Published in final edited form as:

*Int J Tuberc Lung Dis*. 2018 February 01; 22(2): 165–170. doi:10.5588/ijtld.17.0223.

# Spatial clusters of latent tuberculous infection, Connecticut, 2010–2014

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## SUMMARY

**SETTING—**In the United States, tuberculosis (TB) control is increasingly focusing on the identification of persons with latent tuberculous infection (LTBI).

**OBJECTIVE—**To characterize the local epidemiology of LTBI in Connecticut, USA.

**METHODS—**We used spatial analyses 1) to identify census tract-level clusters of reported LTBI and TB disease in Connecticut, 2) to compare persons and populations in clusters with those not in clusters, and 3) to compare persons with LTBI to those with TB disease.

**RESULTS—**Significant census tract-level spatial clusters of LTBI and TB disease were identified. Compared with persons with LTBI in non-clustered census tracts, those in clustered census tracts were more likely to be foreign-born and less likely to be of white non-Hispanic ethnicity. Populations in census tract clusters of high LTBI prevalence had greater crowding, persons living in poverty, and persons lacking health care insurance than populations not in clustered census tracts. Persons with LTBI were less likely than those with TB disease to be of Asian ethnicity, and persons with LTBI were more likely than those with TB disease to reside in a clustered census tract.

**CONCLUSIONS—**Characterizing fine-scale populations at risk for LTBI supports effective and culturally accessible screening and treatment programs.

## RÉSUMÉ

Aux Etats-Unis, la lutte contre la tuberculose (TB) se focalise de plus en plus sur l'identification des personnes ayant une infection tuberculeuse latente (LTBI).

Caractériser l'épidémiologie locale de la LTBI dans le Connecticut, aux Etats-Unis.

Nous avons utilisé les analyses spatiales afin d'identifier, au niveau des secteurs de recensement, les groupes de LTBI et de TB maladie déclarés dans le Connecticut, comparé les personnes et les

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Conflicts of interest: none declared.

populations dans ces groupements avec celles hors des groupements et comparé les personnes avec LTBI à celles avec TB maladie.

Les regroupements spatiaux significatifs de LTBI et de TB maladie au niveau des secteurs de recensement ont été identifiés. Comparés aux personnes avec LTBI dans des secteurs de recensement hors des regroupements, celles dans les regroupements des secteurs de recensement ont été plus susceptibles d'être nées à l'étranger et moins susceptibles d'être de race blanche non hispanique. Les populations des regroupements des secteurs de recensement à prévalence élevée de LTBI étaient davantage exposées a la surpopulation, vivaient plus souvent dans là pauvreté et etaient´ plus souvent dépourvues d'assurance santé que les populations hors de ces regroupements. Les personnes ayant une LTBI ont été moins susceptibles que celles atteintes de TB maladie d'être d'origine asiatique et ont été plus susceptibles d'habiter dans un regroupement d'un secteur de recensement.

Caractériser plus précisément les populations à risque de LTBI contribue à l'efficacité et a l'accessibilité culturelle des programmes de dépistage et de traitement.

## RESUMEN

En los Estados Unidos, el control de la tuberculosis (TB) se centra cada vez más en la detección de las personas que han contráıdo una infección tuberculosa latente (LTBI).

Definir las caracteŕısticas epidemiológicas locales de la LTBI en el estado de Connecticut.

Se realizaron análisis espaciales con el objeto de detectar conglomerados correspondientes a zonas censuales en los casos notificados de LTBI y TB, se compararon las personas y las poblaciones en los conglomerados y fuera de ellos y las personas con diagnóstico de LTBI y de TB.

Se detectaron importantes conglomerados espaciales de LTBI y TB que correspondieron a zonas censuales. Las personas con LTBI que formaban parte de conglomerados en las zonas de censo exhibían mayor probabilidad de haber nacido en el extranjero y menor probabilidad de ser de etnia blanca no hispánica que las personas con LTBI por fuera de los conglomerados. Las poblaciones de los conglomerados en zonas censuales con una alta prevalencia de LTBI exhibían mayor hacinamiento, más personas pobres y más personas sin seguro de enfermedad que las poblaciones por fuera de los conglomerados en zonas de censo. Las personas con diagnóstico de LTBI eran con menos frecuencia de etnia asiática y residían con mayor frecuencia en una zona censual en conglomerados que las personas con enfermedad tuberculosa activa.

La definición a una escala más precisa de las poblaciones con riesgo de contraer la LTBI favorece la eficacia y la accesibilidad cultural de los programas de detección sistemática y de tratamiento.

### Keywords

LTBI; cluster analysis; SaTScan™

MOLECULAR AND EPIDEMIOLOGIC analyses indicate that the majority of incident tuberculosis (TB) disease cases in the United States result from reactivation of latent tuberculous infection (LTBI), which is often attributable to the reactivation of *Mycobacterium tuberculosis* infection acquired in the person's country of origin.[1–6] TB control efforts have thus shifted from identifying TB disease to testing and treating persons at high risk for LTBI and progression to TB disease.[7–11] Because currently available screening tests for LTBI have low predictive value in populations with low LTBI prevalence, the US Preventive Services Task Force (USPSTF) guidelines recommend testing groups at increased risk for LTBI, such as immigrants from high TB incidence countries, or for the development of TB disease.[7–9] Strategies that focus on the testing and treatment of LTBI might result in substantial cost savings by reducing unnecessary testing, and could significantly reduce TB disease burden and transmission.[10,11] Successful focused testing strategies require an understanding of the local epidemiology of LTBI.[7,9,12,13] Using a geographic information system might improve testing programs by identifying areas with significantly high LTBI prevalence. This strategy allows the description of persons with LTBI and underlying populations in each area, thus identifying populations for targeted testing.[14] Molecular analyses combined with spatial analyses have suggested that the transmission patterns of TB disease differ among cities, states, and within urban areas, but similar analyses have not been conducted for LTBI.[15–19] Moreover, comparisons of persons with TB disease and those with LTBI would further refine targeted LTBI testing.

With 1.9 cases per 100000 population in 2015, Connecticut is a low TB incidence state (defined as <3.0 cases/100000);[19] 81% of the 70 TB disease cases reported were among foreign-born persons.[20] The majority of the cases during 2015 did not have genotypic matches and were most likely reactivation TB disease.[19,21]

In the present study, we sought 1) to characterize differences between persons with LTBI and TB disease, 2) to identify significant spatial areas of high TB or LTBI prevalence in Connecticut, and 3) to determine the salient social and demographic characteristics in identified areas of high LTBI prevalence.

## METHODS

### Data sources

Surveillance data collected from persons reported with LTBI and TB over a 4-year period were analyzed to identify high prevalence areas of both conditions. We employed a cross-sectional design to determine the characteristics of persons with LTBI and of the underlying populations in these areas.

For surveillance purposes, LTBI is defined as a positive tuberculin skin test or interferon-gamma release assay and a negative chest radiograph. Providers and laboratories are required to report LTBI to the Connecticut Department of Public Health (CTDPH) if the person is co-infected with the human immunodeficiency virus, has had contact with a known TB case, or is aged <6 years. Providers may also report persons with LTBI tested for other reasons to obtain medication from the CTDPH at no charge. TB disease is a reportable condition in Connecticut; the CTDPH TB Control Program uses the national case definition for TB disease.[22] Surveillance data collected for LTBI and TB disease include demographics, TB risk factors, clinical information, and country of birth; persons are classified as foreign-born or US-born. Additional data collected for foreign-born persons include the month and year of arrival in the United States; persons were classified as arriving in the United States <5 years or ≥5 years before diagnosis.

All reports of LTBI and TB disease among Connecticut residents received between 1 January 2010 and 31 December 2014 were examined, including those reported for non-required reasons. If a person was reported more than once with either condition in the same year, only the first report was retained. Census tract populations and sociodemographic characteristics were obtained from the 2010 US Census Bureau and the American Community Survey 2012 5-year estimates, respectively.[23,24] Characteristics included housing units per square mile (housing density); housing units having >1 occupant per room (household crowding); low educational attainment (defined as persons aged ≥25 years who did not graduate from high school); foreign-born population; population below the federal poverty level; and population without medical insurance.

## Spatial analyses

We performed spatial analyses to identify clusters of residential census tracts having a high prevalence of reported LTBI and TB disease. LTBI and TB disease reports were geocoded using ArcGIS® v10 (Environmental Systems Research Institute, Inc., Redlands, CA, USA) and matched to the centroid of the residential census tract. The circular spatial scan statistic implemented in SaTScan™ v9.3 (Information Management Services, Inc., Boston, MA, USA) was used to detect spatial clusters of census tracts with a high prevalence of reported LTBI or TB disease.[25] By using purely spatial analyses, a discrete Poisson model was applied under the assumption that the numbers of reports of patients with TB disease or LTBI in census tracts were Poisson-distributed. The space-only model uses moving circular windows of varying diameter to identify census tract clusters; the maximum window diameter was set to incorporate ≤25% of the total state population. A Monte Carlo simulation using 999 permutations was used to evaluate each window at $P \leq 0.05$ against the null hypothesis that persons with LTBI or TB disease were equally distributed across all census tracts. SaTScan thus identified groups of adjacent census tracts together having a higher prevalence of either LTBI (LTBI cluster) or TB disease (TB disease cluster) than expected based on the null hypothesis. We did not differentiate between primary and secondary clusters; overlapping clusters were permitted. Census tracts were classified according to whether these were in a high LTBI or TB prevalence cluster. Census tracts with any portion in a significant cluster window were considered to be clustered. Persons with LTBI or TB disease were classified according to whether or not they were based on the census tract of residence.

## Statistical analyses

Characteristics of persons with LTBI or TB disease from the entire state were compared using the Pearson's $\chi^2$test for categorical variables and the Wilcoxon rank-sum test for comparison of ages in years. Individual-level data from persons with LTBI or TB disease in a spatial cluster were compared with those not in a cluster using odds ratios (ORs) for categorical variables and the Wilcoxon rank-sum test for median age. The Wilcoxon rank-sum test was used to compare census tract-level socio-economic characteristics of census tracts in LTBI clusters with those not in a cluster. All statistical analyses were performed using SAS® v9.3 (Statistical Analysis System, Cary, NC, USA). Only geocoded cases were used for cluster analyses.

Because specific cases of LTBI and TB disease are reportable conditions in Connecticut, this study was deemed exempt from review by the CTDPH Human Investigations Committee, Hartford, CT, USA, and considered routine public health practice by the Centers for Disease Control and Prevention, Atlanta, GA, USA.

## RESULTS

During 2010–2014, 9701 persons with LTBI were reported to the CTDPH; the median age was 30 years (range 0–112), 49.7% were male, and 76.3% were foreign-born (Table 1). Of foreign-born persons, *67.9%* had lived in the United States<5 years. During the same period, 365 TB disease cases were reported to the CTDPH. The median patient age was 37 years (range 0–91), 55.6% were male, and 79.2% were foreign-born (Table 1). Among foreign-born persons, 40.8% had lived in the United States <5 years. Among foreign-born persons, those with LTBI had arrived in the United States more recently than those with TB disease (Table 1). Other known TB risk factors were not compared because >40% of LTBI reports had unknown risk factors. Compared with persons having TB disease, those with LTBI were more likely to be in a spatial cluster; when stratified by natality, only foreign-born persons with LTBI were more likely to reside in a cluster.

Of the 9701 LTBI reports, 97.2% were geocoded to a census tract. Persons with LTBI were reported from 768 of 833 (92%) census tracts; census tract LTBI prevalence rates ranged from 0 to 3496 cases/100000 (median 25.4/100000 person-years). SatScan identified nine census tract LTBI clusters, containing 73 census tracts (Figure); 54% of persons with LTBI resided in clustered census tracts. Among persons with LTBI in any of the nine clusters, 93% resided within five of the clusters.

Among persons with TB disease, 97.8% had geocoded addresses. Cases were reported from 349/ 833 (42%) census tracts; among census tracts with TB disease cases, prevalence rates ranged from 2.4 to 23.7 cases/100000 (conditional median 5.6/100000 person-years). The SaTScan method identified six census tract-level TB disease clusters containing 126 census tracts (Figure). Census tracts in clusters contained 38.4% of geocoded reports. Persons with TB disease in clusters were more likely to be Black non-Hispanic (odds ratio [OR] 2.3, 95% confidence interval [CI] 1.4–4.0) or Hispanic (OR 2.1, 95%CI 1.3–3.5), and less likely to be Asian (OR 0.4, 95%CI 0.3–0.7). Other characteristics of persons with TB disease were not different by cluster status. Five of six TB-related clusters overlapped or coincided with five of the LTBI clusters (Figure).

Compared with persons with LTBI not in a cluster, those in a cluster were more likely to be younger, Black non-Hispanic or Hispanic, and foreign-born. Foreign-born persons in a cluster reported more recent arrival in the United States (Table 2). Persons with LTBI born in Africa and the Eastern Mediterranean were more likely to reside in a cluster, while persons born in Europe were less likely to live in a cluster (Appendix Table).* Populations in clustered census tracts had significantly lower educational attainment, greater percentages of persons without medical insurance, and greater levels of poverty, housing density, household crowding, and proportion of foreign-born residents than those not in a cluster (Table 2). Among clusters, persons with LTBI were consistently more likely to be foreign-born than those not in a cluster; the predominant regions of birth among foreign-born persons with LTBI varied (Appendix Table). Greater household crowding, greater proportion of foreign-born population, and greater proportion of population without medical insurance were consistently associated with clustered census tracts. The racial and ethnic composition of the population varied among clusters; for example, the proportion of the population identifying as Hispanic was 2.8% in cluster 1 and approaching 50% in cluster 2 (Appendix Table). The percentage of the population living in poverty was greatest in clusters 2 and 3, but similar to the state level in other clusters.

## DISCUSSION

Although previous studies have investigated spatial clustering of TB disease,[14–18,26] and others have investigated the benefits of focused interventions for LTBI,[8,9,27,28] few have compared LTBI with TB disease or explored the use of spatial methods to inform targeted LTBI testing strategies.[14] Given that the USPSTF recommends targeting testing at specific populations at risk for either LTBI or progression to TB disease, strategies to identify the former, i.e., populations at risk for LTBI, are essential.[9] Our results indicate that screening policies could miss high-risk persons with LTBI, and that significant neighborhood-level socio-economic disparities exist with respect to LTBI prevalence. Persons reported with LTBI and TB disease differed in race/ethnicity; persons identifying as Asian were the largest single group among persons with TB disease, whereas the largest single ethnic group among persons with LTBI was Hispanic. This observation might reflect settlement and screening practices for recently immigrated persons from Central and South America vs. more widespread settlement or residential patterns of persons of Asian origin. The proportion of the underlying population identifying as Hispanic was also greater in most clustered census tracts than in non-clustered census tracts, possibly representing settlement patterns, while the difference in the percentage of the underlying population identifying as Asian was less striking. The low TB prevalence in areas from which many Asian persons with TB disease were reported could lead to reduced screening and a greater rate of progression to active TB disease. Further exploration of the countries of origin of Hispanic persons in high-prevalence areas could inform culturally sensitive screening strategies.

These findings support LTBI screening of foreign-born persons regardless of time since arrival in the United States. At least a quarter of persons with LTBI in clusters, and at least a third of those not residing in clusters, reported arrival in the United States ≥5 years before diagnosis. Foreign-born persons diagnosed with TB disease were more likely to have been in the United States for >5 years than those with LTBI. The risk of reactivation of TB remains high >10 years after arrival,[28–31] and missed opportunities for screening among foreign-born persons with TB disease have been documented.[12] Assuming that the majority of TB infections reviewed were acquired outside the United States, earlier screening and treatment

[*]The appendix is available in the online version of this article, at http://www.ingentaconnect.com/content/iuatld/ijtld/2018/00000022/00000002/art00009

might have prevented TB disease. Specifically, persons with LTBI born in Europe were less likely to reside in an identified cluster; this population has also frequently been found to have TB identified.>10 years after arrival in the United States.[32] While it might not be cost-effective to screen all persons from high-incidence European countries, greater attention should be given to evaluating individual risk in this population.

The cluster analysis indicated significant spatial patterns of LTBI and TB disease statewide. Although the spatial distribution of some LTBI and TB disease clusters overlapped, persons with LTBI were reported from more census tracts across the state than persons with TB disease. Persons with LTBI, however, were more likely than those with TB disease to reside in a spatial cluster, perhaps reflecting increased testing. In Connecticut, local health jurisdictions encompass substantial socio-economic and demographic differences among census tract-level neighborhoods as well as variations in TB disease and LTBI prevalence. This fine scale variation complicates practitioners' and local public health's decision making about population-level risk for LTBI, a component of the USPSTF recommendations.[9] Fine-scale variations in LTBI and TB epidemiology are likely common to other states. Our results are not likely to be generalizable given the substantial spatial and demographic heterogeneity in Connecticut's population, but we highlight the need to conduct fine-scale analyses of LTBI for local decision making.

This cross-sectional study cannot confirm causal associations between the characteristics of census tracts and LTBI prevalence. The greater clustering of high LTBI prevalence census tracts than those with high TB prevalence could have resulted from the higher power of SatScan to detect clusters based on the greater number of LTBI reports. The effect of persons gaining insurance under the Affordable Care Act on reporting for the purpose of obtaining medications is unknown. The analysis included persons with LTBI tested for all reasons, and this might have created spatial bias in the model, given that settlement patterns and screening policies of immigrants and refugees are not uniform across the state; the reasons for LTBI testing were not captured and could not be evaluated. In addition, contact investigations in areas with high TB prevalence are likely to result in the reporting of additional persons with LTBI. Finally, as in previous spatial studies of TB disease, our spatial analysis assumed that LTBI and TB each had independent Poisson distributions across the state. Local transmission of *M. tuberculosis* could violate this assumption by creating spatial dependence,[18,19] as could the settlement patterns of recent immigrants.

In conclusion, characterizing populations at risk for LTBI supports USPSTF recommendations and helps providers prevent missed opportunities for testing.[9,12] Our findings emphasize the need for systematic and complete reporting of LTBI to facilitate the design of neighborhood-level, culturally appropriate screening and case management.[31,33]

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgements

The authors thank the providers and local health departments that report cases of TB disease and LTBI to the state; T Condren, Connecticut Department of Health, Hartford, CT, USA; J Tobias, S Kammerer, and K Bisgard, Centers for Disease Control and Prevention (CDC), Atlanta, GA, USA.

Disclaimer: The findings and conclusions in this report are those of the author(s) and do not necessarily represent the official position of the CDC.

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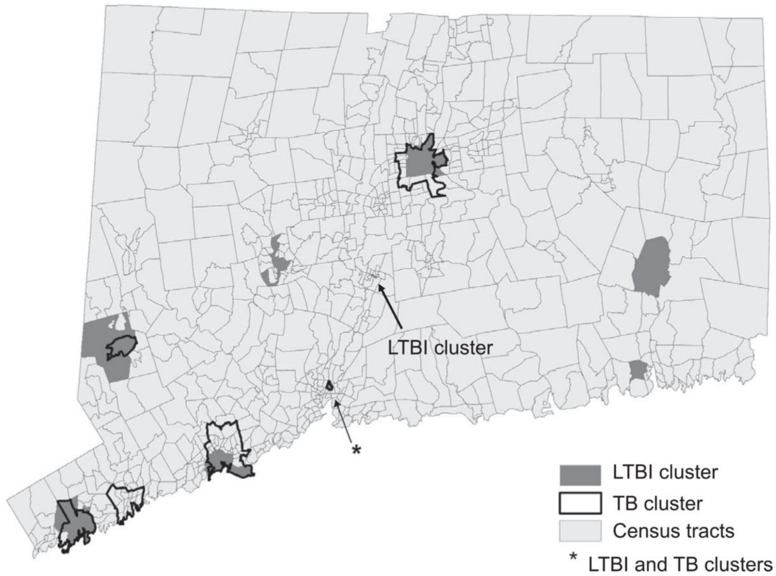


**Figure.**

Significant census tract clusters identified by SaTScan™ as being at high risk for TB disease or LTBI, Connecticut, 2010–2014. LTBI = latent tuberculous infection; TB = tuberculosis.

## Table 1

Comparison of selected characteristics of patients with TB disease and patients with LTBI, Connecticut, 2010–2014

| Patient characteristics | LTBI ($n$ = 9701) $n$ (%) | TB disease ($n$ = 365) $n$ (%) | OR (95%CI)* | $P$ value |
|---|---|---|---|---|
| Geocoded | 9427 (97.2) | 357 (97.8) | | |
| In a cluster | 5111 (52.7) | 137 (37.5) | 1.85 (1.49–2.30) | <0.0001 |
| Male | 4825 (49.7) | 203 (55.6) | 0.79 (0.64–0.98) | 0.0297 |
| Age, years (range) | 30 (0–112) | 37 (0–91) | | 0.0001† |
| Race/ethnicity | | | | |
| White non-Hispanic | 1648 (16.9) | 71 (19.5) | 0.85 (0.65–1.10) | 0.2194 |
| Black non-Hispanic | 211 (21.6) | 70 (19.2) | 1.17 (0.90–1.53) | 0.2397 |
| Hispanic | 2425 (24.8) | 89 (24.4) | 1.03 (0.81–1.32) | 0.7903 |
| Asian | 1737 (17.8) | 135 (37.0) | 0.37 (0.30–0.46) | <0.0001 |
| Foreign-born | | | | |
| Yes | 7395 (76.3) | 289 (79.2) | 1.29 (1.00–1.67) | 0.0509 |
| No | 1514 (15.6) | 76 (20.8) | | |
| Unknown | 792 (8.2) | 0 | | |
| Time in US (foreign-born), years | | | | |
| <5 | 4479 (67.9) | 118 (40.8) | 3.15 (2.48–4.01) | <0.0001 |
| ⩾5 | 2120 (32.1) | 171 (59.2) | | |
| Unknown | 796 (10.8) | 0 | | |
| HIV status | | | | |
| Negative | 2584 (26.7) | 289 (79.4) | 0.0002 (0.00–0.0) | <0.0001 |
| Positive | 184 (1.9) | 26 (7.1) | 0.25 (0.16–0.39) | <0.0001 |
| Not done/unknown | 6923 (71.4) | 49 (13.5) | 16.07 (11.86–21.78) | <0.0001 |

* Pearson's $\chi^2$.

† Wilcoxon rank-sum test.

LTBI = latent tuberculous infection; TB = tuberculosis; OR = odds ratio; CI = confidence interval; HIV = human immunodeficiency virus.

**Table 2**

**A)** Comparison of selected LTBI patient and population characteristics of census tracts within and outside of significant clusters identified by SaTScan™, Connecticut, 2010–2014

| Patient characteristics | Total ($n$ = 9701) $n$ (%) | In a cluster ($n$ = 5111, 54.2%)* $n$ (%) | Not in a cluster ($n$ = 4316, 45.7)* $n$ (%) | OR (95%CI) | $P$ value |
|---|---|---|---|---|---|
| Male | 4825 (49.7) | 2626 (51.3) | 2051 (47.5) | 1.17 (1.1–1.3) | 0.0002 |
| Age, years (range) | 30 (0–112) | 27 (0–103) | 32 (0–112) | | <0.0001† |
| Race/ethnicity | | | | | |
| White non-Hispanic | 1648 (17.0) | 629 (12.3) | 975 (22.6) | 0.48 (0.4–0.5) | <0.0001 |
| Black non-Hispanic | 2111 (21.8) | 1285 (25.1) | 773 (17.9) | 1.54 (1.4–1.7) | <0.0001 |
| Hispanic | 2425 (25.0) | 1365 (26.7) | 996 (23.1) | 1.21 (1.1–1.3) | <0.0001 |
| Asian | 1737 (17.9) | 943 (18.5) | 730 (16.9) | 1.11 (1.0–1.2) | 0.0517 |
| Other | 46 (0.5) | 18 (0.4) | 27 (0.6) | | |
| Unknown | 1734 (17.9) | 871 (17.0) | 815 (18.9) | | |
| Foreign-born | | | | | |
| Yes | 7395 (76.3) | 4337 (84.9) | 2867 (66.4) | 2.84 (2.5–3.2) | <0.0001 |
| No | 1514 (15.6) | 505 (10.0) | 952 (22.0) | | |
| Unknown | 792 (8.2) | 264 (5.2) | 497 (11.5) | | |
| Time in US (foreign-born), years | | | | | |
| <5 | 4479 (60.5) | 3014 (69.5) | 1368 (47.7) | 2.18 (2.0–2.4) | <0.0001 |
| ⩾5 | 2120 (28.7) | 1039 (24.6) | 1027 (35.8) | | |
| Unknown | 796 (10.8) | 284 (0.07) | 472 (16.5) | | |

**B)** Census-tract socio-economic variables (median values shown)

| | All census tracts % | Clustered census tracts % | Non-clustered census tracts % | $P$ value† |
|---|---|---|---|---|
| Housing units/square mile, $n$ | 1576.12 | 4030.8 | 1171.5 | <0.0001 |
| Proportion of households with >1 occupant per room | 2.0 | 4.9 | 1.5 | <0.0001 |
| Proportion of population aged ⩾25 years who did not graduate from high school | 12.4 | 24.8 | 10.0 | <0.0001 |
| Proportion of population foreign-born | 13.5 | 25.0 | 11.64 | <0.0001 |
| Proportion of population below the poverty level | 11.5 | 24.7 | 9.4 | <0.0001 |

| | | | | |
|---|---|---|---|---|
| Proportion uninsured | 9.0 | 17.3 | 7.7 | <0.0001 |

*Excludes 274 not geocoded.

†Wilcoxon rank-sum test.

LTBI = latent tuberculous infection; OR = odds ratio; CI = confidence interval; HIV = human immunodeficiency virus.