BOSTON UNIVERSITY SCHOOL OF PUBLIC HEALTH
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CULMINATING EXPERIENCE COVER PAGE

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Culminating Experience Paper or Project Title: **Misdiagnosis of Latent Tuberculosis Infection by Cross-reactivity to *M. avium* Complex**

Abstract (150-300 words)
**Rationale:** When a person has been infected with M. *avium*, a positive purified protein derivative (PPD) skin test may indicate cross-reacting immunity and not LTBI. In geographic areas with high prevalence of M. *avium* this could lead to substantial misclassification of LTBI.
**Objectives:** To assess misclassification of LTBI resulting from reactivity to M. *avium*, and to determine how this misclassification affects the analysis of risk factors for LTBI.
**Methods:** In a population based survey, participants received a skin test with PPD and *M. avium* sensitin (MaS). A positive reaction to PPD was a reaction of $\geq$ 10mm for HIV uninfected participants and $\geq$ 5 mm for HIV infected participants; a PPD-dominant skin test was a reaction that was 3mm larger than the MaS reaction; a MaS-dominant skin test was a reaction that was 3mm larger than the PPD reaction; a non-dominant reaction was one where the MaS and PPD reactions were within 3mm of each other.
**Measurements and Main Results:** Of 447 randomly-selected persons, 135 (30%) had a positive PPD skin test. Of these, 21 (16%) were MaS dominant, and were therefore misclassified as LTBI. Smaller positive skin test reactions (<15 mm) were more likely to be misclassified (OR = 5.0, 95% CI: 1.9, 13.2). Adjusting for this misclassification had only a small impact on predictors of LTBI.
**Conclusions:** A substantial number of individuals who are diagnosed with LTBI are actually sensitized to MAC. Using MaS in addition to PPD would reduce misdiagnosis and prevent unnecessary treatment, leading to a more efficient and targeted approach to control of tuberculosis.

Key Words: Latent Tuberculosis Infection, *M. avium* Complex, Skin Test, Misclassification

## Introduction

Tuberculosis disease (TB), caused by *Mycobacterium tuberculosis*, is a major cause of morbidity and mortality worldwide.[1] Although most people who are infected with *M. tuberculosis* have latent tuberculosis infection (LTBI) and are not sick or infectious, the bacteria may subsequently become active, a phenomenon known as reactivation TB. The lifetime risk of reactivation tuberculosis in persons with LTBI is estimated at 5 to 10 percent and it can be much higher in certain subpopulations.[2]

The estimated prevalence of LTBI in the civilian, noninstitutionalized U.S. population was 4.2% in 1999-2000.[3] Because the rate of new TB cases is low in the United States, one of the major goals of eliminating TB is prevention of reactivation tuberculosis through screening and treatment of latent tuberculosis infection.[4-6] The CDC recommends a 9 month course of treatment for individuals who have LTBI, and such treatment reduces subsequent TB by 90%.[7]

Screening for LTBI is largely performed using skin testing. Using the standard cutoff in the United States of 10 mm for a positive PPD skin test, the sensitivity of the test for LTBI is approximately 96%.[7,9] However, because there is cross-reactivity between skin test reagents for *M. tuberculosis* and many nontuberculous mycobacteria, the specificity of PPD skin testing varies depending on the prevalence of exposure to nontuberculous mycobacteria.[9-10] *Mycobacterium avium* complex (MAC) infection is the most common cause of nontuberculous mycobacterial disease in the United States.[8] The MaS skin test has been shown to have a high sensitivity (73-83%) and high specificity (97-100%) for MAC infection and disease through studies in both human and animal models.[11-14] Cross-reactions can cause false positive PPD skin tests when not read in

conjunction with skin tests for MAC.[14-15] Unfortunately, no MAC skin test reagents are currently available for diagnostic use in the United States.

Because of the potential toxicities from treatment of LTBI it is important that only individuals who are truly latently infected with *M. tuberculosis* are offered treatment. Misdiagnosis (misclassification) of individuals as having LTBI when they are in fact sensitized to MAC leads to unnecessary treatment, since MAC infection is not associated with later reactivation disease, and is therefore not treated. Knowing that the Southeastern U.S. has a high prevalence of sensitivity to MAC[16], we sought to quantify the degree of LTBI misclassification in a southern Florida population through a dual skin test survey. In addition, we sought to identify risk factors for misclassification and to describe the effects of this misclassification on identification of risk factors for LTBI.

## Materials and Methods

### I. Population-based survey

From January 1, 1998 to September 30, 2000, a population-based survey was performed in Western Palm Beach County, Florida – defined as the area that includes postal zip codes 33430, 33438, 33476 and 33493. To select study participants, a computer program randomly selected 800 addresses from the area's water meter records. Water main records represent all addresses in the area because the high water table in the area makes well water non-potable, and thus piped water is the only source of household water.

One resident was chosen from each selected address identified as a household by use of a random selection table. Persons with a history of blistering on prior tuberculin skin testing were excluded, as were children less than 1 year of age. Houses classified as unoccupied were visited at least 6 times during the study period, including at least twice in the evening and/or on weekends, before beings so classified. Each participant gave informed consent, responded to a standardized questionnaire, and underwent skin testing. Human subjects committees of the Florida Department of Health, Emory University, Boston University, Dartmouth Medical School, and the Centers for Disease Control and Prevention approved the study protocol.

II. Self-identified HIV-infected participants

All HIV-infected residents of the community were invited to enroll in the study and were evaluated by the same protocol that was used in the population-based study, with the exception that the self-identified participants also received anergy skin testing. These self-identified HIV-infected participants were sought by advertising in local media and contacting local HIV/AIDS service organizations and care providers. Most of these participants were referred to the study staff by the local health clinic**,** private practitioners**,** or local HIV service agencies.

III. Skin Tests

Each participant received a skin test with purified protein derivative (PPD; 5 T.U., Connaught, Swiftwater, PA) on the right forearm and with *M. avium* sensitin (MaS 10/2, 1 mcg/ml, Statens Seruminstitut, Copenhagen) on the left forearm. HIV-infected

participants were also skin tested with mumps (MSTA, Connaught, Swiftwater PA) and Tetanus toxoid (diluted 1:10 in albumin-saline diluent, Connaught, Swiftwater PA) to assess anergy. For each antigen, 0.1 ml was injected intradermally. A single study nurse was trained in skin test planting and reading by an experienced skin test investigator (BJM) and subsequently read all tests in the study after 48-72 hours, according to established guidelines. Anergy was defined as failure to demonstrate a reaction of 3 mm or greater to any of the four skin test reagents.

Interpretation of the PPD skin test alone followed established criteria.[7] The study area has a high incidence of TB so all residents were considered to be at "high risk" for LTBI. Thus, a negative reaction to the PPD skin test was a reaction of less than 10 mm to PPD for HIV uninfected participants and less than 5 mm for HIV infected participants, while a positive PPD skin test was a reaction of 10 mm or greater for HIV uninfected participants, and 5 mm or greater for HIV infected participants.

For dual skin testing using PPD and MaS,[11,15] a positive reaction to the PPD skin test was a reaction of greater than or equal to 10 mm to PPD for HIV uninfected participants and greater than or equal to 5 mm for HIV infected participants that was dominant to the MaS reaction – at least 3 mm larger than the MaS reaction. An indeterminate PPD reaction was defined as a PPD reaction that was at least 10 mm for HIV uninfected participants (at least 5 mm for HIV infected participants), but was equal in size (within 3mm) to the MaS reaction. Participants who had a positive PPD skin test that was MaS dominant were considered misclassified.

IV. Risk factor questionnaire

A trained interviewer gave each participant a standardized questionnaire in English, Spanish or Haitian Creole. The survey included questions about sociodemographic information and risk factors for HIV, TB and MAC infection. Information on BCG vaccination was obtained by self-report. Exposure data collected as continuous variables were categorized for analysis. Several of these variables were dichotomized as ever exposed and never exposed.

V. Statistical methods

Univariate statistical associations between misclassication and categorical variables were tested by the chi-square or Fisher's exact test. Ninety-five percent confidence intervals were calculated using a normal approximation of the binomial distribution. Because HIV infection may interfere with a subject's ability to manifest a skin test reaction to either PPD or MaS, the self-identified HIV-infected participants were analyzed separately, and only individuals with CD4 counts > 200 cells/μL were included in the univariate analyses. The LTBI analysis was stratified by birthplace, because of strong differences in LTBI between U.S. and foreign born persons.[17] To identify risk factors for LTBI infection using both the crude and adjusted classification for LTBI, variables that appeared strongly associated with infection ($p \leq 0.20$ in univariate analysis) were analyzed in multivariate models stratified by foreign birth. Variables that remained strongly associated with LTBI were retained in the final model. Statistical analyses were performed by use of SAS version 9.2 (SAS Foundation, Cary, NC).

## Results

I. Study population

Of the 800 addresses selected for the survey, 191 could not be used to select participants because 81 were businesses or vacant lots and 110 were unoccupied. Of the 609 remaining addresses, 447 (73 percent) were fully enrolled, 69 (12 percent) only completed the interview, 92 (15 percent) declined to participate, and one (0.1 percent) was ineligible because of a history of blistering on skin testing. The 69 who completed the interview were similar to the 447 who were fully enrolled by sex, age, employment, income, and birth in the U.S. However, they were more likely to be black but not Haitian (72 percent vs. 59 percent, p=0.03).

II. Skin test reactions

Of the 447 fully enrolled participants, 135 had a positive PPD skin test. Of the 135 participants with a positive PPD skin test, 21 (15.6 percent) were MaS positive and MaS dominant and were thus determined to be misclassified as LTBI. Description of skin test reactions and sizes can be found in table 1. Reactions that were PPD positive and MaS dominant ranged from 10 mm to 18 mm (median 13.5 mm) in participants who were not HIV infected and 5 mm for the participant who was HIV infected. Positive PPD reactions that were not MaS dominant ranged from 10 mm to 35 (median of 17 mm) in participants who were not HIV infected and 6 mm to 20 mm (median 13 mm) in participants who were HIV infected.

III. Risk factors for misclassification

In univariate analyses, size of the PPD skin test reaction was the only variable that was significantly associated with misclassification of LTBI (tables 1 & 2). Smaller positive PPD skin test reactions (<15 mm) were more likely to represent misclassification of LTBI than PPD skin test reactions greater than or equal to 15 mm (OR = 5.0, 95% CI: 1.9, 13.2). Two age groups, 1-20 years old and 41-50 years old had a high degree of misclassification, 3/10 (30%) and 11/26 (42%) respectively, but there was no significant trend by age.

Farm planting and Black race were each associated with a close to three-fold increase in misclassification which neared statistical significance, and these two variables were highly correlated (p = 0.001). However, there were no interactions between them in the multivariate model.

Our previous study of MAC infection in this population identified caring for a cat and soil exposures (such as driving a farm truck or working for a landscaping service) as risk factors for a MaS positive, MaS dominant test.[22] However, neither of these variables were not associated with misclassification of LTBI in the present analysis. Historical predictors such as gender, income, and foreign versus U.S. born were also not associated with misclassification, nor was BCG status, as determined by the presence of a BCG scar.

IV. Self-identified HIV-infected participants

Because there were only seven HIV infected people in the population-based study, we combined these seven participants with the 210 self-identified HIV-infected participants to examine the relationship between misclassification and HIV related

factors. Of the 217 HIV-infected participants 44 (20.2%) had a positive skin test (≥ 5 mm). Three (6.8%) of those with a positive skin test were misclassified as LTBI. Of the 105 participants who had a CD4 count greater than 200 cells/μL, 28 had a positive skin test with only one person misclassified. Comparing the degree of misclassification in the HIV infected population (1/28, 3.6%) to that in the HIV uninfected population (20/132, 15.2%) we found that HIV infected people were less likely to be misclassified than HIV uninfected people (OR = 0.21, 95% CI: 0.03, 1.61).

V. Effects of misclassification on the analysis of risk factors for LTBI

The risk factors for LTBI, defined as a positive PPD skin test only using the CDC criteria in this population were previously reported.[19] After adjusting for misclassification, the associations between 10 out of 17 risk factors and LTBI changed by more than 10% (table 3), but none of these changes were statistically significant. The associations between LTBI and sex, race, age, income, farm worker, employment status, and STD were over-estimated in the foreign-born cohort as well as race in the US born cohort. Conversely, the associations between LTBI and income, employment status, and drug use were under-estimated in the U.S. born cohort. The association between current employment and LTBI became statistically significant in univariate analysis, whereas before adjusting for misclassification, this association was not statistically significant. Adjusting for misclassification did not alter which variables were included in the multi-variate model for the US born cohort, nor did any of the resulting point estimates change significantly. However, in the foreign-born cohort adjusting for misclassification caused

education and age to drop out of the multivariate model as they were no longer significant.

**Discussion**

We found that 16% of positive PPD skin test reactions in our study population were due to cross-reactivity to MaS. After correcting for misclassification, the proportion of people with LTBI decreased from 0.30 (95% CI: 0.26, 0.34) to 0.26 (95% CI: 0.21, 0.30). Although the change is not statistically significant ($p = 0.12$), the sample size was relatively small. Misclassification due to cross-reaction in other geographic areas will be heavily dependent on the prevalence of nontuberculous mycobacteria (NTM) infection in the population under study, with higher degree of misclassification in those populations with increased prevalence of NTM sensitivity. MaS dominant reactions are more common in the Southern U.S.,[19] however, with the increasing prevalence of disease caused by MAC and other NTM in the United States,[20] misclassification will probably also be an issue in many areas.

Misclassification of LTBI was greater with smaller skin test indurations: one third of people with skin test reactions less than 15mm were misclassified, compared to only 9% of people with skin test reactions greater than 15mm. While changing the classification of a positive skin test reaction to 15mm from 10mm would increase the specificity of LTBI diagnosis it would be at the expense of sensitivity, and many people with LTBI would be missed. Using the MaS skin test in addition to the PPD skin test in persons with a PPD skin test reaction <15mm could potentially prevent over-diagnosis of LTBI without missing the true LTBI cases.

Providing MaS skin tests in populations where there is high exposure to MAC would reduce the degree of misclassification of LTBI. Because the current standard of care for treating LTBI is a 9 month course of isoniazid, proper classification would decrease the amount of overtreatment that currently occurs. Treating people who have a false positive test exposes them to the toxicities of treatment without providing any personal benefit or contributing to elimination of tuberculosis in the U.S.

The misclassification identified in this study led to both over and underestimation of the associations between LTBI and its predictors. Although the magnitude of this change was greater than 10% in a number of instances, it was only statistically significant in one instance: the association between employment and LTBI in the U.S. born cohort. These results suggest that misclassification will not probably not have large effects on the validity of epidemiologic studies of risk factors for LTBI and that the clinically meaningful effect of the misclassification is seen on the individual level.

We did not address other factors that can lead to misclassification of LTBI using skin testing, such as misapplication or misreading of reactions. However, we believe that our use of a single well-trained skin test reader minimized such misclassification.Another potential limitation of our study was our assumption that indeterminate reactors (those participants who had positive reactions to both the PPD and MaS skin tests with neither skin test dominant) were sensitized to both *M. tuberculosis* and and MAC. However, if in fact some of these people do not have LTBI then misclassification is greater than we are reporting. A third limitation of our study is our modest sample size. It is possible that with a larger sample size associations such as that between Black race and misclassification would be statistically significant.

Although MAC infection is common in many parts of the world,[15,22-23] preventing misclassification of LTBI by dual skin testing will be most relevant in areas like the U.S., where treating LTBI is standard of care. Our results suggest that a substantial proportion of positive PPD reactions in some areas of the U.S. may in fact be due to MAC and not represent LTBI. If this is the case, then using MaS in addition to PPD would reduce misdiagnosis and prevent unnecessary treatment, leading to a more efficient and targeted approach for the control of tuberculosis. Efforts should be undertaken to increase the availability of MaS in the U.S.

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**Table 1. Skin test characteristics among individuals with a positive PPD skin test, by reaction size to MaS and PPD**

| TST reaction size (mm) | MaS negative | MaS positive, TST dominant | MaS and TST nondominant | MaS dominant | Misclassified as LTBI |
|---|---|---|---|---|---|
| 5-9* | 0 | 0 | 1 | 1 | 1/2 (50) |
| 10-14 | 8 | 2 | 13 | 11 | 11/34 (32.4) |
| 15-19 | 3 | 22 | 31 | 9 | 9/65 (13.8) |
| 20+ | 1 | 23 | 10 | 0 | 0/34 (0) |
| Total (%) | 12 (8.9) | 47 (34.8) | 55 (40.7) | 21 (15.6) | 21/135 (15.6) |

*Included HIV infected persons only

**Table 2. Univariate analysis of predictors of LTBI misclassification in 135 residents of western Palm Beach County, FL.**

| Predictor | PPD+, MaS non-dominant | PPD+, MaS dominant (%) | OR (95% CI) | p value |
|---|---|---|---|---|
| Total | 114 | 21 (15.6) | - | - |
| Female Gender | 53 | 10 (15.9) | Reference | |
| Male Gender | 61 | 11 (15.3) | 0.96 (0.38, 2.4) | 0.92 |
| Race, collapsed | | | | |
| Non-Black | 37 | 3 (7.5) | Reference | |
| Black | 76 | 18 (19.2) | 2.9 (0.83, 11.1) | 0.09 |
| Born in US/Puerto Rico | 47 | 8 (14.5) | Reference | |
| Foreign-Born | 67 | 13 (16.2) | 1.1 (0.43, 2.9) | 0.79 |
| Age (years) | | | | |
| 1-44 | 56 | 8 (12.5) | Reference | |
| 45+ | 58 | 13 (18.3) | 1.57 (0.60, 4.1) | 0.35 |
| Income | | | | |
| <$10,000 | 60 | 10 (14.3) | Reference | |
| $10,000+ | 51 | 11 (17.7) | 1.3 (0.51, 3.3) | 0.59 |
| Farm Planting, ever | 68 | 17 (20) | 2.9 (0.91, 9.1) | 0.06 |
| Farm truck driver, ever | 32 | 3 (8.6) | 0.43 (0.12, 1.6) | 0.19 |
| Lawn/landscape service, ever | 36 | 7 (16.3) | 1.1 (0.40, 2.9) | 0.89 |
| Cared for a cat in the past month | 14 | 1 (6.7) | 0.36 (0.04, 2.9) | 0.31 |
| BCG Scar | 51 | 12 (19.0) | 1.6 (0.62, 4.1) | 0.33 |

**Table 3. Univariate analysis of risk factors for LTBI, stratified by birth location, adjusted and unadjusted for misclassification**

| Characteristic | Category | Crude US-born OR (95% CI) | US-born OR (95% CI) adjusted for misclassification | Crude Foreign-born OR (95% CI) | Foreign-born OR (95% CI) adjusted for misclassification |
|---|---|---|---|---|---|
| **Sex** | Male<br>Female | 2.0 (1.1-3.6) | 1.9 (1.0, 3.6) | 1.9 (0.98-3.5) | 1.7 (0.9, 3.3) |
| **Race** | White & Hispanic<br>African-American | 2.6 (1.2-5.3) | 2.3 (1.1, 5.0) | 4.4 (2.3-8.7) | 2.5 (1.3, 4.8) |
| **Age (years)** | 0-49<br>50+ | 6.6 (3.5-12.5) | 6.9 (3.5, 13.6) | 0.56 (0.28-1.1) | 0.78 (0.39, 1.6) |
| **Education** | Gr 0-6<br>Gr 12+ | 1.8 (1.0-3.3) | 1.8 (.93, 3.5) | 1.0 (0.50-2.1) | 1.1 (.55, 2.4) |
| **Income** | <10,000<br>10,000+ | 2.0 (1.1-3.7) | 2.6 (1.4, 5.1) | 1.3 (0.67-2.4) | 1.1 (0.56, 2.0) |
| **BCG Vaccination** | Yes<br>No | N.A. | N.A. | 2.8 (1.3-6.2) | 2.8 (1.2, 6.6) |
| **Farm Worker** | Yes<br>No | 1.84 (0.87, 3.9) | 2.0 (0.93, 4.4) | 4.2 (2.2, 8.3) | 3.1 (1.6, 5.9) |
| **Employed** | Yes<br>No | 0.72 (0.38-1.4) | 0.45 (0.23, 0.90)* | 1.5 (0.84-2.9) | 1.1 (0.6, 2.2) |
| **STD** | Yes<br>No | 3.8 (2.0-7.3) | 4.0 (2.0, 8.0) | 1.1 (0.40-3.0) | 0.94 (0.34, 2.6) |

*p=0.02