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Time-To-Detection Of M. Tuberculosis As A Predictor Of Infectivity

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Time-to-Detection of *M. tuberculosis* as a predictor of infectivity

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Abstract

INTRODUCTION: Tuberculosis (TB) transmission continues to be problematic in the United States. Contact investigations are essential for identifying new infections and must prioritize limited resources by pursuing more infectious cases. Current infectivity measures like sputum smear grade, chest x-rays, and nucleic acid amplification tests (NAAT) are sub-optimal. Time-to-detection (TTD) of *Mycobacterium tuberculosis* in liquid culture has shown promising results.

OBJECTIVES: Our objective is to examine the relationship between TTD and TB transmission.

METHODS: This study examined a retrospective cohort of pulmonary TB cases with TTD data from 2009-2014 from the King County Laboratory, Seattle, WA. The primary outcome was transmission indicated by previously undiagnosed latent tuberculosis infection (LTBI) in household contacts. The proportion of contacts positive for LTBI was modeled using Poisson regression. TTD, highest smear grade, NAAT, and chest x-ray were assessed for their association with LTBI in contacts.

RESULTS: Of 390 pulmonary TB cases, 92 had TTD and household transmission data. Overall, 76.1% of them had evidence of household transmission. Among all household contacts, 36.5% (187/512) had previously undiagnosed LTBI, including 33% of contacts related to cases with long TTD and 30% with negative smears. Short (0-7 days) TTD was significantly associated with increased LTBI risk compared to long TTD (15+ days) (RR: 1.39; MH X^2 p-value: 0.025) and medium TTD (RR: 1.36; MH X^2 p-value: 0.023). However Poisson modeling of transmission rates did not demonstrate a significant relationship. Multivariate analyses adjusted for highest smear, NAAT, and chest x-ray were also non-significant. All cases with short TTD were smear positive, but positive smears identified 60% more transmission events.

CONCLUSIONS: In this limited study, short TTD was not a promising addition to current infectivity measures. Observational studies of TB transmission are difficult when there are high background rates of LTBI. Any future studies should take place in previously TB-naïve households.

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Introduction

Worldwide, 9.6 million people are estimated to have fallen ill with tuberculosis (TB) in 2014 for a global average of 133 incident cases per 100,000 population[1]. In the United States, 9,421 cases were identified in 2014 with an incidence rate of 3.0 cases per 100,000 population[2]. In low-incidence settings, TB control programs are able to focus on TB elimination, as well as controlling TB disease, by targeting latent TB infection (LTBI).

Contact investigations are important tools for infection control in low-incidence countries[3]. Investigations begin with an index case of TB disease and work to identify any contacts who may have developed LTBI and are at risk for progressing to TB disease or those who already have developed TB disease (referred to as secondary cases). The probability of transmission of TB depends on the infectiousness of the case, intensity of exposure, and susceptibility of contacts[3]. These factors must all be taken into consideration; yet a wide-cast net can yield a very small number of newly acquired LTBI or secondary cases per contact screened[4]. US-based investigations that focus on the contacts of culture-confirmed pulmonary cases can yield fewer than 1% secondary cases and 21% with LTBI[5]. Contact investigations are resource and time-consuming. Public health entities need to be able to prioritize contact investigations that are more likely to yield newly infected contacts. This prioritization hinges on the perceived infectiousness of the case[6,7].

TB transmission depends on the patient's ability to aerosolize bacilli and transmit *Mycobacterium tuberculosis* (MTB)[6,7]. When identified, patients suspected of having TB are evaluated for pulmonary disease. Clinicians then rely on four diagnostic tests to determine infectiousness: sputum smear microscopy, chest radiography, nucleic acid amplification testing (NAAT), and sputum culture.

Sputum smear microscopy has been the most common measure of infectivity. High smear grade is associated with a high burden of disease[8,9]. TB is more prevalent among contacts of heavily smear-positive patients (with sputum smears in the 3+ and 4+ range) than smear-negative patients[7,9,10]. Yet sputum smear sensitivity ranges from 22 to 80% for TB disease[11]. In the US, contact investigations of smear-positive patients have shown 1% of evaluated contacts developing active TB and 27% of contacts contracting LTBI[5].

Additionally, a smear-negative result does not indicate a lack of infectiousness. Across studies, approximately 50% of all cases of pulmonary TB, regardless of HIV status, are smear-negative[12,13]. Studies have estimated that smear-negative, culture-positive cases account for 13 to 18% of secondary cases and 25 to 39% of LTBI among contacts[14-16]. Thus a negative sputum smear result alone does not represent an insignificant transmission risk. Sputum smear results also do not distinguish MTB from other mycobacterial species, viable from unviable organisms, and depend on the patient, the type and degree of pulmonary involvement, the quality of the sputum sample collected, and the skill of the microscopist[11,17,18].

Chest radiography is also considered when determining whether and how to conduct contact investigations. Cavitary lesions visible on x-rays represent the largest number of bacilli[3,19]. A greater presence and extent of cavitary lesions, density of lesions, and amount of lung involved correlate with higher burden of disease[19]. However, chest x-ray interpretations have been shown to be variable across clinicians and TB specialists[20]. There has been work to standardize a chest x-ray reading and recording system; however, it has not been implemented widely[21]. Additionally, HIV positive individuals are less likely to have cavitary disease[22] and patients with diabetes mellitus tend to have atypical chest x-ray presentations[23].

NAATs, such as the Xpert MTB/RIF test, are more specific than microscopy and also faster[24]. A recent meta-analysis that evaluated 125 studies reported pooled sensitivity and specificity to be 85 and 97%, respectively[25]. However, both measures varied significantly across studies, so much so that the

authors concluded that "summary measures of diagnostic accuracy are not clinically meaningful"[25]. NAAT does not differentiate between viable, dormant, and non-viable intact MTB bacilli shed during effective TB treatment[26]. Additionally, NAAT is not consistently used by providers despite being recommended by the CDC because of concerns of cost-effectiveness in high-income, low-incidence settings[27,28].

Culture has been used as the gold standard for TB disease diagnosis. It is the most sensitive method for TB detection and requires fewer bacilli to produce a positive result[3]. Liquid culture methods, as compared to solid culture, have decreased culture time to as few as 2 days while still preserving sensitivity[29-31]. The decreased time-to-detection (TTD) for MTB in culture presents an opportunity for public health officials to have in-hand culture results while launching contact investigations.
In previous studies, TTD has been evaluated as a viable alternative to colony counting and thus an adept measure of bacillary load[32-34]. Pre-treatment TTD has been shown to be associated with other indicators of bacterial load and disease severity, including sputum smear grading, extensive parenchymal disease, and number of cavities on a chest x-ray[34-36]. Because short TTD correlates with other measures of greater bacillary load, TTD has the potential to be a new tool to measure infectivity. Already, TTD has been studied as an indicator for the length of respiratory isolation[18]. It has also been studied as a predictor for transmission to contacts[15].

This study seeks to build on the existing literature, which argues that short TTD is associated with high risk of TB transmission. Prior literature modeled transmission as a binary contact positivity variable whereas this study aims to look at the rate of positive contacts. This study also adjusts for contacts with prior positive TB screening results, something previous studies have not done.

Methods

Study Population

King County is the largest county in Washington with a population of approximately 2.1 million people. In King County, all TB cases are recorded on the Report of a Verified Case of Tuberculosis (RVCT) form, which is then stored in the Public Health Information Management System (PHIMS). Between 2009 and 2014, 672 cases of TB were counted in King County. For this study, we began by excluding 216 extrapulmonary-only TB cases, 7 cases diagnosed post-mortem, and 59 cases that were not culture confirmed via sputum or bronchiolar lavage specimens.

For the remaining 390 active pulmonary TB cases, we performed detailed medical record review, collecting data on the earliest specimen to produce a positive culture result (which is of most interest to contact investigations), the date of collection of the specimen, the smear grade associated with the specimen, the highest smear grade reported for any specimen, and the date the highest smear grade specimen was collected.

Based on these data, we observed inconsistent reporting across laboratories of the date a specimen was tested versus date reported. To eliminate interlab variability which could affect measurement of the independent variable, only King County Laboratory reports were considered and medical record data was extracted for the first culture-positive specimen at the King County Lab. Additional exclusion criteria included specimens in which organisms other than MTB were found, specimens with a lab error, lab records that could not be located, and cases that did not have a King County Lab record. Specimens with no growth and therefore no time-to-detection (TTD) were also excluded. If the first culture-positive specimen was excluded, the case was also excluded. Finally, specimens collected after anti-TB treatment was begun were excluded from TTD analysis so as to prevent the effect of slower growth from treatment. The final cohort of individuals with culture growth and who were not yet receiving anti-TB treatment totaled 124 individuals [**Figure 1**].

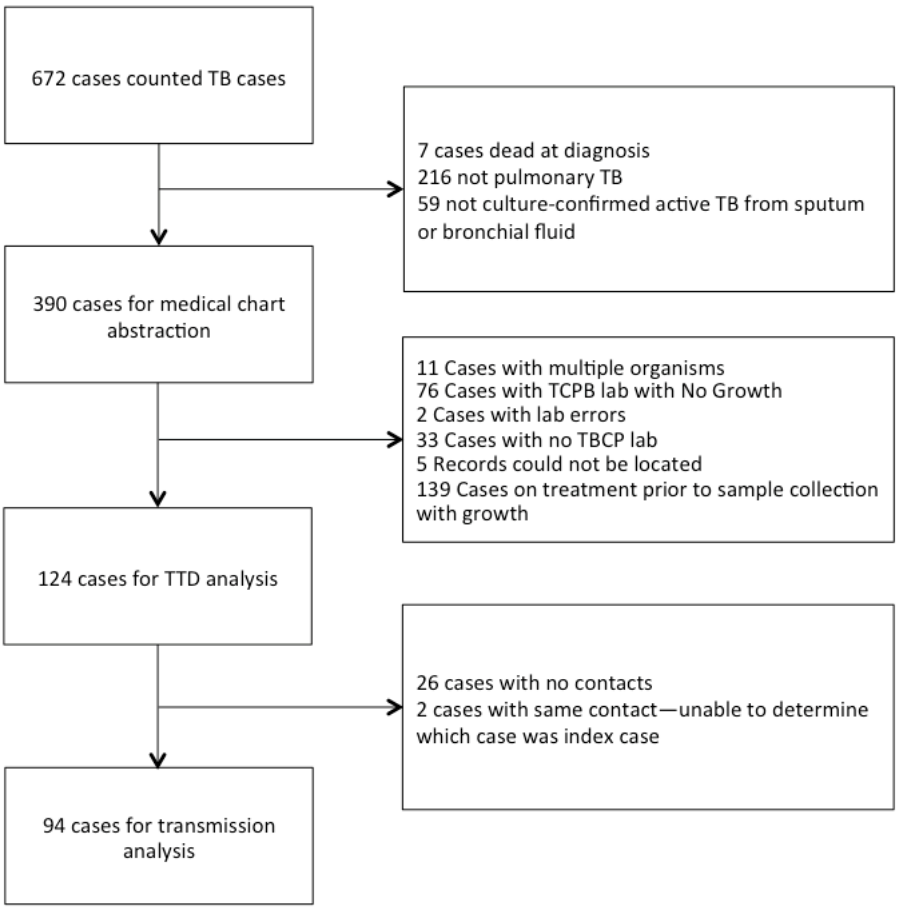

Figure 1: Study Population for TTD Analysis

Measures

The primary independent variable of interest was time-to-detection (TTD). Using King County Lab Report data, TTD was calculated as the date the sample was tested by smear microscopy—at which time aliquots are put into culture—to the date the preliminary acid-fast bacilli (AFB) culture result was tested. If there was no report of a preliminary AFB culture, the final culture testing date was used.

Consistent with the previous study, we treated TTD as a dichotomous variable (<9 days or >=9 days as used in O'Shea et al.)[15]. In addition, given that there is relatively little research on TTD as a predictor of infectivity, we explored TTD as continuous and categorical. The categorical cut points of 0-7 days, 8-14 days, and 15+ days follow week intervals. The shorter TTD is, the more useful it is for informing contact investigation strategies when they begin. Thus the first two weeks were distinguished from any other time frame.

In addition, highest smear grade reported for any specimen was extracted from medical record data. Smear grade was categorized as a 3-level variable: negative/indeterminate, 1+/2+, and 3+/4+.

Additional clinical variables extracted from the PHIMS RVCT records included diagnostic results of NAAT and radiographic grade of chest x-ray. Radiographic grade of chest x-ray was conducted by two expert TB specialists and reported via the RVCT form. The chest x-ray variable combined 3 surveillance variables from the RVCT form and categorized the results as (1) normal x-ray, (2) abnormal, non-cavitary x-ray, and (3) cavitary x-ray. One case in the sample demonstrated a miliary x-ray and was classified as

abnormal, non-cavitary for this study after a second expert review by the same specialists. Other clinical variables extracted from the PHIMS database include extrapulmonary TB disease, previous TB diagnosis, HIV status, diabetes, TNF-alpha antagonist therapy, end-stage renal disease, immunosuppression (non HIV/AIDS), and post-organ transplantation.

Sociodemographic covariates were also extracted from the PHIMS database and included age, sex, place of birth, and race/ethnicity.

The dependent variable of interest was LTBI infection in contacts of a case. Contacts of cases were identified following the King County TB Control Program protocol using the concentric circle approach. Contact data were recorded in a county-controlled MS Access database. Exclusion criteria included contacts with no record of a tuberculin skin test (TST) or QuanitFERON-TB Gold test (QFT) result, individuals with a positive TST 2 or more months prior to the case starting anti-TB treatment, and contacts with a known prior positive QFT. The remaining susceptible contacts were considered positive for LTBI if they were QFT- or TST-positive (induration >=5 mm).

Primary analysis focused on household contacts of cases to better isolate true transmission events. Secondary analyses expanded the contact pool to include household contacts and all contacts exposed in the workplace, school, nursing home, shelter, jail, and "other" locations [**Figure 2**].

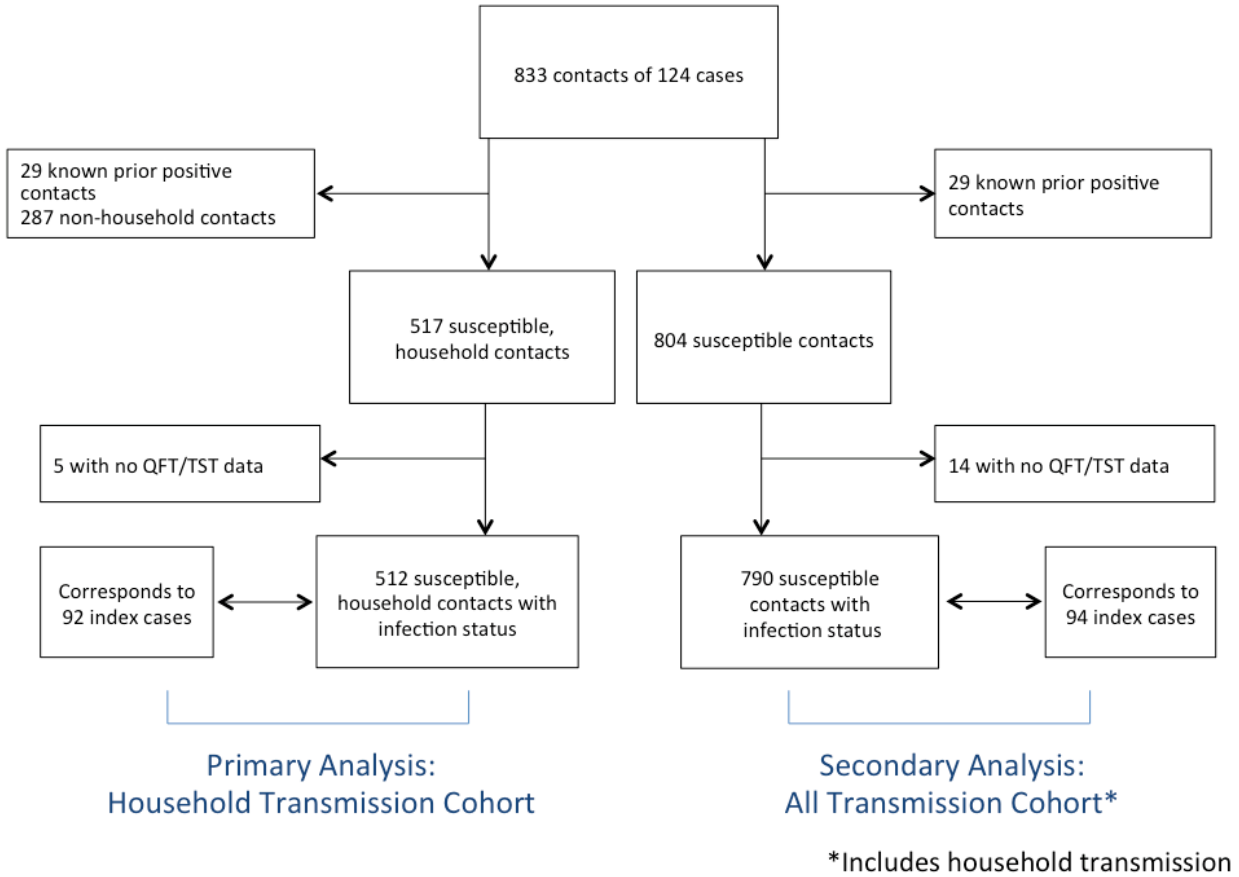

Figure 2. Study Population for Transmission Analysis

Laboratory Methods

Samples were assessed via smear microscopy using two methods: the direct microscopy Carbolfuchsin method using the Ziehl-Neelsen hot acid-fast stain, and the fluorescent microscopy

method which uses auramine stain in the Morse, Blair, Weiser and Sproat fluorescent procedure. Samples were cultured for up to 56 days using the BACTEC MGIT 960 Mycobacterial Growth Indicator Tube system (Becton Dickinson; Franklin Lakes, NJ). Cultures were then assessed for colony identification using Gen-Probe AccuProbe for MTB. TTD was defined in days from the date the specimen was plated for microscopy, at which time aliquots were created and inoculated into culture, to the date the specimen demonstrated sufficient fluorescence to trigger the growth detection system. King County Laboratory conducted smear microscopy and specimen culture and identification. The Washington State Lab conducted all Nucleic Acid Amplification Testing (NAAT) using real-time PCR that targets insertion sequence 6110.

Statistical Analysis

We explored TTD as continuous, binary, and categorical in the correlation analyses that compared TTD with the existing infectivity measures: highest smear grade, chest x-ray, and NAAT. We used Spearman's rank correlation to assess the correlation between TTD (modeled as a continuous variable) and existing diagnostic tests (smear grade, chest radiographic grade, and NAAT). When modeling TTD as a categorical variable, chi-square tests and Fisher's exact tests were used. Sample characteristics were also evaluated using chi-square test or Fisher's exact test when expected cell counts were <5.

We decided *a priori* that in the transmission model, TTD would be modeled by weeks (0-7 days, 8-14 days, and 14+ days) as these categories had the greatest practical relevance to a clinical setting. Contact investigations usually begin following a positive NAAT or culture result, with some exceptions. NAAT is much more expedient, with results coming back in days rather than weeks. Thus contact investigations can begin soon after the initial specimens are collected. For TTD to be most useful in informing a contact investigation and raising suspicion of transmission, clinicians would want to know whether MTB grew within the first two weeks, with a greater importance given to cultures that grow in the first week.

We stratified case characteristics by TTD and assessed for statistical differences using chi-square and Fisher's exact tests. We did the same for contact characteristics. We also modeled the relationship between contact characteristics and LTBI status using logarithmic regression.

The number of LTBI-positive contacts was tabulated as count data for each case. Total contacts evaluated per case were also tabulated. The transmission event rate—indicated by the proportion of contacts positive for LTBI per case—was modeled using Poisson regression with the Pearson's chi-square statistic adjustment for overdispersion. The number of LTBI-positive contacts was the numerator; number of total contacts was the denominator; and the natural log of the total number of contacts was the offset term.

First, we did univariate analysis using Mantel-Haenszel chi-square tests to examine the relationship between the total number of LTBI-positive contacts and TTD, smear grade, NAAT, and chest radiographic grade. Second, Poisson regression was used to analyze the univariate association between transmission event rate and TTD, smear grade, NAAT, and chest radiographic grade. Third, we analyzed multivariate Poisson models that included TTD in combination with the three other tests, to determine the added value of TTD. A final model included all of the tests. We also introduced case characteristics—specifically sex, HIV status, and age—into each model and assessed the impact.

All statistical analyses were conducted using the SAS 9.3 software package.

Results

Sample Characteristics

A total of 124 out of 390 (31.8%) active pulmonary TB cases were included for TTD analysis. These cases had MTB culture growth in the King County Lab prior to beginning anti-TB treatment. Mean age of the group was 46.3 years old; 62.9% of the group was male [**Table 1A**]. A large proportion of the sample was foreign-born (86.3%), with the predominant ethnic group being non-Hispanic Asian (62.1%). Age, sex, place of birth, and race/ethnicity did not vary significantly by TTD in weeks.

Characteristics of TB disease such as highest sputum smear grade and NAAT did vary significantly by TTD in weeks (p-values: <.001 and 0.011, respectively) [**Table 1B**]. Highest sputum smear grade followed a bimodal distribution with the two largest categories being "Negative" smear grade (30.7%) and 4+ smear grade (28.2%). Overall, 63.7% of the sample was NAAT-positive; however, a considerable proportion of cases did not have a NAAT result (21.8%). Chest radiographic grade did not vary significantly by TTD in weeks.

Risk factors for disease were also examined. The most prevalent risk factor in the sample was diabetes (19.4%) but it did not vary significantly by TTD in weeks. Nine cases had extrapulmonary TB disease in addition to their pulmonary TB; 9 had been previously diagnosed with TB; 2 cases were HIV positive; 1 case had end-stage renal disease, and 3 cases had immunosuppression that was not related to HIV/AIDS. None of these risk factors were associated with TTD in weeks. No individuals in the sample had TNF-alpha antagonist therapy or post-organ transplantation.

Table 1A. Characteristics of Cases with Culture Growth and No Treatment by TTD (N=124)

Characteristic	Totals		Time-to-Detection			P-Value
	N	%	0-7 days	8-14 days	15+ days	
Age						0.790 *
0-14	2	1.6	0	1	1	
15-24	18	14.5	1	6	11	
25-44	46	37.1	7	17	22	
45-64	30	24.2	4	12	14	
>=65	28	22.6	5	14	9	
Sex						
Male	78	62.9	11	34	33	0.562
Female	46	37.1	6	16	24	
Place of birth						0.106
USA	17	13.7	1	11	5	
Outside USA	107	86.3	16	39	52	
Race/Ethnicity						0.420 *
Non-Hispanic White	12	9.7	1	8	3	
Hispanic or Latino	8	6.5	2	3	3	
Non-Hispanic Black or African American	25	20.2	4	8	13	
Non-Hispanic Asian, Native Hawaiian or Other Pacific Islander	79	63.7	10	31	38	

*Indicates Fisher's Exact Test; otherwise Chi-Squared test was used

Table 1B. Characteristics of Diagnostic Tests by TTD (N=124)

Characteristic	Totals		Time-to-Detection			P-Value
	N	%	0-7 days	8-14 days	15+ days	
Highest Sputum Smear Grade						**<.001** *
Negative	38	30.7	0	10	28	
Inconclusive	10	8.1	0	7	3	
1+	18	14.5	1	8	9	
2+	12	9.7	1	6	5	
3+	11	8.9	3	6	2	
4+	35	28.2	12	13	10	
Chest radiographic grade (N=117)						0.842 *
Normal	2	1.7	0	1	1	
Abnormal, Not cavitary**	87	74.3	11	33	43	
Abnormal, Cavitary	28	23.9	5	12	11	
NAAT (N=96)						**0.037** *
Negative	17	17.7	0	6	11	
Positive	79	82.3	12	39	28	

*Indicates Fisher's Exact Test; otherwise Chi-Squared test was used
**Includes miliary case (N=1)

TTD Distribution

Among 124 cases of active pulmonary TB, TTD ranged from 3 days to 63 days. Median was 14 days and mean was 16.3 days (standard deviation: 9.6). The distribution was skewed right [**Figure 3**].

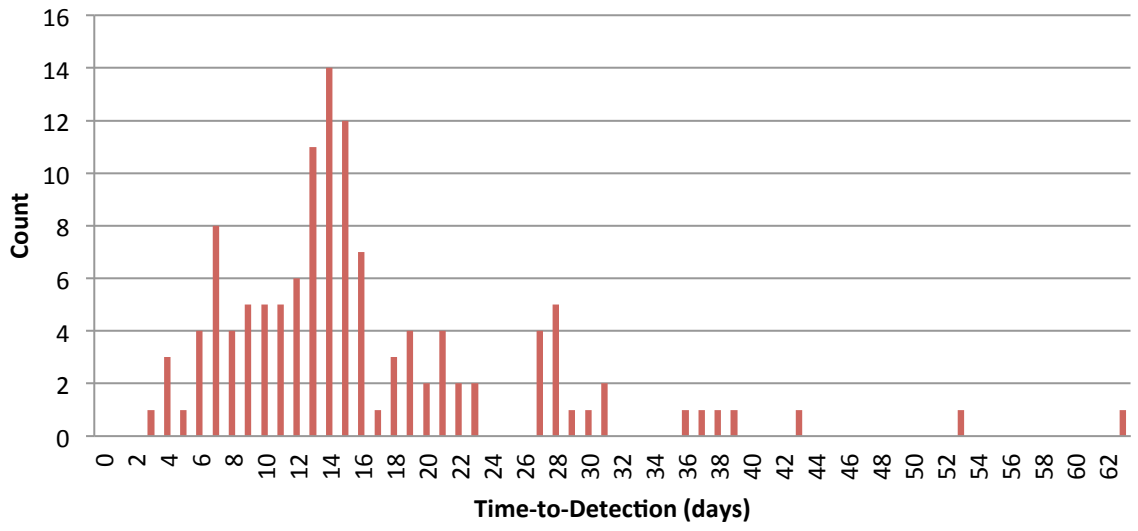

Figure 3. Distribution of TTD in Case Cohort with Culture Growth and No Treatment (N=124)

For this study, TTD was categorized into a 3-level categorical variable. A previous study followed a dichotomization approach[15]. Distributions within each category are noted in **Table 2A** and **2B**.

Table 2A and B. Number of Cases by two TTD Categorization Schemes (Categorical and Dichotomous); N=124

TTD by weeks	N	%
1-7 days	17	13.71
8-14 days	50	40.32
15+ days	57	45.97

TTD Category	N	%
<9 days	21	16.94
>=9 days	103	83.06

For transmission analysis, the cohort was limited to 92 cases with household contacts. In this cohort, TTD ranged from 3 to 43 days. Median was 13 days and mean was 14.4 (days standard deviation: 7.7). The distribution was still skewed right yet had fewer outliers [**Figure 4**].

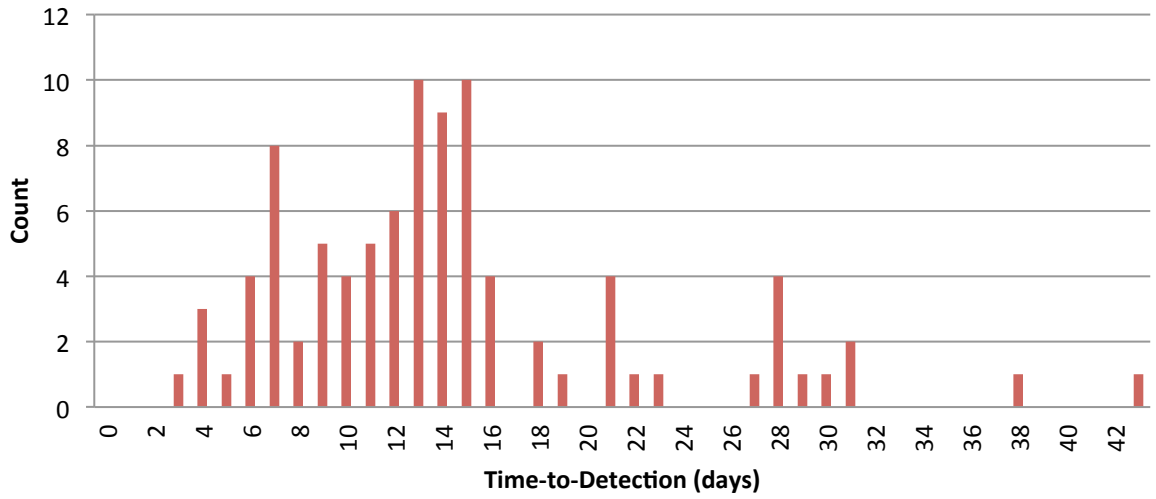

Figure 4. Distribution of TTD in Household Transmission Cohort (N=92)

TTD categorization by week followed a similar but more normalized distribution as with the TTD analysis cohort (N=124) [**Table 3A and 3B**].

Table 3A and B. Number of Cases with Household Contacts by TTD Categories; N=92

TTD by weeks	N	%
1-7 days	17	18.48
8-14 days	41	44.57
15+ days	34	36.96

TTD Category	N	%
<9 days	19	20.65
>=9 days	73	79.35

Correlation Between TTD and Smear Grade/Chest X-Ray/NAAT

Among cases with culture growth that had yet to undergo anti-TB treatment (N=124), TTD modeled as continuous [**Table 4A**], binary [**Table 4B**], and categorical [**Table 4C**] all correlated significantly with highest sputum smear grade. Chest x-ray (described as a 3-level variable: normal; abnormal, not cavitary; and abnormal, cavitary) did not correlate with any of the TTD categorizations. NAAT demonstrated a significant correlation with TTD as a continuous and 3-level variable, but not with the dichotomous variable.

Table 4A. Correlation between TTD (Continuous) and Diagnostic Tests

	Correlation coefficient	P-Value
Highest Smear grade (N=124)	-0.41796	**<.001**
Chest X-ray (N=117)	-0.09674	0.300
NAAT (N=96)	-0.2216	**0.030**

*Spearman's correlation for nonparametric variables

Table 4B. Correlation between TTD (Dichotomous) and Diagnostic Tests

	Table Value	P-Value
Highest Smear grade (N=124)	3.44E-07	**0.001***
Chest X-ray (N=117)	0.0607	0.403*
NAAT (N=96)	0.0412	0.065*

*Indicates Fisher's Exact Test; otherwise Chi-Squared test was used

Table 4C. Correlation between TTD (Categorical) and Diagnostic Tests

	Table Value	P-Value
Highest Smear grade (N=124)	1.77E-13	**<.001***
Chest X-ray (N=117)	0.0098	0.842*
NAAT (N=96)	6.1221	**0.047**

*Indicates Fisher's Exact Test; otherwise Chi-Squared test was used

Also of note, the smear grade of the TTD specimen significantly correlated with highest smear grade but the correlation was not perfect (Spearman's correlation coefficient: 0.668, p-value: <.001). There were instances in which the smear grade associated with the TTD specimen was negative yet the highest smear grade archived was a 4+.

Transmission Analysis

Transmission was analyzed using two contact groups: household contacts only and all contacts. Out of 124 cases, 94 (75.8%) had 790 total susceptible contacts (either household or non-household) that completed screening [**Table 5A**]. Of these, 92 (97.9%) cases had household contacts (N=512); 16 of the 94 (17.0%) cases had non-household contacts (N=278). The household contact cohort is considered the most accurate representation of true transmission and is the primary focus of analysis. All contacts are parsed out by household or non-household contacts in **Table 5B**.

Table 5A. Total Number of Contacts by TTD Week

	All Contacts				
	Total Cases		Total Contacts		Contacts per case
	N	%	N	%	Mean
Time-to-Detection					
0-7 days	17	18.1	191	24.2	11.2
8-14 days	41	43.6	269	34.1	6.6
15+ days	36	38.3	330	41.8	9.2
	94		790		8.4

ANOVA F-Test of means p-value: 0.3815

Across all contacts, short TTD was associated with the greatest number of identified contacts followed by long TTD and then medium TTD (11.2, 9.2, and 6.6, respectively), however this relationship was not significant [**Table 5A**].

Table 5B. Number of Contacts by TTD Week—Stratified by Contact Type

	Household Contacts Only					Non-Household Contacts Only				
	Cases with Household Contacts		Household Contacts		Contacts per case	Cases with Non-Household Contacts		Non-Household Contacts		Contacts per case
	N	%	N	%	Mean	N	%	N	%	Mean
Time-to-Detection										
0-7 days	17	18.1	131	25.6	7.7	3	18.8	60	21.6	20.0
8-14 days	41	43.6	223	43.6	5.4	5	31.3	46	16.6	9.2
15+ days	34	38.3	158	30.9	4.6	8	50.0	172	61.9	21.5
	92		512		5.6	16		278		17.4

ANOVA F-Test of means p-value: 0.0609 ANOVA F-Test of means p-value: 0.6582

Household contacts stratified by case TTD show that cases with short TTD had the highest average number of identified contacts [**Table 5B**]. Across all cases, the mean number of household contacts identified per case was 5.6 contacts/case. Cases with short (0-7 days), medium (8-14 days), and long TTD (15+ days) had an average of 7.7, 5.4, and 4.6 identified household contacts per case, respectively. Non-household contacts do not show this same relationship and instead the greatest number of identified contacts per case occurs in the long TTD strata (21.5 contacts/case), followed by short TTD and medium TTD with 20.0 and 9.2 contacts/case, respectively.

In contrast to the original cohort, the cohort with household transmission data showed a significant association between place of birth (US-born vs foreign-born) and TTD (p-value: 0.027), with median TTD being disproportionately represented among the 9 US-born cases [**Table 6A**]. Demographic characteristics such as age, sex, and race/ethnicity were also not significantly associated with TTD.

Similar to the original cohort of 124 cases, the cohort limited to those with household transmission data demonstrated a significant association between TTD in weeks and highest sputum smear grade (p-value: 0.003) [**Table 6B**]. NAAT was no longer significantly associated with TTD (p-value: 0.294). Chest radiographic grade continued to not be significantly associated with TTD.

Table 6A. Characteristics of Cases with Household Transmission Data (N=92)

Characteristic	TOTALS		Time-to-Detection			P Value
	N	%	0-7 days	8-14 days	15+ days	
Age						0.725 *
0-14	1	1.1	0	1	0	
15-24	9	9.8	1	3	5	
25-44	40	43.5	7	17	16	
45-64	22	23.9	4	9	9	
>=65	20	21.7	5	11	4	
Sex						
Male	59	64.1	11	29	19	0.410
Female	33	35.9	6	12	15	
Place of birth						**0.015** *
USA	9	9.8	1	7	1	
Outside USA	83	90.2	16	34	33	
Race/Ethnicity						0.707 *
Non-Hispanic White	7	7.6	1	5	1	
Hispanic or Latino	7	7.6	2	3	2	
Non-Hispanic Black or African American	18	19.6	4	6	8	
Non-Hispanic Asian, Native Hawaiian or Other Pacific Islander	60	65.2	10	27	23	

*Indicates Fisher's Exact Test; otherwise Chi-Squared test was used

Table 6B. Characteristics of Diagnostic Tests by TTD among Cases with Household Transmission Data (N=124)

Characteristic	TOTALS		Time-to-Detection			P Value
	N	%	0-7 days	8-14 days	15+ days	
Highest Sputum Smear Grade						**0.003** *
Negative	16	17.4	0	4	12	
Inconclusive	8	8.7	0	6	2	
1+	14	15.2	1	7	6	
2+	12	13.0	1	6	5	
3+	10	10.9	3	6	1	
4+	32	34.8	12	12	8	
Chest radiographic grade (N=87)						0.984 *
Normal	2	2.3	0	1	1	
Abnormal, Not cavitary**	60	69.0	11	25	24	
Abnormal, Cavitary	25	28.7	5	11	9	
NAAT (N=74)						0.294 *
Negative	11	14.9	0	6	5	
Positive	63	85.1	12	33	18	

*Indicates Fisher's Exact Test; otherwise Chi-Squared test was used
**Includes miliary case (N=1)

Risk factors for disease present in the cohort included extrapulmonary TB disease, previous TB diagnosis, HIV, diabetes, and non-HIV/AIDS immunosuppression. Diabetes was the most prevalent risk

factor (20.7%). Extrapulmonary TB disease (5 cases), previous TB diagnosis (6 cases), HIV (2 cases) and immunosuppression (2 cases) were uncommon. No risk factor was significantly associated with TTD.

Household contacts were significantly more likely to be infected if they were older (p-value: <.001) [**Table 7**]. Contacts who were 25-44, 45-64, and 65+ years old experienced 2.65, 3.35, 3.87 times the odds of being infected, respectively, as compared to contacts younger than 15. Household contact infection rates also varied significantly along racial/ethnic lines. Non-Hispanic blacks experienced 2.76 times the odds of being infected as compared to Non-Hispanic whites (95% CI: 1.19-6.38). Non-Hispanic Asian, Hawaiian, or other Pacific Islander experienced 3.46 times the odds (95% CI: 1.74-6.89). Household contacts were also more likely to be foreign-born (59.2%) and foreign-born contacts were 8.61 times as likely to be infected as US-born contacts (95% CI: 5.66-13.09).

Table 7. Characteristics of Household Contacts (N=512)

Contact Characteristic	Contacts		TB Infection Status			Likelihood of Infection		
			Infected		P-Value	Odds Ratio	95% CI	
	N	%	N	Row %			Lower	Upper
Age (N=760)					**<.001**			
0-14	137	17.3	29	21.2		Reference		
15-24	200	25.3	32	16.0		0.71	0.41	1.24
25-44	200	25.3	77	38.5		2.33	1.42	3.84
45-64	138	17.5	54	39.1		2.39	1.40	4.08
>=65	85	10.8	29	34.1		1.93	1.05	3.54
Sex (N=784)					0.145			
Male	365	46.6	113	31.0		1.26	0.92	1.72
Female	419	53.4	110	26.3		Reference		
Race (N=704)					**<.001**			
Non-Hispanic White	149	21.2	14	9.4		Reference		
Hispanic or Latino White	58	8.2	9	15.5		1.77	0.72	4.35
Non-Hispanic Black or African American	79	11.2	27	35.2		5.01	2.44	10.29
Non-Hispanic Asian, Hawaiian or Other Pacific Islander	396	56.3	158	39.9		6.40	3.56	11.50
Other*	22	3.1	6	27.3		3.62	1.22	10.73
Place of birth (N=790)					**<.001**			
USA	334	42.3	31	9.28		Reference		
Outside USA	393	49.8	184	46.82		8.61	5.66	13.09
Unknown	63	8.0	10	15.87		1.84	0.85	3.98
Contact Place Exposed (N=7T90)					**<.001**			
Other	57	7.2	3	5.3		0.10	0.03	0.31
Private Residence	512	64.8	187	36.5		Reference		
School	150	19.0	14	9.3		0.18	0.10	0.32
Shelter/Single Residence Occupancy	8	1.0	1	12.5		0.25	0.03	2.03
Work	63	8.0	20	31.8		0.81	0.46	1.42
Household Contact (N=790)								
Household Contact	512	64.8	187	36.5		3.63	2.47	5.35
Non-Household Contact	278	35.2	38	13.7		Reference		
HIV Positive (N=790)	3	0.4	2	66.7	0.197	5.06	0.46	56.06

P-values calculated using chi-square or Fisher's exact test. Odds ratios calculated using logistic regression.
*Other race includes Native, Other, Mixed Race, and Hispanic Asian

Among household contacts, the aggregate LTBI prevalence was 36.5% (187/512). Among all contacts, including non-household contacts, the aggregate LTBI prevalence was smaller at 28.5% (225/790).

Our initial examination of the bivariate relationships between proportion of LTBI among contacts and the diagnostic test were examined using naïve Mantel-Haenszel chi-square tests. The proportion of LTBI-positive household contacts for short, medium, and long case TTD was 45.8%, 33.6%, and 32.9%, respectively [**Table 8**]. Contacts of cases with short TTD (0-7 days) were 39.2% more likely to be infected than the contacts of cases with long TTD (15+ days), and this relationship was significant (p-value 0.025). Contacts of cases with short TTD were also 36.2% more likely to be infected than those of medium TTD cases (p-value: 0.023).

Short TTD appears to identify the greatest proportion of LTBI-positive contacts (45.8%) in comparison to a highly positive 3+/4+ smear (40.8%) or any positive smear (38.4%) [**Table 8**]. However, short TTD only identified 60 LTBI-positive contacts whereas 3+/4+ smear identified 113 LTBI-positive contacts, including 57/60 of the short TTD contacts. Any positive smear identified 155 LTBI-positive contacts including all positive short TTD contacts.

Table 8. LTBI Among Household Contacts by Case Characteristics

Case Characteristic	LTBI-Positive Contacts	Total Contacts	LTBI-Positive Contacts (Row %)	Rate Ratio	P-Value
All Cases	187	512	36.5		
Time-To-Detection					
0-7 days	60	131	45.8	1.392	**0.025**
8-14 days	75	223	33.6	1.022	0.883
15+ days	52	158	32.9	Reference	
Smear					
Negative/Inconclusive	32	108	29.6	Reference	
1+/2+	42	127	33.1	1.116	0.572
3+/4+	113	277	40.8	1.377	**0.043**
Smear					
Negative	32	108	29.6	Reference	
Positive	155	404	38.4	1.295	**0.028**
Chest radiographic grade (N=487)					
Normal	1	3	33.3	Reference	
Abnormal, not cavitary	122	339	36.0	1.080	0.924
Abnormal, cavitary	63	145	43.4	1.303	0.727
NAAT (N=411)					
Negative	15	64	23.4	Reference	
Positive	129	347	37.2	1.586	**0.035**

P-values calculated using Mantel-Haenszel chi-square tests

When we reexamine these relationships using the final Poisson statistical model for the analysis, this time examining the percentage of cases that had at least one household contact, TTD was not significant (p-value: 0.087) [**Table 9; Model 1.1, Household Transmission**]. The difference in transmission rates between medium TTD and long TTD continued to be non-significant. Highest smear grade, chest radiographic grade, and NAAT results were also not significantly associated with household transmission in univariate analyses [**Table 9; Model 1.2-1.4, Household Transmission**].

In contrast, cases with short TTD and medium TTD were 63.0% and 50.3%, respectively, more likely to transmit to any contact (household or non-household) compared to long TTD and this

relationship was significant (p-value: 0.023 and 0.043, respectively) [**Table 9; Model 1.1 All Transmission**].

Short and medium TTD continued to be significantly associated with increased transmission to all contacts in bivariate models that adjusted for highest smear grade and chest radiographic grade [**Models 2.2, 2.3 All Transmission**] and that adjusted for NAAT and chest radiographic grade [**Model 3.3, All Transmission**]. In the trivariate model that adjusted for highest smear grade and chest radiographic grade, cases with medium TTD had a 54.2% higher rate of transmission to any contact than cases with long TTD, and this relationship was significant (p-value: 0.045) [**Model 3.1, All Transmission**].

In the full model, TTD week, adjusted for highest smear grade, chest radiographic grade, and NAAT result, was not significantly associated with household transmission [**Model 4.1, Household Transmission** in **Table 9]**. In the All Transmission model, cases with medium TTD, adjusted for highest smear grade, chest radiographic grade, and NAAT, were 71.0% more likely to transmit to any contact than cases with long TTD (p-value: 0.045) [**Model 4.1, All Transmission**]. However, a likelihood ratio test of all variables in the quadrivariate model demonstrated that no infectivity measure was a statistically significant predictor of all transmission.

Age, sex, and HIV status covariates were also included in the models detailed in Table 9, however their inclusion did not affect results thus they were not presented.

Table 9. Predictors of Transmission from Cases

Variable	Household Transmission (N=92)*		All Transmission (N=94)**	
	Rate Ratio	P-Value	Rate Ratio	P-Value
MODEL 1. UNIVARIATE MODELS				
Model 1.1.Transmission Rate = TTD				
Time to Detection				
0-7 days	1.392	0.087	1.630	**0.023**
8-14 days	1.022	0.906	1.503	**0.043**
15+ days	Reference		Reference	
Model 1.2. Transmission Rate = Smear				
Smear Grade				
Negative/Inconclusive	Reference		Reference	
1+/2+	1.116	0.646	0.655	0.120
3+/4+	1.377	0.118	1.088	0.714
Model 1.3.Transmission Rate = CXR				
Chest X-Ray				
Normal	Reference		Reference	
Abnormal, not cavitary	1.080	0.937	0.979	0.987
Abnormal, cavitary	1.303	0.786	0.745	0.815
Model 1.4. Transmission Rate = NAAT				
NAAT				
Negative	Reference		Reference	
Positive	1.586	0.103	1.149	0.699
MODEL 2. BIVARIATE MODELS				
Model 2.1. Transmission Rate = TTD + Smear				
Time to Detection				
0-7 days	1.242	0.341	1.440	0.157
8-14 days	0.978	0.907	1.395	0.117
15+ days	Reference		Reference	
Smear Grade				
Negative/Inconclusive	Reference		Reference	
1+/2+	1.103	0.691	0.664	0.128
3+/4+	1.242	0.354	0.924	0.757
Model 2.2. Transmission Rate = TTD + NAAT				
Time to Detection				
0-7 days	1.359	0.206	1.781	**0.030**
8-14 days	1.015	0.945	1.746	**0.022**
15+ days	Reference		Reference	
NAAT				
Negative	Reference		Reference	
Positive	1.453	0.205	1.225	0.576
Model 2.3. Transmission Rate = TTD + CXR				
Time to Detection				
0-7 days	1.344	0.117	1.590	**0.028**
8-14 days	1.139	0.464	1.558	**0.029**
15+ days	Reference		Reference	
Chest X-Ray				
Normal	Reference		Reference	
Abnormal, not cavitary	0.993	0.994	0.845	0.892
Abnormal, cavitary	1.159	0.881	0.700	0.774

MODEL 3. TRIVARIATE MODELS	Household Transmission*		All Transmission**	
Model 3.1. Transmission Rate = TTD + Smear + CXR	RR	P-Value	RR	P-Value
Time to Detection				
0-7 days	1.323	0.210	1.538	0.094
8-14 days	1.126	0.526	1.542	**0.045**
15+ days	Reference		Reference	
Smear Grade				
Negative/Inconclusive	Reference		Reference	
1+/2+	1.077	0.756	0.671	0.146
3+/4+	1.058	0.808	0.830	0.476
Chest X-Ray				
Normal	Reference		Reference	
Abnormal, not cavitary	0.950	0.959	1.041	0.981
Abnormal, cavitary	1.106	0.921	0.905	0.936
Model 3.2. Transmission Rate = TTD + Smear + NAAT				
Time to Detection				
0-7 days	1.386	0.240	1.495	0.199
8-14 days	1.024	0.917	1.529	0.103
15+ days	Reference		Reference	
Smear Grade				
Negative/Inconclusive	Reference		Reference	
1+/2+	0.908	0.741	0.588	0.136
3+/4+	0.912	0.755	0.831	0.601
NAAT				
Negative	Reference		Reference	
Positive	1.496	0.218	1.235	0.603
Model 3.3. Transmission Rate = TTD + NAAT + CXR				
Time to Detection				
0-7 days	1.357	0.188	1.759	**0.032**
8-14 days	1.152	0.503	1.816	**0.020**
15+ days	Reference		Reference	
NAAT				
Negative	Reference		Reference	
Positive	1.346	0.315	1.189	0.645
Chest X-Ray				
Normal	Reference		Reference	
Abnormal, not cavitary	0.749	0.780	0.630	0.729
Abnormal, cavitary	0.827	0.856	0.563	0.669
MODEL 4. QUADRIVARIATE MODELS				
Model 4.1. Transmission Rate = TTD + Smear + CXR + NAAT				
Time to Detection				
0-7 days	1.543	0.108	1.667	0.105
8-14 days	1.212	0.381	1.710	**0.045**
15+ days	Reference		Reference	
Smear Grade				
Negative/Inconclusive	Reference		Reference	
1+/2+	0.951	0.859	0.588	0.128
3+/4+	0.779	0.365	0.702	0.302
Chest X-Ray				
Normal	Reference		Reference	
Abnormal, not cavitary	0.757	0.792	0.869	0.915
Abnormal, cavitary	0.829	0.861	0.798	0.866
NAAT				
Negative	Reference		Reference	
Positive	1.538	0.186	1.242	0.604

*Cases (N=92) with Transmission Modeled as LTBI among Household Contacts Only

**Cases (N=94) with Transmission Modeled as LTBI among All Contacts

Discussion

Time to Detection as a Predictor of Transmission

The primary analyses of this study focused on risk of probable transmission to household contacts and showed that in this group, short TTD was associated with a greater proportion of LTBI-positive results compared to medium and long TTD, and this relationship was statistically significant. Yet the proportion of LTBI identified by short TTD was only 5 percentage points greater than that identified by 3+/4+ smears. In addition, 3+/4+ smears identified 113 infections, 53 more than short TTD, including 95% of the cases identified by short TTD.

Though short TTD was not significantly associated with transmission in univariate or multivariate analyses, the univariate point estimate was the same as that seen in the LTBI proportion analysis and thus implicates a lack of power to detect statistical significance. The analyses also show that highest smear grade—the current standard metric for infectivity—also performed poorly at predicting household transmission. NAAT and chest radiographic grade also demonstrated insignificant relationships, however, they also suffered from smaller sample sizes.

Unexpectedly, the "All Transmission" cohort, which included non-household contacts, did demonstrate significant predictors of transmission in several models including the TTD univariate model and the quadrivariate model. Across all contacts, cases with short and medium TTD were associated with a 63.0% and 50.3% greater transmission rate as compared to cases with long TTD, not adjusting for other diagnostic tests.

In the quadrivariate model, only medium TTD remained significantly associated with transmission. In comparison to long TTD, medium TTD was associated with 70.1% greater transmission rate than long TTD, after adjusting for highest smear, chest radiographic grade, and NAAT, and represented a higher relative rate of transmission than short TTD.

The consistently insignificant results in the household transmission models are likely due to the high background rates of infection. Among household contacts, 33% were associated with cases with long TTD and 30% were linked to cases with negative smears. Household contacts were more likely to be foreign-born (59.2%) and foreign-born individuals in the sample were more likely to be infected than US-born contacts. In the literature, foreign-born contacts are more likely to be infected prior to immigrating to the United States[37-39]. Because there is no way to distinguish between newly or previously acquired LTBI, infections from previous exposures cannot be excluded. Thus, a high background rate of infection in household contacts likely contributes to the high proportion of LTBI seen in the contacts of cases with long TTD (32.9%), and it becomes harder to find a statistically significant difference in infection rates.

Non-household contacts, by contrast, yielded a greater proportion of US-born individuals. The proportion of foreign-born contacts in the "All Contacts" transmission group was 49.8%--almost 10 percentage points less than household contacts. US-born contacts are less likely to have LTBI thus the background rate of LTBI decreases and it becomes easier statistically to find a difference between TTD strata. However the non-household contact group has limitations of its own and therefore was not used for primary analyses. Non-household contacts are less likely to have as high an exposure to the case as household contacts and therefore are less likely to be a true transmission event from the index case. Across all contacts, household contacts had greater odds of infection than non-household contacts. However this is not necessarily always the case. Some individuals may spend more time outside the home and, for example, at the workplace with coworkers. This level of detail is not contained in the contact data.

Additionally, the sample of non-household contacts is heavily affected by large contact investigations. Among non-household contacts, the largest group of contacts associated with a single

case was a school-based investigation in which 95 contacts were screened, which produced 8 (8.4%) LTBI-positive contacts. These large-scale investigations skew results. Though cases with short TTD tended to have more contacts per case including household contacts per case, on average there were more non-household contacts per case for the long TTD group.

Because we predicted there to be lower levels of exposure among non-household contacts, we expected the household contact transmission models to produce more significant results. Overall, the transmission rate among household contacts was greater than the rate across all contacts. However it appears that the background rate of infection greatly impacted the power needed to find statistical significance.

Representativeness of the Sample

The case sample appeared to be demographically representative of TB nationally. Overall, 62.9% of the group was male, in keeping with nationwide findings that men are around 1.5 to 2 times more likely to have TB than women[2]. A large proportion of the sample was foreign-born (86.3%), with the predominant ethnic group being non-Hispanic Asian (62.1%). Nationwide averages show that 66% of reported TB cases occurred among foreign-born persons and that Asian, Native Hawaiian and Pacific Islander ethnic groups disproportionately have the greatest rates of TB[2]. Seattle is an international hub for immigration, specifically from East African and East Asian countries. Thus there is a greater proportion of foreign-born cases in the county than across the United States[40].

The household transmission case cohort (N=92) differed significantly from 298 excluded pulmonary TB cases by highest smear grade, culture status, NAAT, anti-TB treatment prior to specimen collection, extrapulmonary TB disease, and HIV status. Culture status and anti-TB treatment were part of the inclusion/exclusion criteria and thus the difference was by design. The household transmission case cohort was more likely to have higher smear grades and positive NAAT than the excluded cases, and was less likely to have extrapulmonary TB disease and HIV.

Limitations

There were profound limitations unique to this study as well as limitations that are common to the field of observational TB research. Specific to this study, there are challenges to the underlying data validity. The specimen analyzed for TTD is the first culture-positive specimen analyzed at the King County Public Health Lab. It is not necessarily the diagnostic specimen. In fact, most cases are diagnosed in the community and then referred to the county TB Control Program. The main consequence of this time lag between diagnosis and analysis is that many of the cases began their TB treatment, which has been shown to impact culture growth[35,36]. We buffered against this impact by excluding cases that had begun treatment prior to the date of collection of the TTD specimen (N=139; 35.6%) resulting in 124 cases. It was important for the study to specifically use the King County Lab results because it has consistent record-keeping of dates tested versus dates reported which allowed for a systematic and accurate calculation of TTD. Inter-laboratory variability could lead to measurement error in the predictor variable. There were 33 cases with no King County Lab (8.5%). By employing strict measures to improve data quality, sample size was reduced, and consequently statistical power.

Measurement of TTD posed other challenges, as well. Culture samples are supposed to only be cultured for 56 days, after which they are determined culture-negative. Yet one case in the TTD analysis cohort (N=124) had a TTD of 63 days. Additionally, the fluorescence that indicates growth has to be recorded by a lab technician. If the culture specimen reaches critical mass for the MGIT system to detect fluorescence during the weekend, the date tested would only be recorded the following workday. Therefore holidays and weekends could have caused non-differential misclassification of TTD.

Another limitation to using the first culture-positive specimen from the King County Lab is that it is not necessarily the specimen with the shortest TTD. There could have been other samples with a

different culture growth time. However the first culture-positive specimen is what is practically useful to contact investigations thus that is the sample we used.

NAAT data came from the PHIMS database RVCT records—the standard report required for every diagnosed TB case—and had substantial missingness. Of cases included for TTD analysis and household transmission analysis, 22.6% and 19.6% did not have NAAT results, respectively.

Chest radiographic grade categorization may have driven non-significant associations. In this study, the variable was classified into three categories (normal; abnormal, non-cavitary; and abnormal, cavitary). Other studies have included categorizations that distinguish between unilateral and bilateral cavitary disease, a single cavitation and multiple, as well as predominantly alveolar and predominantly interstitial infection[15,22]. It has been shown that multiple cavitations are associated with a shorter TTD and greater burden of disease[41]. Thus a 3-tier categorization may have been too coarse. However a greater number of categories would have also reduced sample sizes and thus power.

Transmission analysis introduces an additional set of limitations. The primary challenge to determining whether transmission occurred is discerning whether a contact's LTBI truly came from the case in this study. There is no way to genotype LTBI thus transmission from a given source case cannot be genotypically confirmed. Additionally, LTBI is common worldwide. The WHO estimates that more than 2 billion people --or a quarter of the global population--have LTBI[42]. Foreign-born contacts come from a variety of high-TB prevalence countries thus it is likely that exposure occurred before immigrating.

Foreign-born contacts are also more likely to have received the BCG vaccine, which can lead to an unreliable TST result. BCG vaccine has been shown to variably interfere with TST reactivity[43]. Thus it becomes additionally challenging to determine whether or not the TST results are a product of LTBI or the vaccine. Older contacts are also more likely to be LTBI-positive from a previous exposure[2]. In this study, contact age was significantly associated with LTBI. It is also difficult to account for contact susceptibility. HIV infection data among contacts is unreliable as well as documentation of other risk factors.

Finally, it is challenging to appropriately account for opportunities for transmission. In general, household contacts are thought to have greater exposure to the case, than non-household contacts. However it is not always the case. Overall, it is difficult to account for the length of exposure, and this level of detail is not contained in the contact data.

These contact characteristics, which speak to contact susceptibility, likely confounded the results and due to the modeling technique could not be appropriately adjusted for.

Future Studies

Those conducting future analyses may want to refine the contact group and remove foreign-born contact TST results. Considering a large proportion of foreign-born individuals are BCG-vaccinated, QFT is be a more reliable measure of infection. Another possibility is to limit the contact cohort to individuals who have a record of a negative TST and then convert to a positive result. These would represent the most accurate true transmission events and thus could provide the most accurate measure of transmission.

Additionally, studies may want to consider modeling techniques other than Poisson regression. Though Poisson was able to take into account the number of LTBI-positive contacts within the context of the total number of contacts, it could not adjust for contact susceptibility.

Finally, future surveillance efforts must make a better effort to collect complete data on contacts in contact investigations. Only through thorough cleaning was the dataset usable.

Conclusions

While TTD appears to have some ability to discriminate between more and less infectious TB cases, we were unable to show it added to current infectivity measures, especially to the use of 3+/4+ smear grade positivity. Sample size also contributed greatly to the lack of statistical power. There are substantial challenges to conducting observational studies of TB transmission, particularly where there are high background rates of LTBI. As one clinician said, “Smear [the current gold standard of infectivity] being non-significant validates the difficulty of telling what actually happens with transmission in contact investigations.” Future studies to determine the usefulness of diagnostic tests to predict transmission should take place in previously TB-naïve households.

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