

Tuberculosis screening for international students at a Midwestern liberal arts college

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10 Abstract

Participants: 318 international students at Macalester College screened for latent tuberculosis infection via tuberculin skin tests (TST) from 2004-2008. **Objective:** To estimate positive TST probability based on countries of residency and history of BCG vaccination. **Methods and Results:** 52% of students had a positive TST. Logistic regression modeling shows that a positive TST is insignificantly correlated with history of BCG vaccination ($p=0.910$) but is significantly negatively correlated with residence in the European Union ($p=0.00502$) and the Middle East ($p=0.00451$), and positively correlated with residence in North America ($p=0.00151$). **Conclusions:** There is a significant relationship between TST result and residence in three regions. The surprising positive correlation for North America is explained by examining those 52 students who resided in North America, 7 of whom had only resided in the United States in spite of being born abroad. For more useful predictive models, we recommend additional patient history data to gather.

Tuberculosis is a common and potentially deadly infectious disease, caused by the bacterium *Mycobacterium tuberculosis*, which has infected nearly one-third of the world's population. While tuberculosis (TB) most commonly attacks the lungs, it can also affect the central nervous system, the lymphatic system, the circulatory system, the genitourinary system, bones, joints and even the skin. Symptoms often include fever,

chills, night sweats, appetite loss, weight loss, heightened fatigue, chest pain, and a prolonged cough that can produce blood ^[1].

30 While the probability of transmission between individuals depends upon many factors, it greatly increases if TB becomes active and remains untreated; a person with active but untreated TB can infect 10-15 people per year ^[2]. Although some countries offer vaccines such as the bacille Calmette-Guérin (BCG) vaccine, these vaccines are typically administered in countries where TB is endemic in order to reduce rates of
35 invasive disease, such as meningitis ^[3,4].

Within a small community such as Macalester College, a liberal arts college in St. Paul, Minnesota with roughly 1900 students enrolled, a first step in decreasing the probability of transmission is to regularly check a high-risk population for active and/or latent TB. Although Macalester's Winton Health Services has yet to discover a
40 Macalester student with active TB, latent TB, dormant within the lungs of an individual, can eventually develop into active TB. Individuals who test positive for latent TB (see protocol for testing positive as explained below) with no risk factors have a 10% chance of developing active TB over a lifetime; this chance increases to 30% if the individual has diabetes. If the individual is HIV positive, the likelihood of developing active TB is
45 7-10% per year ^[5]. The identification and treatment of those with latent TB infection (LTBI) is therefore key to controlling the disease and decreasing the chances of a future active TB outbreak on campus.

According to the national TB surveillance data published by the Centers for Disease Control and Prevention (CDC) in 1997, 39% of active TB cases in the United States are
50 in foreign born individuals, with the percentage significantly increasing from 1986-1993

[2]. The CDC therefore states that one of the largest risk factors for contracting TB is being born, traveling, or living in a foreign [6]. For this reason, Macalester tests every international student, accounting for 12% of the student population, and a small number of domestic students born outside of the United States at the beginning of every school year via a Mantoux/PPD (Purified Protein Derivative) tuberculin skin test (TST). During this skin test, 0.1 ml of PPD, an antigen taken from dead tuberculosis bacteria, containing 5 tuberculin units, is injected into the forearm. There it forms a palpable, raised and hardened bump called an induration, just underneath the skin's surface. If the induration no longer remains after 48-72 hours, the skin test is negative and "0 mm" is recorded in health data records. If an induration does remain after the allotted time and is less than 5 mm in diameter, the TST is still considered negative. If, however, the induration is at least 5 mm, then the skin test result depends not only upon the size of the induration but also the patient's risk of being infected with TB or progression to active disease if infected. A TST is positive at ≥ 5 mm if the patient is immunodeficient, has had recent contact with someone with active TB, or has a chest x-ray showing fibrotic changes (scarring) from a previous TB infection. A TST is positive at ≥ 10 mm if the patient is a recent arrival (< 5 years) from a country where TB is considered endemic, or if the patient has lived in a congregate setting (camp, military, dorms, etc), or if the patient is on immunosuppressive drugs, for example, steroids, cancer therapy, or certain arthritis drugs. Finally, a TST is positive at ≥ 15 mm even if the patient does not fall into any of the above categories [1]. It is important to note that the size of the induration is not an indication of the severity of the (latent) infection as the TST is mediated by an individual's immune system [7]. If the patient tests positive for latent TB, a chest x-ray is

used to determine if the result is due to previous scarring (from a previous latent TB
75 infection) or due to active TB. If the chest x-ray is normal or shows only old scarring, the
patient is encouraged to take Isoniazid (INH), a medication to treat LTBI, before it can
become active disease. A negative chest x-ray could indicate that the infection resides
elsewhere in the patient's body—in his/her bones, organs, etc. Further tests are then made
in order to determine if actual infection is present and where it harbors in the patient's
80 body, if not in the lungs ^[8]. Table 1 summarized the Mantoux/PPD test interpretation
protocol just described.

The purpose of the present study is to examine the skin test results of Macalester
students tested during the last five years, to elucidate the relationship between positive
TST and the particular background of each student, including the regions that s/he has
85 resided in and whether or not s/he received the BCG vaccination during childhood.
Another study of TST results among international students, conducted at a Midwestern
community college in Iowa in 2000, reported aggregate summary statistics for TST result
and administration of INH ^[9]. Of the 11,000 students enrolled at the community college,
391 were international students, representing 70 different countries. In the present study,
90 we build on that work by performing logistic regression modeling on our own data, and
by considering the role played by geographic region.

The rest of the paper is organized as follows. In Section 1, we give a brief description
of the data set used as well as a description of our model of choice, based upon logistic
regression ^[10]. In Section 2, we provide our results, which indicate that there is not a
95 significant relationship between a history of BCG vaccination and positive TST but there
is between positive TST and three of the ten geographic regions considered. There is a

significantly negative relationship between having a positive TST and residing in the Middle East or the European Union, while there is a significantly positive relationship between having a positive TST and residing in North America. In Section 3, we offer explanations for our results, including the surprising positive relationship between positive TST and residing in North America. Finally, we conclude with recommendations for improved data gathering in order to strengthen future research.

1. Methods

Our data is drawn from 318 Macalester students (311 international students, 7 US citizens born abroad) tested for tuberculosis via Mantoux/PPD tests during the years 2004-2008. The variables in the data set are as follows:

- **TST** indicates the student's PPD test result based on Table 1.
- **Africa, Asia, Central America, Europe, European Union, Middle East, North America, Oceania, South America, and The Caribbean** are indicators of regions in which each student; see appendix. The Europe region consists of the European countries that are not in the European Union.
- **BCG** is an indicator of whether or not the student had a history of BCG vaccination.
- **Year** indicates the academic year in which the student was tested.

We compiled an Excel spreadsheet from anonymous paper records provided by Winton Health Services and validated the inputted information by randomly checking 10% of the data. We then used the statistical programming language **R** to analyze the data. We chose TST as the response variable. Because of the dichotomous nature of our response variable, we used logistic regression to model the probability P of positive TST, as defined by the protocol given in Table 1. In logistic regression, we use the model $P = \frac{e^{(b+m_1x_1+\dots+m_kx_k)}}{1+e^{(b+m_1x_1+\dots+m_kx_k)}}$ where $x_1\dots x_k$ are explanatory variables and $b, m_1\dots m_k$ are coefficients to be estimated by the method of maximum likelihood^[10]. For

example, if x_1 =Africa, x_2 =Asia, and so forth, then $x_j=1$ for each region the student has lived in and $x_j=0$ for each region in which the student has not lived. Using the estimated
125 coefficients will yield the estimated probability of a positive TST for a particular student.

2. Results

Here we summarize results for our sample of 318 students (see Table 2). Of 317 students (1 missing data point), 165 (52%) had a positive TST. Out of 250 students (68 missing data points representing students unable to recall their BCG history), 156
130 (62.4%) were vaccinated with BCG when they were younger. Of the 156 students who received the BCG vaccine, 78 tested positive (50%), with one missing data point. Of the 94 students who did not receive the BCG vaccine, 48 tested positive (51.1%).

To test for a statistically significant relationship between the TST result and the BCG vaccine, we used logistic regression to model the probability of a positive TST given history of BCG vaccination. The coefficient on BCG indicates a negative, but
135 statistically insignificant ($p=0.910$), relationship between vaccine history and a positive TST (see Table 3).

To examine the relationship between the TST result and region of residency, we used logistic regression to model the probability of a positive TST given region(s) lived
140 in. We find three significant relationships; having resided in the European Union ($p=0.00502$) and the Middle East ($p=0.00451$) prove to have significantly negative relationships with having a positive TST, while having resided in North America ($p=0.00151$) has a significantly positive relationship (see Table 4). We discuss this surprising finding in the next section.

145 We also compare the probability of a positive TST given that a student has or has
not resided in a particular region as calculated using simple data proportions to the
probability of a positive TST given that the student has only resided in that particular
region, as calculated using logistic regression (see Table 5). The first two columns of
Table 5 do not control for the other countries the student has lived in, while logistic
150 regression, column 3, does. As an example, consider the region Africa. 127 students
neither lived in Africa, nor had a positive TST. Another 127 students did not live in
Africa, but had a positive TST. 22 students both lived in Africa and had a positive TST.
18 students lived in Africa but did have a positive TST. In order to calculate the
conditional probability of testing positive if the student has not lived in Africa, divide the
155 number of students who neither lived in Africa nor tested positive (127) by the total
number of students who did not live in Africa (127+127). In order to calculate the
conditional probability of testing positive given the student has lived in Africa, divide the
number of students who both lived in Africa and tested positive (22) by the total number
of students who lived in Africa (18+22). These two probabilities can be seen in the first
160 row, first and second column of Table 5. Using the logistic regression based model
TST~Region, the probability of testing positive given that the student has only lived in
Africa is computed using the equation for P, as defined in the previous section.

The probability of positive TST if the student has not lived in a given region is
highest if s/he has not lived in the European Union. This probability is lowest if s/he has
165 not lived in North America. The probability of positive TST if the student has lived in a
given region is highest if s/he has lived in North America. The probability is lowest if
s/he has lived in the Middle East. Finally, the probability of positive TST if the student

has only lived in a given region is highest if s/he has only lived in North America. This probability is lowest if s/he has only lived in the Middle East (See Table 5).

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3. Comment

While a Mantoux/PPD skin test is a valuable tool, it has a number of limitations. Several factors can lead to a false-positive or a false-negative test result. Nontuberculous mycobacteria, the BCG vaccination, subjective interpretation of area of induration, and the administration of an incorrect antigen have been known to cause a false-positive test result. Cutaneous anergy (the inability to react to a skin test on account of a weakened immune system), a recent TB infection, a recent live-virus vaccination, overwhelming TB disease, certain viral illnesses (such as measles and chickenpox), incorrect method of administration (too little antigen or a subcutaneous injection), and an incorrect interpretation of the skin test result have all been known to cause a false-negative test result ^[1].

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Our results seem consistent with those of a previous study conducted at a Midwestern community college ^[9]. In the fall of 1997, 34% of the international students at the community college had a positive TST. This percentage increased to 60% in the spring of 1998 ^[9]. The positive test rate among Macalester's international students is, however, greater than the 22.9% positive test rate found in the early 1990's study orchestrated by the CDC/American College Health Association (ACHA) in their survey of international students among colleges and universities across the United States ^[11]. This 27.1% difference could be a result of the global increase in TB disease burden that has occurred over the past 10-15 years. A second conjecture is that Macalester's higher rates of

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190 positive TST simply reflect a higher proportion of students from regions with greater TB
burden and/or higher rates of BCG vaccination. This conjecture cannot, however, be
confirmed due to the unavailability of data from other colleges concerning students'
countries of residency. Nonetheless, earlier studies conducted in the 1980's calculated the
rate of positive skin test results among international students at three different colleges to
195 be around 50%, again similar to our result ^[12,13,14].

Of the 318 Macalester individuals evaluated, 156 had previously received the BCG
vaccine. As mentioned, this vaccine is only offered in countries where TB is endemic and
it is usually given sometime during childhood ^[3]. About 50% of the 156 individuals who
received the vaccine still had a positive TST. It is important to note that the BCG vaccine
200 can make one more sensitive to tuberculin, depending upon the strain of BCG used and
the group vaccinated ^[1]. That is, the BCG vaccine can, in some circumstances, cause a
false-positive reaction to a Mantoux/PPD skin test ^[15,16,17,18,19,7]. Previous studies have
shown that the BCG vaccine has a protective effect of 0-80%, lasting for at most 15 years
^[3,4]. The approximately 50% of Macalester students testing positive despite receiving the
205 vaccine therefore proves consistent with previous studies.

While the model of the relationship between positive TST and history of BCG
vaccine lacks statistical significance (see Table 3), in a model of positive TST and region
of residency, there are three geographic regions that have significant relationships with
positive TST (see Table 4). The European Union and the Middle East both have
210 significantly negative relationships with positive TST, while North America has a
significantly positive relationship with the response variable. In other words, our model
indicates that the probability of positive TST significantly decreases if the student has

lived in the European Union or the Middle East, but increases significantly if the patient has lived in North America.

215 While our sample is not an entirely true representation of the global population, considering the more privileged economic and social position of the average Macalester international student, we can make some general comparisons between rates of positive TST at Macalester and global TB incidence. The probability of contracting TB greatly increases in medically underserved, low-income populations including those with a high
220 prevalence of HIV, as well as among the homeless, prisoners, and injection drug users ^[1]. Considering that the average international student at Macalester does not come from such a community, the negative coefficient on the European Union and the Middle East are as expected. It seems surprising, however, that residing in North America (Canada, Greenland and the United States) correlates with a positive TST, considering that the
225 incidence of TB in North America is comparatively low. Of the 318 students tested, there were 52 students who had lived in North America. Of the 52, there were 7 students who only lived in North America, but who were born abroad, and all 7 resided permanently in the United States. These 7 students also had a positive TST. We conjecture that these 7 were only tested as a preliminary step of checking the status of a previous positive TST.
230 Alternatively, perhaps they contracted TB during infancy while abroad or became more susceptible to TB because they were born abroad. If either proved to be the case, it would explain the unexpected, significantly positive coefficient on North America.

As a result of our study, we make several recommendations for improved data gathering in order to strengthen future investigations. First, we recommend recording the
235 length of time spent within each country. With this information one could predict a more

accurate probability of testing positive based not only upon region but also upon the amount of time spent within each region. In order to better analyze the effectiveness of the preventive medication, INH, we recommend documenting when students opt to take INH. Finally, other risk factor information such as whether the student is HIV positive, 240 smokes more than 20 cigarettes a day, or has diabetes mellitus ought to be recorded, as these known factors increase one's likelihood of progressing to active tuberculosis [1].

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Appendix

Table 1. Classification of the Mantoux/PPD skin test reaction.

Diameter of induration after 48-72 hours: Skin Test Result:	< 5 mm	≥ 5 mm	≥ 10 mm	≥ 15 mm
	Negative	Positive if the patient:	Positive if the patient:	Positive in any person, including persons with no known risk factors for TB
		-Is immuno-deficient Or -Has had recent contact with someone with active TB Or -Has a chest x-ray showing fibrotic changes (scarring) from a previous TB infection	-Is a recent arrival (< 5 years) from a country where TB is considered endemic Or -Has lived in a congregate setting (camp, military, dorms, etc) Or - Is on immuno-suppressive drugs, for example, steroids, cancer therapy, or arthritis drugs	

Table 2. Breakdown of TST test results by BCG vaccine status.

	Did not receive BCG vaccine	Received BCG vaccine
Negative Mantoux/PPD (TST = 0)	46	77
Positive Mantoux/PPD	48	78

(TST = 1)

Table 3. A summary of the model TST~BCG, where BCGY indicates having received the shot.

Coefficients:

	Estimate	Std. Error	Z value	Pr (> z)
(Intercept)	0.04256	0.20633	0.206	0.837
BCGY	-0.02966	0.26150	-0.113	0.910

Table 4. A summary of the model TST~ Africa + Asia + Central America + Europe + European Union + Middle East + North America + Oceania + South America + Caribbean. The numbers in bold indicate the significant p-values for the model.

Coefficients:

	Estimate	Std. Error	Z value	Pr (> z)
(Intercept)	0.29773	0.33709	0.883	0.37712
Africa	0.13102	0.38691	0.339	0.73488
Asia	-0.20986	0.32012	-0.656	0.51210
Caribbean	-0.96622	0.55870	-1.729	0.08374
Central America	-0.21706	0.57469	-0.378	0.70565
Europe	0.34050	0.35045	0.972	0.33125
European Union	-0.92820	0.33082	-2.806	0.00502
Middle East	-1.44101	0.50737	-2.840	0.00451
North America	1.12278	0.35394	3.172	0.00151
Oceania	0.59970	0.81592	0.735	0.46234

South America -0.07267 0.63215 -0.115 0.90848

Table 5. Breakdown of probability of positive TST by region. The numbers in bold indicate the significant p-values for the model of TST by region.

Region	Probability of testing positive if the student has not lived in a given region	Probability of testing positive if the student has lived in a given region	Probability of testing positive if the student has only lived in a given region
Africa	0.5000	0.5500	0.6056
Asia	0.4936	0.5217	0.5220
Caribbean	0.5184	0.3636	0.3388
Central America	0.5054	0.5333	0.5202
Europe	0.5000	0.5370	0.6544
European Union	0.5434	0.4000	0.3474
Middle East	0.5240	0.3043	0.2417
North America	0.4669	0.6923	0.8054

Oceania	0.5035	0.6250	0.7104
South America	0.5018	0.6154	0.5560

Africa

Angola
Botswana
Burk Faso
Egypt
Ethiopia
Ghana
Ivory Coast
Kenya
Malawi
Mali
Morocco
Mozambique
Nigeria
Rwanda
South Africa
Senegal
Sierra Leone
Sudan
Swaziland
Tanzania
Uganda
Zambia
Zimbabwe

Asia

Afghanistan
Bangladesh
Cambodia
China
Georgia
Hong Kong
India
Indonesia
Japan
Kazakhstan
Korea
Malaysia
Mongolia
Nepal
Pakistan
Philippines
South Korea
Singapore
Sri Lanka
Taiwan
Thailand
Vietnam

Central America

Costa Rica
Guatemala
Honduras
Mexico
Nicaragua

Europe

Albania
Bosnia
Bulgaria
Croatia
Moldova
Norway
Romania
Russia
Serbia
Ukraine

European Union

Austria
Cyprus
Czech Republic
Denmark
Estonia
Finland
France
Germany
Greece
Hungary
Italy
Latvia
Netherlands
Poland
Slovakia
Spain
Sweden
Turkey
United Kingdom
 England
 Wales

Middle East

Iraq
Israel
Jordan
Lebanon
Oman
Palestine
Saudi Arabia
Syria
United Arab Emirates

North America

Canada
Greenland
United States

Oceania

Australia
Guam
New Zealand
Tahiti

South America

Argentina
Bolivia
Chile
Colombia
Ecuador
Peru
Uruguay

Caribbean

Antigua
Jamaica
Trinidad