immigration status and when they immigrated to the US, history of Bacilli Calmette-Guerin (BCG) vaccination and years since last BCG, type of employment, number of household members and family income, housing conditions to assess for homelessness,

HIV status of participant if known and any household members who is HIV+ or has lived in a shelter, clinically significant diseases, smoking and drug history will all be ascertained initially and then will be reassessed at the subsequent visits. Questions about travel by either the subject or household members will be ascertained both during the time of the study as well as travel history prior to study participation. Travel will be defined as a trip of more than 1 wk to a country with a high prevalence of tb. High prevalence countries will be defined as countries that have a tb rate of >100 cases/100,000. Questions about travel will include the country visited, the length of stay and how many visits. Questions will also be asked about household visitors and the country the visitor was from and whether they had any illnesses or symptoms suggestive of tb. Any known or suspected contact with an individual who has tuberculosis both here and in the endemic country will be ascertained.

E. Study Subjects

Individuals who are already known to have a documented positive tst result or previously treated tuberculosis are ineligible to participate. Individuals who have contact with persons who have tuberculosis here in this country will also be ineligible if independent confirmation of the contact's tuberculosis status is ascertained via the Department of Health's tb registry. Individuals who have a positive tst result at baseline or after the 2 step method when appropriate, will also be ineligible Only those HCP with negative tst results at baseline will be recruited to participate in this project.

F. Recruitment of Subjects

Subjects will be recruited from the Associates of Internal Medicine (AIM) clinic and affiliated clinics at Columbia Presbyterian Medical Center (CPMC). A letter will be sent to all primary care providers, including the residents, attendings and nurse practitioners regarding the purpose and design of the study. For those who are interested in helping to carry out the study, the questionnaires will be distributed to their office with a description on how to administer the questionnaires. In addition, the CDC's recommendation on how and when to treat LTBI will be included in this packet and a contact number at the Department of Health in case any questions may arise. Flyers will also be distributed at the AIM clinic for patients interested in participating in the study.

G. Confidentiality of Study Data

In order to safeguard the confidentiality of the study data and the identity of the study subjects, all data will be coded with a unique code number for all study subjects and data will be stored in a secure location, accessible only to the investigators.

H. Potential Conflict of Interest.

This does not pertain to the project.

I. Location of the Study

Since the study being proposed involves minimal risk to the subjects, the study can take place at the provider's office or clinic.

J. Potential Risks

A potential risk would be a false positive tst reading that may lead to a subject taking prophylaxis treatment and being subjected to the risks of this treatment.

K. Potential Benefits

The benefits to the subject of more frequent tst screening would be the opportunity to detect and treat LTBI, decreasing their risk of developing active tb. The main benefit would be to that of society in general because the results will provide information to support recommendations on whether adults traveling to a tb endemic country places an individual at high enough risk to warrant more frequent screening with tst. There is currently not enough data on adults to support or refute such a recommendation.

L. Compensation to subjects

No monetary compensation will be provided.

M. Cost to Subjects

The only additional costs to the subject as a result of participating in this study would be the personal transportation costs incurred by patients for going to the clinic to have their tst read.

N. References

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