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Epidemiology of Culture-Negative Pulmonary Tuberculosis — Alameda County, 2010–2019

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Abstract

Context: Patients with culture-negative pulmonary TB (PTB) can face delays in diagnosis that worsen outcomes and lead to ongoing transmission. An understanding of current trends and characteristics of culture-negative PTB can support earlier detection and access to care.

Objective: Describe epidemiology of culture-negative PTB.

Design, Setting, Participants: We utilized Alameda County TB surveillance data from 2010–2019. Culture-negative PTB cases met clinical but not laboratory criteria for PTB per U.S. National Tuberculosis Surveillance System definitions. We calculated trends in annual incidence and proportion of culture-negative PTB using Poisson and weighted linear regression, respectively. We further compared demographic and clinical characteristics among culture-negative versus culture-positive PTB cases.

Results: During 2010–2019, there were 870 cases of PTB, of which 152 (17%) were culture-negative. The incidence of culture-negative PTB declined by 76%, from 1.9/100,000 to 0.46/100,000 (p for trend <.01), while the incidence of culture-positive PTB reduced by 37% (6.5/100,000 to 4.1/100,000, p for trend=.1). Culture-negative PTB cases were more likely than culture-positive PTB cases to be younger (7.9% were children <15 years old vs. 1.1%, $p < .01$), recent immigrants within 5 years of arrival (38.2% vs. 25.5%, $p < .01$), and have a TB contact (11.2% vs. 2.9%, $p < .01$). Culture-negative PTB cases were less likely than culture-positive PTB cases to be evaluated due to TB symptoms (57.2% vs. 74.7%, $p < .01$), or have cavitation on chest

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imaging (13.1% vs. 38.8%, $p < .01$). At the same time, individuals with culture-negative PTB were less likely to die during TB treatment (2.0% vs. 9.6%, $p < .01$).

Conclusions: The incidence of culture-negative PTB disproportionately declined compared to culture-positive TB and raises concern for gaps in detection. Expansion of screening programs for recent immigrants and TB contacts and greater recognition of risk factors may increase detection of culture-negative PTB.

Keywords

pulmonary tuberculosis; sputum/microbiology; epidemiology; public health; surveillance

INTRODUCTION

Although tuberculosis (TB) incidence rates have decreased in the United States (U.S.),[1] TB elimination has been difficult to achieve.[2,3] Delays in TB diagnosis are a major obstacle, which lead to ongoing household and community transmission.[4] Consequently, there have been multiple public health efforts to improve TB screening, build capacity for diagnostic testing, and increase access to TB treatment.[5,6]

Despite these efforts, one group that has been particularly challenging to reach are individuals with clinically-diagnosed, culture-negative pulmonary TB (PTB), which accounts for 13%–15% of PTB cases in the U.S.[1,7] These individuals may have subtle symptoms or atypical radiographic signs that can lead to missed or delayed diagnoses.[7] At the same time, this is an important group to identify as early treatment may prevent progression to more severe disease and in turn worsen morbidity and disease transmission.

Greater awareness of the epidemiology and clinical presentation of culture-negative PTB is needed to guide clinicians and increase case detection. In this paper, we utilized ten years of TB surveillance data from Alameda County, California to examine trends in culture-negative PTB cases, and to compare demographic and clinical characteristics among culture-negative and culture-positive PTB cases.

METHODS

Setting

Alameda County has a population of 1.7 million individuals, of which 33% are non–U.S.-born.[8] During 2010–2019, TB case rates in Alameda County varied from 7.4 to 12.3 per 100,000 population,[9] and the county had between the third and seventh highest TB rate among all California counties.[10] Alameda County is the only high TB burden California County without a public health funded TB clinic that would generally conduct TB prevention activities, such as screening and treatment of latent TB infection (LTBI) and TB among new immigrants and contacts to infectious PTB cases. Instead, the TB Section partners with community physicians and health centers to promote screening activities, guide evaluation and treatment of LTBI among contacts, and provide oversight for the treatment of TB disease.[11,12] With limited resources, directly observed therapy (DOT) is prioritized according to California Department of Public Health (CDPH) criteria for high risk individuals.[13]

Surveillance System

Under California state law, healthcare providers are mandated to report all TB cases to local health jurisdictions (California Code of Regulations Title 17 §2500), and all laboratories must submit *Mycobacterium tuberculosis* isolates to local public health laboratories (California Code of Regulations Title 17 §2505). Local health jurisdictions are required to collect and report data regarding TB cases to the California Department of Public Health TB Control Branch using the Report of Verified Case of Tuberculosis (RVCT) form.[14] This form contains information on demographic and clinical characteristics and treatment outcomes for TB cases.

Study population and Definitions

We included all confirmed TB case-patients reported by the Alameda County Public Health Department (ACPHD) TB Program during January 1, 2010 through December 31, 2019. A confirmed TB case was defined according to the U.S. National Tuberculosis Surveillance System as meeting the clinical or laboratory criteria for diagnosis of TB.[14] The clinical criteria for diagnosis of TB required all of the following four criteria: 1) a positive tuberculin skin test result or interferon-gamma release assay (IGRA); 2) other signs and symptoms compatible with TB; 3) treatment with two or more anti-TB medications; and 4) a completed diagnostic evaluation. As part of a routine diagnostic evaluation for TB, ACPHD recommends collection of 3 sputum samples for acid-fast bacilli (AFB) smear and culture for diagnostic and infection control purposes.[12] The laboratory criteria for diagnosis of TB requires any one of the following criteria: 1) isolation of *M. tuberculosis* complex from a clinical specimen; or 2) positive nucleic acid amplification test (NAAT) for *M. tuberculosis* complex; or 3) AFB identified on a clinical specimen when a culture is unavailable or is falsely negative or contaminated.[14] In Alameda County, all provider diagnoses are reviewed by ACPHD and classified as fulfilling clinical and/or laboratory criteria.

A TB case was classified as pulmonary type if the only anatomic site of TB disease was pulmonary; extra-pulmonary if the only site(s) of TB disease was a non-pulmonary site; and both extra-pulmonary and pulmonary if sites of TB disease were both pulmonary and non-pulmonary. A culture-positive PTB case was defined as detection of *M. tuberculosis* complex in any respiratory specimen (e. g. trachea, lung, upper respiratory or tracheal fluids, bronchial fluid, pleural fluid, gastric aspirate) for a patient with PTB. A culture-negative PTB case was defined as a patient who met clinical criteria for TB but did not meet laboratory-based criteria of isolation of *M. tuberculosis* complex from a respiratory or other specimen. Similar to other TB programs in the U.S., ACPHD requires that all culture-negative PTB cases are counted as part of the surveillance system only if there is clinical documentation of radiographic or clinical response to treatment of TB disease. As NAAT positivity fulfills laboratory criteria, culture-negative PTB cases represented only those who had NAAT negative results or were not done. We excluded individuals who were NAAT positive but culture negative for *M. tuberculosis* complex.

For the purposes of analyses regarding pulmonary TB, we excluded case-patients who had any site of extrapulmonary TB (EPTB), and is consistent and comparable with previous analyses.[7] Having a TB contact was defined as a known recent history of a close contact with an infectious TB patient. In the RVCT form, TB evaluation due to an abnormal chest X-ray refers to imaging performed for another indication other than TB. Because this analysis of TB surveillance data was conducted to enable ACPHD to monitor, assess and inform local TB public health interventions, no human subject review was required by an institutional review board.

Statistical Analysis

Annual case rates for culture-negative PTB cases were calculated as the number of culture-negative PTB cases divided by the Alameda County population for each year. Trends in annual culture-negative and culture-positive PTB case rates were assessed using Poisson regression, with the calendar year as a linear predictor. Trends in the proportion of PTB cases that were culture-negative PTB were assessed using weighted linear regression. Significance for trend or proportion was defined as a *P*-value <.05. Given the low number of children less than 15 years old, we did not further stratify into smaller age groups to prevent inadvertent disclosure. Bivariate comparisons of demographic and clinical characteristics and outcomes were performed between culture-positive and culture-negative PTB cases were conducted using the Chi-square test or Fisher's exact test to compare all categorical variables, or the Kruskal-Wallis test to compare continuous variables. Individuals with missing data or testing not done were excluded from the comparison. All analyses were conducted with R version 4.0.2. The packages *stats*, *MASS*, *sfsmisc* (v1.1–11), and *ggplot2* were used.

RESULTS

During 2010–2019, ACPHD reported a total of 1,370 TB cases (Figure 1). There were 870 cases of PTB only; of these PTB cases, 152 (17%) had culture-negative PTB. During 2010 to 2019, the incidence rate of culture-negative PTB decreased 76% from 1.9/100,000 to 0.46/100,000 (*P* for trend <.01) (Figure 2). In comparison, the incidence rate of culture-positive PTB decreased 37% from 6.5/100,000 to 4.1/100,000 (*P* for trend=.1). The percent of PTB cases that were culture-negative PTB decreased from 23% to 10% from 2010 to 2019 (*P* for trend=.01) (Figure 3).

Comparisons of demographic and clinical characteristics among culture-negative and culture-positive PTB case-patients are provided in Table 1. Compared to culture-positive PTB, culture-negative PTB patients were more likely to be younger (7.9% aged < 15 years old vs. 1.1%, *P* <.01), and more likely to have a known TB contact (11.2% vs 2.9%; *P*<.01). Culture-negative PTB patients were also more likely to be evaluated for TB primarily due to an abnormal chest x-ray (26.3% vs 15.3%; *P*<.01) or as part of a contact investigation (8.6% vs 1.7%; *P*<.01), and less likely due to TB symptoms (57.2% vs 74.7%; *P*<.01). Culture-negative PTB was less common in non-U.S.-born individuals (76.3% vs 87.7%; *P*<.01), but of the non-U.S.-born, a significantly higher percentage of patients with culture-negative PTB arrived in the U.S. within 5 years of their TB diagnosis (38.2% vs 25.5%;

P<.01) when compared with culture-positive PTB patients. The median age was similar among those who recently immigrated to the U.S. within 5 years with culture-negative vs culture-positive PTB, (Culture-negative PTB median 35 years old, interquartile range (IQR) 21.5 – 56.5, culture-positive PTB median 34 years old, IQR 24–56, *P* = .79). A significantly lower percentage of culture-negative vs. culture-positive PTB patients had diabetes (17.1% vs 29.1%; *P*<.01), while proportions did not significantly differ for those with end-stage renal disease or immunosuppression.

Differences in clinical and radiographic characteristics were detected among culture-negative compared to culture-positive PTB case-patients. Patients with culture-negative PTB were significantly less likely to have evidence of a cavity by either chest radiography (6.7% vs 20.2%; *P*<.01) or computed tomography (CT) chest scan (17.3% vs 42.4%; *P*<.01). Compared to culture-positive PTB patients, a larger proportion of culture-negative PTB patients did not have a NAAT conducted (76.3% vs 50.9%; *P*<.01). When evaluated over time (Supplemental Digital Content Figure 1), a lower proportion of NAATs were conducted in culture-negative PTB cases compared to culture-positive PTB cases during 2010–2014, but use increased and was similar by 2019. In terms of TB outcomes, a lower percentage of culture-negative PTB patients died during TB therapy (2.0% vs 9.6%; *P*<.01).

When comparisons of demographic and clinical characteristics were stratified by AFB smear microscopy status, we detected similar findings as noted in our comparison of culture-negative to culture-positive PTB case-patients (Supplemental Digital Content Table 1). An additional finding was that smear-negative PTB cases (culture-negative or culture-positive) were less likely to have cavitary disease seen on x-ray or CT imaging than smear-positive, culture-positive PTB.

DISCUSSION

An understanding of the trends and characteristics of culture-negative PTB is essential to guide TB elimination efforts in the United States. In a large, diverse county in Northern California, we found that the overall incidence of cases from culture-negative PTB was decreasing, and at a significantly faster rate than for culture-positive PTB cases. Culture-negative PTB cases had several differences from culture-positive PTB, and tended to be younger, recent immigrants, and were identified more often as part of contact investigations rather than by TB symptoms. At the same time, they were less likely to die during TB treatment. While changing epidemiology may have contributed to the faster decline in culture-negative PTB cases, our findings also highlight that TB screening and contact investigation programs may need to be strengthened to reduce delayed or missed diagnoses.

Alameda County's annual TB case rates have been trending downward, from 12.6/100,000 to 7.4/100,000 in the years 2010 to 2019, and aligns with national trends.[15] While both culture-negative and culture-positive PTB incidence have decreased, culture-negative PTB cases reduced by 76% compared to 37% in culture-positive PTB. While the reasons for this decline need to be further explored, there are several possibilities to consider. It may be due to an overall change in the epidemiology of TB disease in the county, or greater detection of microbiological confirmed cases as we found higher use of NAATs over time. The improved

NAAT use over time may be due to public health education on TB symptoms and promoted use of NAAT directly on clinical samples.[16] At the same time, the national proportion of clinically-diagnosed TB reduced by only 19% (16.8% to 13.6% from 2010–2019).[1] Based on the demographic and clinical characteristics of culture-negative PTB cases, the large reduction raises concerns for missed or delayed diagnoses.

We found that immigrants who arrived within 5 years were more likely to have culture-negative PTB. The majority of U.S. TB cases are diagnosed in non-US born persons,[1] and other studies have also shown that culture-negative PTB is more common in recent immigrants.[17–19] In a study by Liu et al, they found that among newly arrived U.S. immigrants and refugees, 47% of TB diagnoses were culture-negative.[17] While evaluation of recent immigrants with possible TB disease (class B notifications) have been successful in increasing the yield of TB diagnoses,[18] there are challenges in implementation. Of the 101,000 class B notifications from 2014–2019, only 67% completed TB evaluation once they arrived in the U.S..[19] As county TB programs are responsible for assessing immigrants with class B notifications to complete their TB evaluations, interventions are needed to bolster TB program capacity in order to increase case detection.

Contact investigation also supports early detection of TB, and we found that culture-negative PTB cases were more likely to be evaluated due to a known TB contact. Individuals diagnosed with TB during a contact investigation were likely infected recently, and so early TB disease may be more paucibacillary and lead to negative culture results. This is also reflected in our finding that culture-negative TB cases were less likely to have cavitation on chest imaging as a marker of severe disease. A Centers for Disease Control and Prevention (CDC) study reported that of the TB cases diagnosed in close contacts of culture-positive TB cases, 51% were diagnosed clinically and had culture-negative TB disease.[20] However, there are obstacles to effective contact investigation. One assessment found that 20% of TB contacts were not examined in the U.S. during 2003–2012.[21] Interviews with eleven urban TB programs in the U.S. found that there were a wide range of policies regarding contact investigation, staff had limited training, and there was informal quality monitoring.[22] The same study also found that barriers for TB contacts included communication and cultural challenges, limited clinic hours, inadequate staffing, and stigma.[22] A strong contact investigation program is an essential component of public health TB programs,[3] and plays an important role in early detection of TB disease.[6]

Clinical characteristics among culture-negative PTB cases detected in these analyses may be important for guiding prevention efforts. In particular, culture-negative PTB cases were younger and less likely to be identified through symptoms. Children have paucibacillary TB disease with subtle, non-specific symptoms including fever and failure-to-thrive, making TB diagnosis difficult and leads to delays in treatment initiation.[23] Moreover, an analysis from New York also found that that culture-negative PTB cases were less likely to be symptomatic and less likely to have cavitation on chest imaging, suggesting that culture-negative PTB reflects an earlier state in the spectrum of TB disease.[7] Given the multiple benefits to early TB diagnosis (i.e., improved outcomes,[24,25] eligibility for shorter treatment regimens,[26] and reduced community transmission[6]), it is important to have a low threshold to complete a TB evaluation in individuals with risk factors even if classic signs or symptoms are not present.

There are limitations to our analyses. First, the case definition of culture-negative PTB relied on laboratory and clinical data that is provided to the public health department by healthcare providers. While there is potential for misclassification of TB cases, a standardized form was used, and our overall incidence trends were consistent with national data. Second, subgroup analyses were limited by low numbers, including those with end-stage renal disease, immunosuppression other than HIV, or living in a long-term care facility. Third, specific TB symptom characteristics like cough, fever, and weight loss, were not available in the surveillance data. While this analysis was focused on one county which limits generalizability, Alameda County is diverse with urban and rural cities and it is within a state with a relatively high TB burden. Therefore, the findings in these analyses may be applicable to other settings in the U.S. that conduct a large number of TB evaluations.

In conclusion, we found that culture-negative PTB incidence declined from 2010–2019, but this decline was disproportionate to the reduction in culture-positive PTB cases during the same period. While the cause of the sharp decline is likely multi-factorial and needs further investigation, it raises concern for missed opportunities for earlier diagnosis of TB. Additional interventions are needed to strengthen TB screening and active case-finding programs by healthcare providers and public health programs to recognize culture-negative PTB, in order to improve TB outcomes and support TB elimination.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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IMPLICATIONS FOR POLICY AND PRACTICE

- Greater efforts are needed to increase the case detection of culture-negative PTB.
- Public health programs that evaluate recent immigrants and TB contacts are valuable for identifying culture-negative PTB and should be further expanded and strengthened.
- Because culture-negative PTB cases may be challenging to recognize due to the lack of symptoms and cavitation on imaging, clinicians should have a low threshold to complete a TB evaluation if an individual has risk factors.

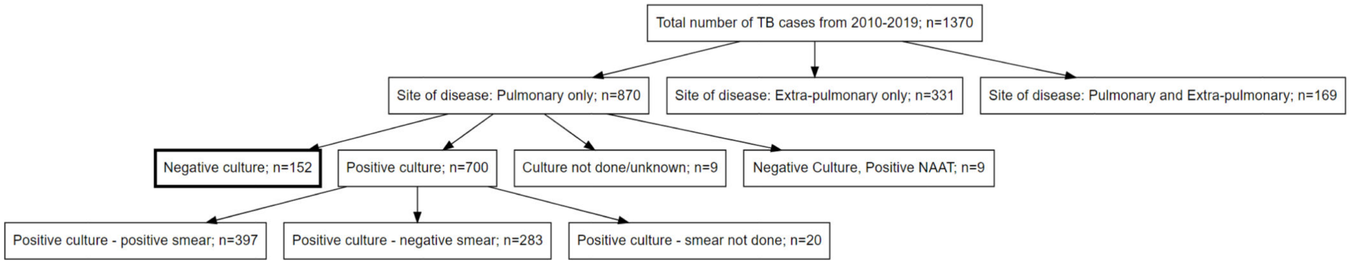
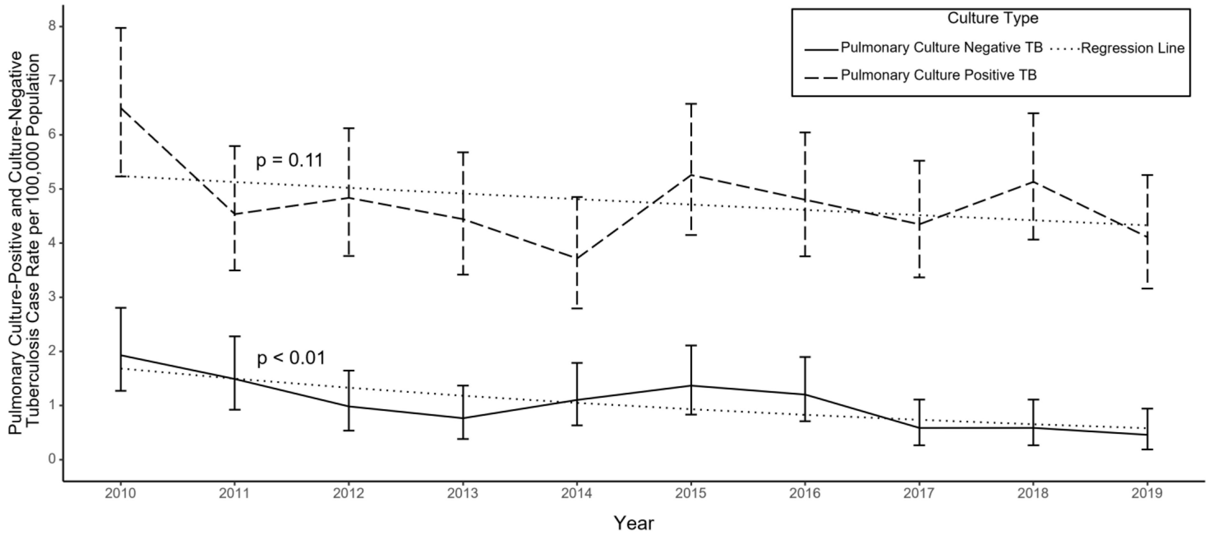
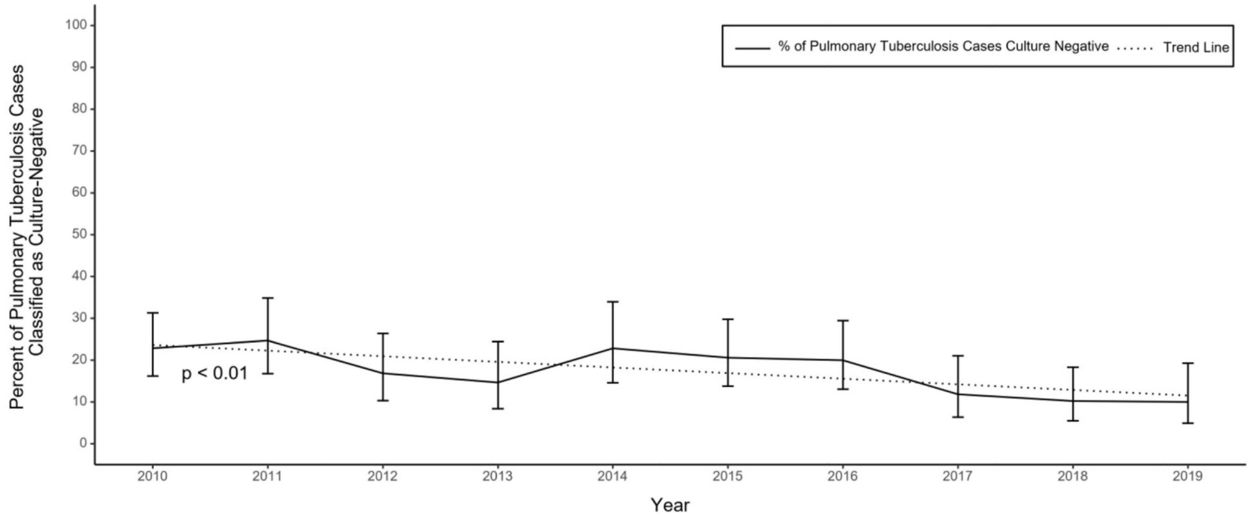


Figure 1:
Flowchart of TB case classification, Alameda County, 2010–2019



Culture Negative Case Rate/100,000	1.9	1.5	1.0	0.76	1.1	1.4	1.2	0.58	0.58	0.46
Culture Positive Case Rate/100,000	6.5	4.5	4.8	4.4	3.7	5.2	4.8	4.4	5.1	4.1

Figure 2:
Pulmonary TB incidence rates per 100,000 population, by culture status, Alameda County, 2010–2019



Percent of Pulmonary TB Cases Classified as Culture-Negative	22.9	24.7	16.9	14.7	22.9	20.6	20.0	11.8	10.2	10.0

Figure 3:
Proportion of pulmonary TB cases defined as culture-negative, Alameda County, 2010–2019

Table 1:

Demographic and clinical characteristics of culture-negative pulmonary TB cases compared to culture-positive pulmonary TB cases in Alameda County, 2010–2019

Characteristic	Culture-Negative PTB (N=152)[a]	Culture-Positive PTB (N=700)[a]	P-value[b]
Demographic			
Age, median years (Interquartile Range)	56.5 (31–68)	57 (36–74)	.13
Age Category, n (%)			<.01
0–14 years	12 (7.9)	8 (1.1)	
15–24 years	17 (11.2)	64 (9.1)	
25–44 years	26 (17.1)	158 (22.6)	
45–64 years	49 (32.2)	204 (29.1)	
≥65 years	48 (31.6)	266 (38)	
Birth sex male, n (%)	90 (59.2)	441 (63)	.43
Race/ethnicity, n (%)			<.01
Hispanic	20 (13.2)	73 (10.4)	
Non-Hispanic			
Asian/ Pacific Islander	95 (62.5)	529 (75.6)	
Black/African American	21 (13.8)	48 (6.9)	
White	13 (8.6)	43 (6.1)	
Other	3 (2.0)	7 (1.0)	
Non-U.S.-born[b]	116 (76.3)	613/699 (87.7)	<.01
Arrived in US <5 years prior to TB	42/110 (38.2)	150/589 (25.5)	<.01
Arrived in US ≥5 years prior to TB	68/110(61.8)	439/589 (74.5)	
TB Risk factors, n (%)			
Long-term care facility resident	2 (1.3)	17 (2.4)	.55
Contact of an Infectious TB Case	17 (11.2)	20 (2.9)	<.01
Diabetes	26 (17.1)	204 (29.1)	<.01
End-stage renal disease	3 (2.0)	14 (2.0)	1
Immunosuppression (not HIV))	6 (3.9)	44 (6.3)	.36
Primary reason for evaluation			<.01
TB Symptoms	87 (57.2)	523 (74.7)	
Abnormal CXR	40 (26.3)	107 (15.3)	
Contact Investigation	13 (8.6)	12 (1.7)	
Other	12 (7.9)	58 (8.3)	
Clinical			
HIV Status[d]			
HIV positive	6 (3.9)	15 (2.1)	.25
HIV negative	98 (64.5)	497 (71)	
Status unknown	38 (25.0)	126 (18)	-

Characteristic	Culture-Negative PTB (N=152)[a]	Culture-Positive PTB (N=700)[a]	P-value[b]
Other[c]	10 (6.6)	62 (8.9)	-
NAAT done	36 (23.7)	344 (49.1)	<.01
PPD			
PPD not done	69 (45.4)	466 (66.6)	<.01
PPD done[d]	80 (52.6)	198 (28.3)	
PPD Positive	64/80 (80.0)	168/198 (84.8)	.4
PPD Negative	16/80 (20.0)	30/198 (15.2)	
Unknown	3 (2.0)	36 (5.1)	-
IGRA			
IGRA not done	65 (42.8)	322 (46)	.39
IGRA done[d]	87 (57.2)	363 (51.8)	
IGRA positive	68/87 (78.2)	281/363 (77.4)	.13
IGRA Negative	18/87 (20.7)	60/363 (16.5)	
IGRA Indeterminate	1/87 (1.1)	22/363 (6.1)	
Unknown	0 (0.0)	15 (2.1)	-
Radiologic exam			
X-Ray – Miliary	3/149 (2.0)	8/670 (1.2)	.43
X-ray - Chest Cavity	10/149 (6.7)	136/674 (20.2)	<.01
CT - Miliary	3/110 (2.7)	17/497 (3.4)	1
CT – Cavity	19/110 (17.3)	212/500 (42.4)	<.01
CT or X-ray Miliary or Cavity	20/152 (13.1)	271/698 (38.8)	<.01
TB Treatment Method			
Only directly observed treatment	32 (21.1)	163 (23.3)	<.01
Only self-administered treatment	50 (32.9)	86 (12.3)	
Both	70 (46.1)	425 (60.7)	
Unknown	0 (0)	26 (3.7)	
Died During Therapy	3 (2.0)	67 (9.6)	<.01

CT: Computed Tomography; HIV: Human immunodeficiency virus; IGRA: Interferon-gamma release assay; NAAT: Nucleic-acid amplification test; PPD: Purified Protein Derivative; PTB: pulmonary TB; US: United States

[a.]Denominator indicated if different than total due to missing data or test not done.

[b.]The $\chi 2$ or Fisher exact test was used to compare categorical variables; the Kruskal-Wallis Rank Sum test was used to compare continuous variables.

[c.]Other category includes: test not offered, test done and results unknown, test refused

[d.]Comparison done among those who had test completed