



## Using Geographic Disaggregation to Compare Tuberculosis Epidemiology Among American Indian and Alaska Native Persons—USA, 2010–2020

Yuri P. Springer<sup>1</sup>, J. Steve Kammerer<sup>1</sup>, Derrick Felix<sup>1</sup>, Katherine Newell<sup>2,3</sup>, Megan L. Tompkins<sup>3</sup>, Jamie Allison<sup>3</sup>, Louisa J. Castrodale<sup>3</sup>, Bruce Chandler<sup>3</sup>, Kathryn Helfrich<sup>3</sup>, Michelle Rothoff<sup>3</sup>, Joseph B. McLaughlin<sup>3</sup>, Benjamin J. Silk<sup>1</sup>

<sup>1</sup>Centers for Disease Control and Prevention, National Center for HIV, Viral Hepatitis, STD, and TB Prevention, Division of Tuberculosis Elimination, Atlanta, GA, USA

<sup>2</sup>Epidemic Intelligence Service, Centers for Disease Control and Prevention, National Center for State, Tribal, Local, and Territorial Public Health Infrastructure and Workforce, Division of Workforce Development, Atlanta, GA, USA

<sup>3</sup>Alaska Division of Public Health, Section of Epidemiology, Anchorage, Alaska, USA

### Abstract

**Background**—American Indian and Alaska Native (AIAN) populations are frequently associated with the highest rates of tuberculosis (TB) disease of any racial/ethnic group in the USA. We systematically investigated variation in patterns and potential drivers of TB epidemiology among geographically distinct AIAN subgroups.

**Methods**—Using data reported to the National Tuberculosis Surveillance System during 2010–2020, we applied a geographic method of data disaggregation to compare annual TB incidence and the frequency of TB patient characteristics among AIAN persons in Alaska with AIAN persons in other states. We used US Census data to compare the prevalence of substandard housing conditions in AIAN communities in these two geographic areas.

**Results**—The average annual age-adjusted TB incidence among AIAN persons in Alaska was 21 times higher than among AIAN persons in other states. Compared to AIAN TB patients in other states, AIAN TB patients in Alaska were associated with significantly higher frequencies of multiple epidemiologic TB risk factors (e.g., attribution of TB disease to recent transmission,

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✉Yuri P. Springer, [vkh3@cdc.gov](mailto:vkh3@cdc.gov).

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previous diagnosis of TB disease) and significantly lower frequencies of multiple clinical risk factors for TB disease (e.g., diagnosis with diabetes mellitus, end-stage renal disease). Occupied housing units in AIAN communities in Alaska were associated with significantly higher frequencies of multiple measures of substandard housing conditions compared to AIAN communities in other states.

**Conclusions**—Observed differences in patient characteristics and substandard housing conditions are consistent with contrasting syndromes of TB epidemiology in geographically distinct AIAN subgroups and suggest ways that associated public health interventions could be tailored to improve efficacy.

### Keywords

Alaska; American Indian and Alaska Native (AIAN) persons; Disaggregation; Health disparities; Substandard housing; Tuberculosis

## Introduction

Indigenous persons throughout the world routinely experience a disproportionate burden of tuberculosis (TB) disease [1]. In the USA, indigenous American Indian and Alaska Native (AIAN) persons are frequently associated with the highest TB rates of any racial and ethnic group [2–4]. Annual TB incidence among non-Hispanic single-race AIAN persons was on average 12 times that among non-Hispanic single-race White persons during 2009–2019 [4]. Additionally, AIAN persons with TB are often associated with relatively high frequencies of clinical and sociobehavioral TB risk factors (e.g., diagnosis with diabetes mellitus or end-stage renal disease or chronic renal failure, use of illicit substances or alcohol to excess, experiencing homelessness) that can increase the probabilities of infection and adverse disease outcomes [2–4]. These and other TB-related health disparities coincide with and reflect the impacts of the unequal distribution of social determinants of health (SDOH) on health outcomes [5, 6].

Administrative classification schemes used to stratify health data by race and ethnicity typically categorize persons into a small number of broadly defined groups [e.g., 7], an imprecise approach that may be problematic for characterizing persons of AIAN race. AIAN persons are defined by the US Census as individuals having origins in any of the original peoples of North and South America (including Central America) who maintain tribal affiliation or community attachment [7]. Following from this, the AIAN race group is an aggregate demographic category that includes persons who may identify as American Indian, Alaska Native, or both may identify with one or more other races and with Hispanic or non-Hispanic ethnicity and may be members of one or more of 574 tribes distributed across North America and currently recognized by the US government [8]. The result is a highly heterogeneous group associated with a diversity of sociocultural, historical, linguistic, geographic, ethnic, and multiracial characteristics. While aggregation can simplify analyses and reporting of public health data and streamline the development and implementation of public health programs, it can also obscure important health differences between aggregated subgroups and introduce programmatic inefficiencies through one-size-fits-all interventions. As efforts to address health disparities intensify, the utility of disaggregation to characterize

the health of specific subgroups more precisely and accurately is increasingly recognized [9, 10].

Within the USA, Alaska is associated with the highest number of AIAN tribes and population fraction of AIAN persons and frequently has the highest TB incidence of any state. Of the 574 AIAN tribes in the USA that are currently federally recognized, 227 (39.5%) are located in Alaska; the only other state in which more than 100 tribes are located is California ( $N = 104$ , 18.1%) [8] (note that the present day and historical geographic associations of many tribes are highly disparate, generally due to policies and actions of the US government such as the Indian Removal Act of 1830 and attendant forced relocations of AIAN persons and communities [11]). Alaska also has the highest per capita number of tribes of any state: 30.8 per 100,000 residents in 2020 compared to a median value of 0.03 per 100,000 residents in other states (range = 0–1.0) [8, 12]. During 2010–2020, the annual percentage of Alaska residents who identified with AIAN race was the highest of any state in every year (mean across years = 19.5%) and was on average 11.5 times the national percentage (1.7%) [12]. Concurrently, the annual TB incidence in Alaska was the highest or second highest of any state in every year (mean across years = 8.4 cases per 100,000 persons) and was on average 2.8 times the national incidence (mean across years = 3.0 cases per 100,000 persons); among these Alaska TB cases, 73.3% were in non-Hispanic single race AIAN persons [13]. These data suggest that compared to other states, the AIAN population in Alaska may be culturally and demographically unique and differ fundamentally in terms of TB epidemiology.

In this investigation, we applied a geographic method of data disaggregation involving a binary categorization of the state in which TB cases were counted (Alaska versus states other than Alaska) to characterize the epidemiology of TB among AIAN persons in the USA. Our approach parallels that of other investigations into AIAN health that stratified analyses geographically by the US Indian Health Service (IHS) region, of which Alaska is one [14–17]. We estimated annual TB incidence and the frequencies of select demographic, clinical, and sociobehavioral characteristics of TB patients to describe the variation between these two AIAN analytic groups. Additionally, to explore the potential contributions of SDOH to epidemiologic differences observed between groups, we compared the prevalence of substandard housing conditions in AIAN communities in these two geographic areas. Housing quality is widely recognized as an SDOH that underlies patterns and inequalities associated with numerous health conditions including respiratory diseases [18–20]. Our objective was to describe variation in TB epidemiology within geographically distinct groups of AIAN persons that could inform the development of more precisely tailored and effective TB prevention and control efforts in AIAN communities.

## Methods

### Study Design

We analyzed data on cases of TB disease reported to the Centers for Disease Control and Prevention's (CDC) National Tuberculosis Surveillance System (NTSS). Our analyses included all incident reports that met the case definition [21] during January 1, 2010–December 31, 2020, were counted within any of the 50 states or DC, and occurred in a

person who was US-born (i.e., born in the USA or a US-affiliated jurisdiction, or outside the USA to at least one parent with US citizenship) and who self-reported their country of birth as the USA (or for whom no country of birth was recorded). Using self-reported data on patient race and ethnicity and the state in which each case was counted (the patient's state of residence at the time of their TB evaluation), we assigned cases to one or two of four race/geography groups: (i) AIAN Alaska: cases in AIAN persons (defined in this investigation as any person who identified with AIAN race, irrespective of ethnicity and including both single race and multiracial persons) counted in Alaska, (ii) AIAN other states: cases in AIAN persons counted in a state other than Alaska (including DC), (iii) AIAN US: all cases in AIAN persons counted in the USA, and (iv) White US: all cases in non-Hispanic single race White persons counted in the USA. The AIAN US group consists of all cases assigned to the AIAN Alaska and AIAN other state groups. As a result, neither of these subgroups could be compared to the AIAN US group statistically due to non-independence.

### TB Incidence and Patient Characteristics

All analyses of TB epidemiology were stratified by race/geography group. We calculated age-adjusted annual TB incidence (cases per 100,000 persons) using population estimates from the US Census Bureau's American Community Survey (ACS) 5-year public use microdata sample (PUMS) dataset [22] and direct standardization to the 2010 US population [23]; associated 95% confidence intervals (CIs) were calculated using the log Student's *t* method [24] with variance of incidence based on PUMS person-weights. We compared annual incidence among race/geography groups using incidence rate ratios (IRRs) and associated CIs calculated using the normal approximation (Wald) method. The White US and AIAN other states groups were used as references, the former because it consistently has the lowest annual TB incidence among race/ethnicity groups [21] and the latter only for direct comparison with the AIAN Alaska group. Characteristics of TB patients were similarly compared using prevalence ratios (PRs) and CIs or using chi-square tests. We calculated PR CIs using the normal approximation (Wald) method if the numerator for the nonreference group was  $> 10$  and otherwise using a bootstrap method with 10,000 replicates. We defined statistical significance as  $P < 0.05$ . To identify and compare the proportion of cases attributed to recent transmission among race/geography groups, we used the plausible source case method [25] and molecular surveillance data generated using spoligotyping and 24 locus mycobacterial interspersed repetitive units variable number of tandem repeats (MIRU-VNTR) molecular typing methods and collected by CDC's National Tuberculosis Genotyping Service during 2011–2020. In analyses of recent transmission, we only considered cases in patients  $\geq 15$  years of age because *Mycobacterium tuberculosis* isolates from sputum cultures needed for genotyping cannot be obtained consistently from younger patients.

### Housing Quality

We used an area-based measures approach involving data from the 2020 US Census ACS 5-year estimate dataset [12] to estimate the prevalence of substandard housing conditions in AIAN communities. We defined these communities by identifying all census tracts in Alaska, and in states other than Alaska (including DC), in which AIAN persons constituted 50% of the resident population. For each group, we estimated the average percentage of

occupied housing units across census tracts that was associated with one or more of the four measures of substandard housing estimated as part of the ACS and reported in table B25123: overcrowding (≥ 1 occupant per room), incomplete kitchen facilities, incomplete plumbing facilities, and ≥ 30% of household income spent on rent or monthly owner costs. For broader comparison, we also estimated average percentages for a national reference group consisting of all census tracts in the USA. We compared percentages for these three groups statistically using 95% CIs calculated using the normal approximation (Wald) method.

## Results

Among 108,755 incident TB cases reported to NTSS during 2010–2020, 33,309 (30.6%) were counted within one of the 50 states or DC and in a US-born patient whose country of birth was the USA (or for whom no country of birth was recorded). Of these, 1388 (4.2%) and 10,807 (32.4%) were categorized into the AIAN US and White US race/geography groups, respectively. Of the AIAN US cases, 499 (36.0%) were also categorized into the AIAN Alaska group; the remaining 889 (64.0%) were categorized into the AIAN other states group.

### TB Incidence

Age-adjusted annual TB incidence (cases per 100,000 persons) for the AIAN Alaska group (range = 25.69–46.74) was significantly higher than for the AIAN other states and White US groups in all years and did not exhibit any significant temporal trends in magnitude based on overlapping CIs for annual incidence estimates (Fig. 1, Sup Table 1). Annual incidence for the AIAN other states (range = 0.95–3.32), AIAN US (range = 1.69–4.30), and White US (range = 0.26–0.69) groups all exhibited significant declines in magnitude from maxima in 2010 to minima in 2020 (based on nonoverlapping CIs). Overall, annual incidence for the AIAN US group was consistently lower than for the AIAN Alaska group and higher than for the AIAN other states group; annual incidence for the White US group was significantly lower than for all other race/geography groups in all years (Fig. 1, Sup Table 1). Relative to the White US group, age-adjusted annual IRRs for the AIAN Alaska group increased significantly from a minimum of 59.90 in 2010 to a maximum of 114.58 in 2020 (Fig. 1, Sup Table 1). By comparison, annual IRRs for the AIAN other states (range = 2.80–5.07) and AIAN US (range = 5.09–7.54) groups varied through time but did not exhibit any consistent temporal trends. Relative to the AIAN other states group, annual IRRs for the AIAN Alaska group increased significantly through time from 12.45 in 2010 to 31.36 in 2019 (Fig. 1, Sup Table 1). Results involving crude annual TB incidence and associated IRRs were qualitatively similar and are provided for reference (Sup Fig. 1, Sup Table 2).

### TB Patient Characteristics—AIAN Alaska and AIAN Other States Groups Compared with White US Group (Reference)

Relative to TB patients in the White US group, significantly higher percentages of patients in the AIAN Alaska and AIAN other states groups were < 15 years of age (1.7% versus 16.6% and 8.5%, respectively; both comparisons  $\chi^2 = 178.3$ ,  $P = 0.0001$ ). The percentage of patients that were female was significantly higher in the AIAN other states group compared

to the White US group (31.6% versus 44.4%,  $\chi^2 = 62.0$ ,  $P = 0.0001$ ); the percentage in the AIAN Alaska group (35.7%) did not differ from the White US group (Sup Table 3).

Among TB patients of all ages, those in the AIAN Alaska group were significantly more likely than patients in the White US group to have been diagnosed with TB previously (PR = 2.85), to have had a positive sputum culture recorded for their current TB episode (PR = 1.31), and to have successfully completed treatment for their current TB episode (PR = 1.09); they were significantly less likely to have died during treatment for their current TB episode (PR = 0.39) and to have had cavitary disease on chest radiograph or chest computed tomography scan (PR = 0.70) (Fig. 2, Sup Table 3). No significant differences were observed between patients in the AIAN other states and White US groups for any of these patient characteristics.

Among TB patients  $\geq 15$  years of age, patients in both the AIAN Alaska and AIAN other states groups were significantly less likely than patients in the White US group to have been immunosuppressed because of a condition other than HIV/AIDS or a medication (PR = 0.11 and PR = 0.50, respectively) and significantly more likely to have their current episode of TB disease attributed to recent transmission (PR = 3.89 and PR = 1.46). Patients in both groups were also more likely than patients in the White US group to have reported using excess alcohol (PR = 2.32 and PR = 1.63), using non-injection drugs (PR = 1.77 and PR = 1.56), being primarily unemployed (PR = 1.78 and PR = 1.27), or experiencing homelessness (PR = 1.69 and PR = 1.33) during the 12 months prior to their TB diagnosis (Fig. 2, Sup Table 3, Sup Table 4). Compared to patients in the White US group, patients in the AIAN other states group were significantly more likely and those in the AIAN Alaska group were significantly less likely to have been diagnosed with end-stage renal disease or chronic renal failure (PR = 2.94 and PR = 0.27, respectively) and with diabetes mellitus (PR = 2.15 and PR = 0.09) (Fig. 2, Sup Table 3, Sup Table 4).

### **TB Patient Characteristics—AIAN Alaska Group Compared with AIAN Other States Group (Reference)**

Relative to TB patients in the AIAN other states group, a significantly higher percentage of patients in the AIAN Alaska group was  $< 15$  years of age ( $\chi^2 = 20.6$ ,  $P < 0.0001$ ) and a significantly lower percentage were female ( $\chi^2 = 10.1$ ,  $P = 0.001$ ) (Sup Table 3).

Among TB patients of all ages, those in the AIAN Alaska group were significantly more likely than those in the AIAN other states group to have been diagnosed with TB previously (PR = 2.42), have had a positive sputum culture recorded for their current TB episode (PR = 1.24), have had pulmonary disease (PR = 1.14), and have successfully completed treatment for their current TB episode (PR = 1.11); they were significantly less likely to have died during treatment for their current TB episode (PR = 0.33), have had cavitary disease on chest radiograph or chest computed tomography scan (PR = 0.64), and to have been sputum smear positive for acid-fast bacilli (PR = 0.76) (Fig. 3, Sup Table 3).

Among TB patients  $\geq 15$  years of age, those in the AIAN Alaska group were significantly less likely than those in the AIAN other states group to have been diagnosed with diabetes mellitus (PR = 0.04) or end-stage renal disease or chronic renal failure (PR = 0.09), have



been HIV positive (PR = 0.05), have been immunosuppressed because of a condition other than HIV/AIDS or a medication (PR = 0.22), and have reported using injection drugs during the 12 months prior to their TB diagnosis (PR = 0.40); they were significantly more likely to have their current episode of TB disease attributed to recent transmission (PR = 2.67) and have reported using excess alcohol (PR = 1.42) and being primarily unemployed (PR = 1.40) during the 12 months prior to their TB diagnosis (Fig. 3, Sup Table 3, Sup Table 4).

### Housing Quality

In the 2020 ACS dataset, 21 of 177 (11.9%) census tracts in Alaska and 206 of 84,237 (0.2%) census tracts in states other than Alaska had resident populations of which 50% were AIAN persons and were selected to represent AIAN communities in the area-based analysis. These groups of census tracts included 17,565 and 186,054 occupied housing units, respectively (Sup Table 5, Sup Table 6). Compared to AIAN communities in states other than Alaska, AIAN communities in Alaska were associated with significantly higher mean percentages of occupied housing units with 1 measures of substandard housing (49.3% versus 32.7%; 31.8% nationally), 2 measures of substandard housing (19.2% versus 7.6%; 1.9% nationally), 3 measures of substandard housing (5.7% versus 1.6%; 0.1% nationally), and all four measures of substandard housing (0.5% versus 0.1%; 0.01% nationally) (Fig. 4, Sup Table 5, Sup Table 6). Significantly higher percentages of occupied housing units in AIAN communities in Alaska had 1 occupants per room (overcrowding: 23.0% versus 12.0%; 3.5% nationally), 1.5 occupants per room (severe overcrowding: 11.0% versus 5.1%; 1.2% nationally), incomplete kitchen facilities (13.7% versus 5.6%; 0.9% nationally), and incomplete plumbing facilities (20.4% versus 7.3%; 0.4% nationally) (Fig. 4, Sup Table 5, Sup Table 6).

### Discussion

Using geographic criteria to disaggregate data on TB cases reported among AIAN persons in the USA during 2010–2020, we identified at least two important differences in TB epidemiology between AIAN persons in Alaska and AIAN persons in other states. First, annual age-adjusted TB incidence over the 11-year investigation period was on average 21 times higher among AIAN persons in Alaska compared to AIAN persons in other states; IRRs increased gradually during 2010–2017 (mean = 17.9) and then sharply during 2018–2020 (mean = 28.7). On average, annual age-adjusted TB incidence for the AIAN Alaska group was 84 times that for the White US group. Second, the frequencies of various patient characteristics that are risk factors for TB disease varied significantly between the AIAN Alaska and AIAN other states groups. Multiple comorbidities that are clinical risk factors were significantly less common among patients in the AIAN Alaska group, while certain sociobehavioral and epidemiologic risk factors were significantly more common. These findings demonstrate that aggregating AIAN TB patients in Alaska and in other states together into a single analytic or reporting group masks epidemiologic variation between these subgroups.

While the exceedingly high rates of TB disease among AIAN persons in Alaska caused age-adjusted incidence for the AIAN US group to exceed that for the AIAN other states

group in all years, the mean absolute annual difference between the AIAN other states and AIAN US groups (0.93 cases per 100,000 persons) was perhaps smaller than might have been expected given the much larger absolute mean difference observed between the AIAN Alaska and AIAN US groups (34.8 cases per 100,000 persons). This was because as an annual average, AIAN persons in Alaska accounted for only 2.82% of the national AIAN population. The AIAN population in states other than Alaska was on average 34.4 times larger than the AIAN population in Alaska and therefore exerted a disproportionate effect on incidence estimated for the AIAN US group by substantially increasing the associated denominator (Sup Table 2). In contrast, AIAN persons in Alaska accounted for an annual average of 37.0% of AIAN TB cases nationally; this proportion increased from 24.0 to 40.9% during 2010–2013, declined gradually to 30.6% in 2017, and then increased sharply to a high of 47.7% in 2019 and 2020. Thus, although the size of the AIAN population in Alaska is relatively small, its proportional contribution to the TB burden in AIAN persons is large. Together, these findings suggest that TB control efforts among AIAN persons in Alaska involve a focal population that is relatively small numerically but could contribute substantially to reducing TB incidence among AIAN persons nationally. For example, the prevention of just 10 TB cases in AIAN persons 45–64 years of age in Alaska during 2020 would have reduced age-adjusted incidence in the AIAN Alaska group by 33% (from 29.79 to 20.09 cases per 100,000 persons) and incidence in the AIAN US group by 13% (from 1.69 to 1.47 cases per 100,000 persons).

Our examination of patient characteristics identified several significant clinical and epidemiologic differences between AIAN TB patients in Alaska and in other states. Notably, AIAN patients in Alaska were < 0.10 times as likely to also be diagnosed with diabetes mellitus, HIV, or end-stage renal disease or chronic renal failure, 0.22 times as likely to have been immunosuppressed at the time of TB diagnosis, and 0.64 times as likely to have had cavitary disease. These clinical risk factors are associated with an increased probability of experiencing adverse outcomes of TB disease [26–30]; corresponding to lower prevalence of these risk factors, we found that AIAN patients in Alaska were 0.33 times as likely as AIAN patients in other states to die during TB treatment. These results are likely influenced by low frequencies of these conditions in underlying Alaskan populations. For example, a comparison of annual diabetes prevalence during 2006–2017 among AIAN persons 18 years of age consistently found the lowest prevalence in the Alaska IHS region; prevalence in other IHS regions was two- to four-times higher [16]. During 2009–2019, the annual prevalence of end-stage renal disease among non-Hispanic AIAN persons in Alaska was on average five times lower than that among non-Hispanic AIAN persons in all other states [31]. These results are also consistent with our finding that relative to the White US group, the age distributions of patients in the AIAN US, AIAN other states, and especially AIAN Alaska groups were all strongly right-skewed. Among AIAN TB patients in Alaska, the percentage < 15 years of age (16.6%) was nearly double that for AIAN patients in other states (8.5%).

In contrast to results involving clinical risk factors, AIAN TB patients in Alaska were 2.67 times as likely to have their TB disease attributed to recent transmission and 2.42 times as likely to have a previous diagnosis of TB compared to AIAN TB patients in other states. These results are indicative of ongoing TB transmission in AIAN communities



in Alaska. Findings that, when compared with AIAN TB patients in other states, AIAN TB patients in Alaska were 1.40 times as likely to have been primarily unemployed, 1.27 times as likely to have experienced homelessness, and 1.42 times as likely to have used alcohol to excess during the 12 months prior to their TB diagnosis suggest that economic, social, and behavioral risk factors may contribute to *M. tuberculosis* transmission among AIAN persons in Alaska. Although additional empirical support is needed, these results are consistent with contrasting syndromes of TB epidemiology in our focal groups. Among AIAN persons in Alaska, 60.2% of TB cases were attributed to ongoing transmission, perhaps catalyzed by socioeconomic and sociobehavioral risk factors; disease severity and associated adverse outcomes in TB patients may be relatively limited by the low prevalence of clinical comorbidities. Among AIAN persons in other states, the fraction of TB cases attributable to reactivation of latent TB infection (LTBI) was comparatively higher, the frequency of secondary infections more limited, and the likelihood of severe disease and adverse outcomes in patients elevated by a higher prevalence of clinical comorbidities. Within this framework, tailored TB control efforts in AIAN communities in Alaska might prioritize greater surveillance sensitivity to detect new cases, improved responsiveness to interrupt secondary transmission, and sociobehavioral and socioeconomic interventions to reduce the risk of *M. tuberculosis* transmission and delays in diagnosis and treatment of TB disease. In AIAN communities in other states, programs might emphasize LTBI testing and treatment, improved access to and use of high-quality, coordinated clinical care services for patients, and the strengthening of integrated programs to improve the overall health of community members.

Studies describing health disparities routinely report findings stratified by race and ethnicity, yet the fact that these demographic characteristics are merely proxies for the SDOH that act as the mechanistic drivers of unequal health outcomes is widely recognized for TB [5, 6] including for TB in indigenous persons [32]. Consistent with our findings of disparities in TB incidence, our area-based analyses of substandard housing conditions indicated that the frequencies of overcrowding and severe overcrowding in AIAN communities in Alaska were roughly twice those in AIAN communities in other states and more than six times the national reference value. Household crowding has been linked to elevated risks of both TB exposure and disease development in multiple investigations [33–35]; several involved indigenous communities in Canada which, like US AIAN communities, are associated with high TB incidence and numerous socioeconomic disadvantages, including pervasive housing deficiencies [36]. Studies in individual Canadian Inuit villages found significant positive associations between crowding and the odds of TB infection and disease development among persons living with someone with smear-positive TB [37] and between crowding and LTBI prevalence after controlling for other SDOH [38]; results of a third study conducted across multiple indigenous Canadian communities indicated that an increase in crowding of 0.1 persons per room at the community level was associated with a 40% increase in the probability of 2 TB cases occurring [39].

Similarly, our area-based analyses indicated that the frequencies of incomplete kitchen and plumbing facilities were over twice as high in AIAN communities in Alaska compared to those in other states and more than 15 times the national reference value. Incomplete kitchen facilities could be correlated with poor diet or inadequate nutrition

which have been positively associated with TB infection, disease development, and adverse treatment outcomes [40, 41] including in indigenous communities [42]; nutrition-associated immunologic deficiencies may be implicated [43]. Alternatively, deleterious pulmonary impacts of alternative cooking methods such as the use of biomass fuels that reduce indoor air quality could also increase TB incidence [44–46]. Mechanistic links between indoor plumbing and the epidemiology of a respiratory disease seem unlikely; incomplete plumbing facilities could contribute to reduced hygiene and health in general but are likely an indicator of poverty and socioeconomic marginalization. While cor-relative in nature and requiring additional data, analyses, or interventions to demonstrate causality, the observed positive associations between TB incidence and substandard housing conditions in AIAN communities are consistent with findings of other investigations and with mechanisms of TB transmission and disease development in general [18]. They provide a reminder that TB has long been recognized as a social disease, the meaningful control, and perhaps ultimate elimination of which will require not only effective biomedical interventions but also programs that address and reduce systemic disparities in the social, economic, and environmental drivers of TB epidemiology [5, 6, 47].

Extremely high rates of TB disease and associated mortality among AIAN persons in Alaska have been documented for at least 100 years [48–51]. While TB rates in Alaskan AIAN communities have declined markedly during the twentieth century, they remain consistently higher than in most other racial/ethnic groups and localized geographic areas in the USA [2–4, 21]. Some fraction of the disparity in TB burden between AIAN persons in Alaska and in other states is almost certainly rooted in ongoing challenges in providing timely access to quality healthcare in rural, geographically remote Alaska villages [52] and the persistence of environmental factors ideal for *M. tuberculosis* transmission in these settings (e.g., cold climate that increases time spent indoors, substandard housing conditions with limited ventilation, multigenerational occupancy, and crowding) [53, 54]. The use of active surveillance for TB case finding in Alaska might also result in greater surveillance sensitivity favoring higher case counts compared with other states. Perhaps in part because TB cases in AIAN patients constitute a disproportionate fraction of Alaska's total annual TB burden (mean = 73% during 2010–2020, the highest of any state/jurisdiction) [55], the state's TB control program utilizes multiple active surveillance methods in AIAN communities. These include contact tracing and targeted testing following the identification of cases of active TB disease and community-wide testing events ("sweeps") routinely conducted in rural villages. Sweeps are typically undertaken in villages where there is concern for ongoing *M. tuberculosis* transmission (i.e., one or more recently documented cases or outbreaks) and involve a multiday testing clinic focused on screening contacts of previous TB patients, school students and staff, and any community members interested in participating. Persons without a documented history of TB disease are screened using purified protein derivative skin tests; participants with induration indicative of possible latent TB infection [56] are referred to their nearest subregional or regional clinic for TB evaluation, which may include inter-feron-gamma release assay testing, chest radiography, and sputum collection. Sputa testing is particularly encouraged for persons with a history of TB, who self-report any TB symptoms on interview, or who have had close contact with a TB patient. Such intensive methods of active TB surveillance in Alaskan AIAN

communities may not be employed by TB control programs in other states. Interestingly, while we found significantly lower rates of both smear positivity and cavitary disease (indicators of advanced TB disease) among AIAN TB patients in Alaska compared to those in other states, a result consistent with earlier identification of cases through active surveillance, we also found that over twice as many AIAN TB cases in Alaska were attributed to recent transmission.

Our investigation had several limitations. While NTSS reporting guidelines specify that patient race and ethnicity should be ascertained via self-report, the method considered the gold standard for collection of these data [57], misclassification arising from reporting biases (e.g., social desirability) may still occur, and patient race and ethnicity information may occasionally be collected from alternative sources that may not capture self-reported data (e.g., electronic health records). Racial/ethnic misclassification is a problem of particular relevance for AIAN persons and generally leads to undercounting [10, 58]. All of our data on TB incidence and patient characteristics for the AIAN Alaska group were collected by a single TB control program and thus could be biased by associated programmatic idiosyncrasies (e.g., surveillance methods or effort). While useful for characterizing the nature and completeness of TB treatment, insights into the effectiveness or adequacy of treatment provided by administrative data may be limited. For example, we found that when compared with AIAN TB patients in other states, AIAN TB patients in Alaska received directly observed therapy and successfully completed TB treatment at significantly higher rates yet were still associated with higher TB incidence. Our analyses of TB patient characteristics did not control for variation in the frequencies of reported conditions in underlying populations. Finally, because most public health surveillance systems do not collect SDOH-related data from patients, our analyses of substandard housing conditions necessitated an ecologic approach; the housing conditions we reported for AIAN communities might not accurately describe the actual homes of the TB patients whose cases were included in our analyses.

It is important to note that our TB-related findings are based on data collected from AIAN TB patients and may not reflect broader patterns in AIAN populations. For example, while our results indicate that AIAN TB patients are more likely than White TB patients to have used alcohol to excess during the 12 months prior to their TB diagnosis, data from the general population suggest that rates of binge and heavy drinking among AIAN and White persons are comparable; rates of abstinence from alcohol use are significantly higher among AIAN persons [59]. Similarly, our consideration of a single SDOH should not be construed as a suggestion that substandard housing conditions represent the sole or even principal SDOH affecting the epidemiology of TB among AIAN persons. Numerous and varied SDOH likely underly the health patterns reported herein [60], and more dedicated analyses are warranted to characterize their respective contributions to disparities in TB-related risks and outcomes.

The longstanding disparities in TB disease burden associated with AIAN populations in the USA appear particularly egregious when viewed through a health equity lens. While TB may have been present in these populations at relatively low levels during the pre-colonial period, the current epidemic, along with those of multiple other devastating

infectious diseases, was initiated and accelerated through contact with and exploitation and oppression by non-native colonists [50, 61–63]. Despite this history, AIAN communities have made seminal contributions to clinical research, including advances in methods of TB prevention and control, that benefits all Americans [64]. AIAN persons played critical roles in the early testing of the Bacille Calmette-Guérin (BCG) TB vaccine [65, 66] and of isoniazid chemotherapy for preventing and treating TB disease [50, 67, 68]. While TB incidence in AIAN populations has fallen considerably during the twentieth century [50, 63], the resilience of AIAN persons and communities across the USA continues to be challenged by the impacts of intergenerational historical trauma and ongoing socioeconomic marginalization and disenfranchisement perpetuated through systemic and institutional racism [69–71], poverty and a dearth of socioeconomic opportunities [72, 73], limited access to high-quality healthcare [74–76], and substandard housing conditions [54, 77], each of which contributes to lower life expectancy, lower quality of life, and higher rates of many adverse health conditions [15], evidenced most recently by the COVID-19 pandemic [78, 79]. Our findings reinforce the need for AIAN health promotion efforts that address clinical, behavioral, economic, and social determinants of health and are designed and implemented through collaborations led or meaningfully guided by tribes and tribal communities. The collection, equitable sharing, and intentional analyses of accurate and granular health data, particularly involving patient race and ethnicity, are critical to precisely characterize patterns of health and tailor effective interventions [10, 80, 81].

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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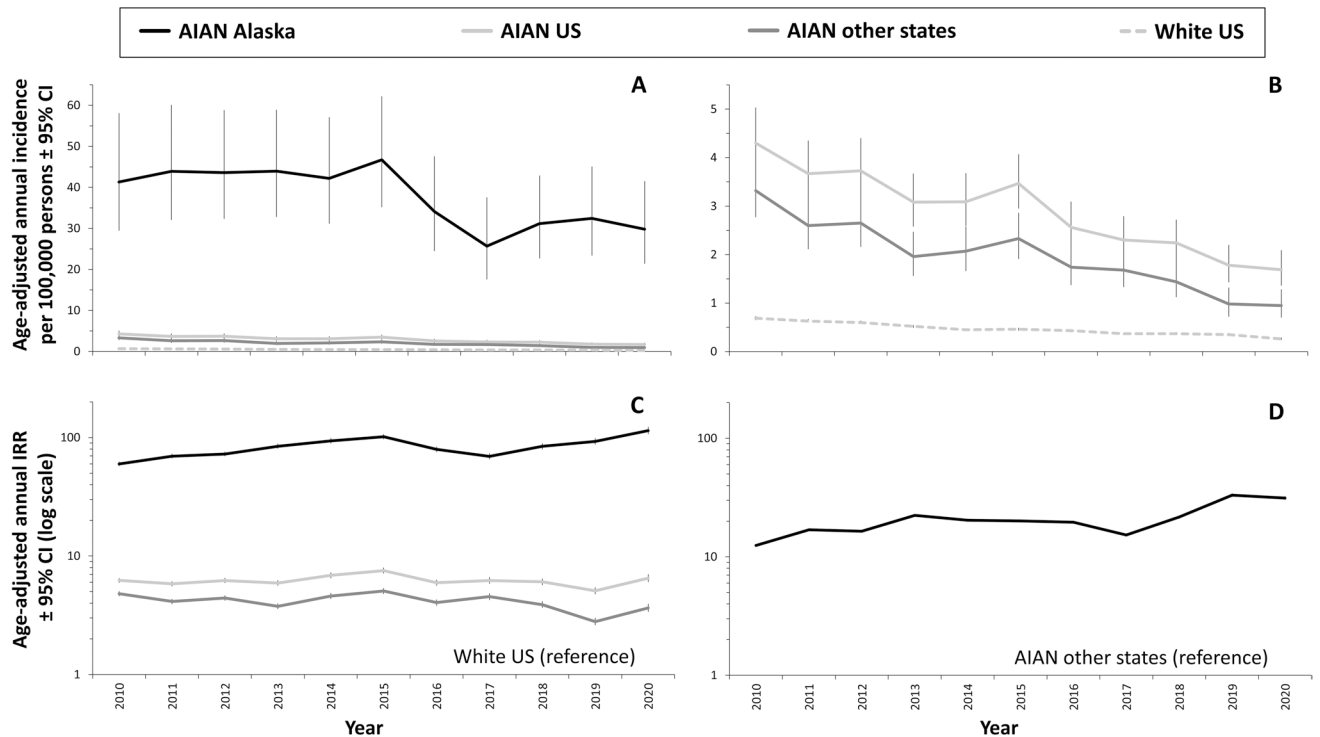
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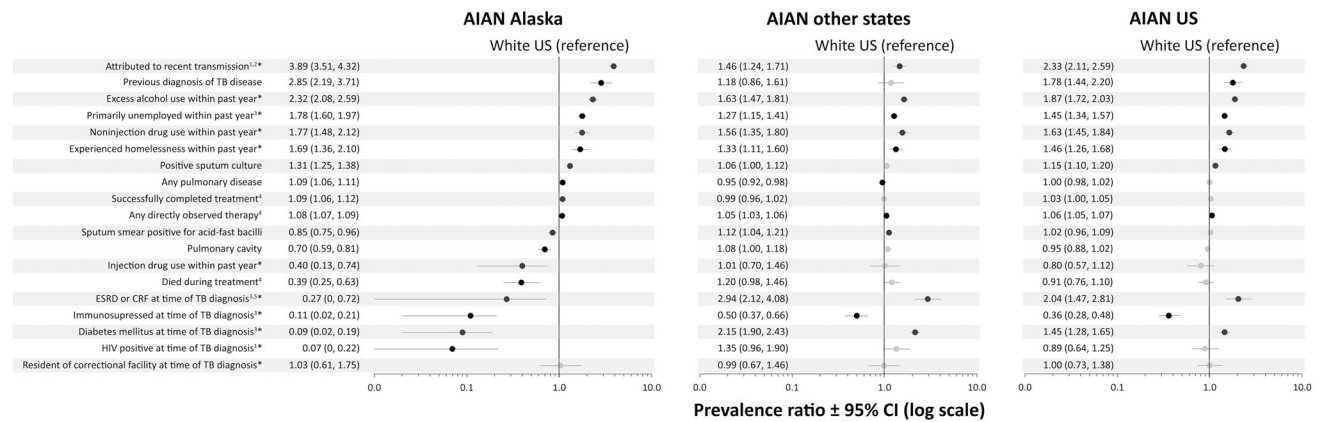


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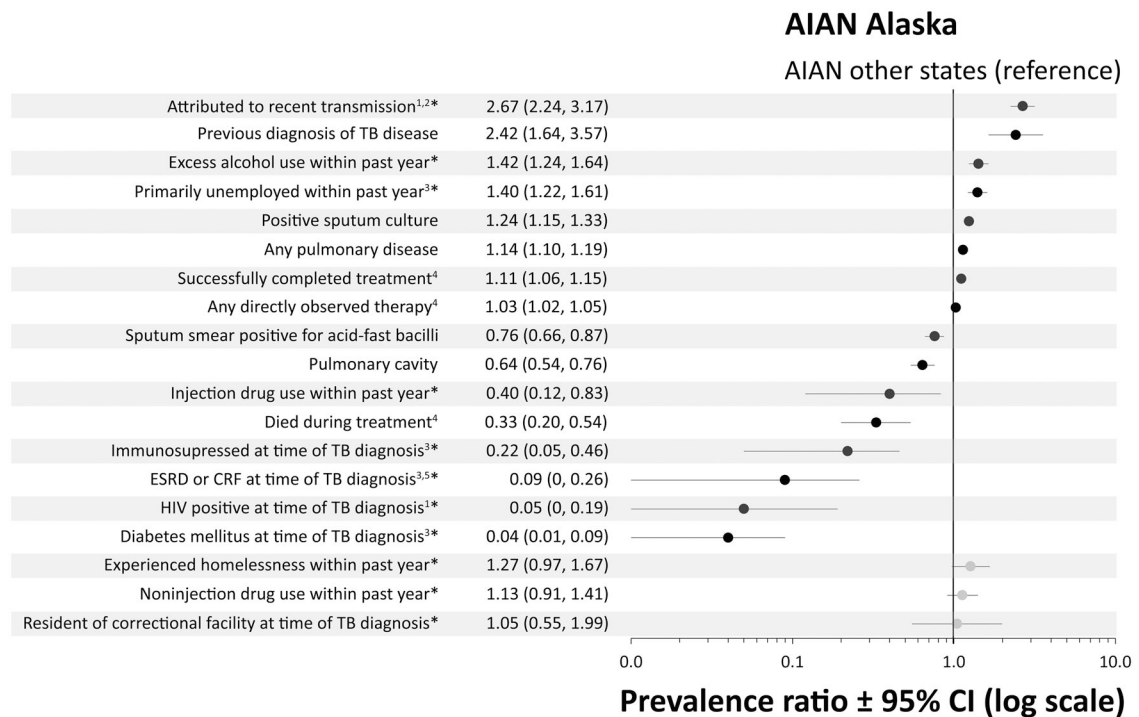
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**Fig. 1.**

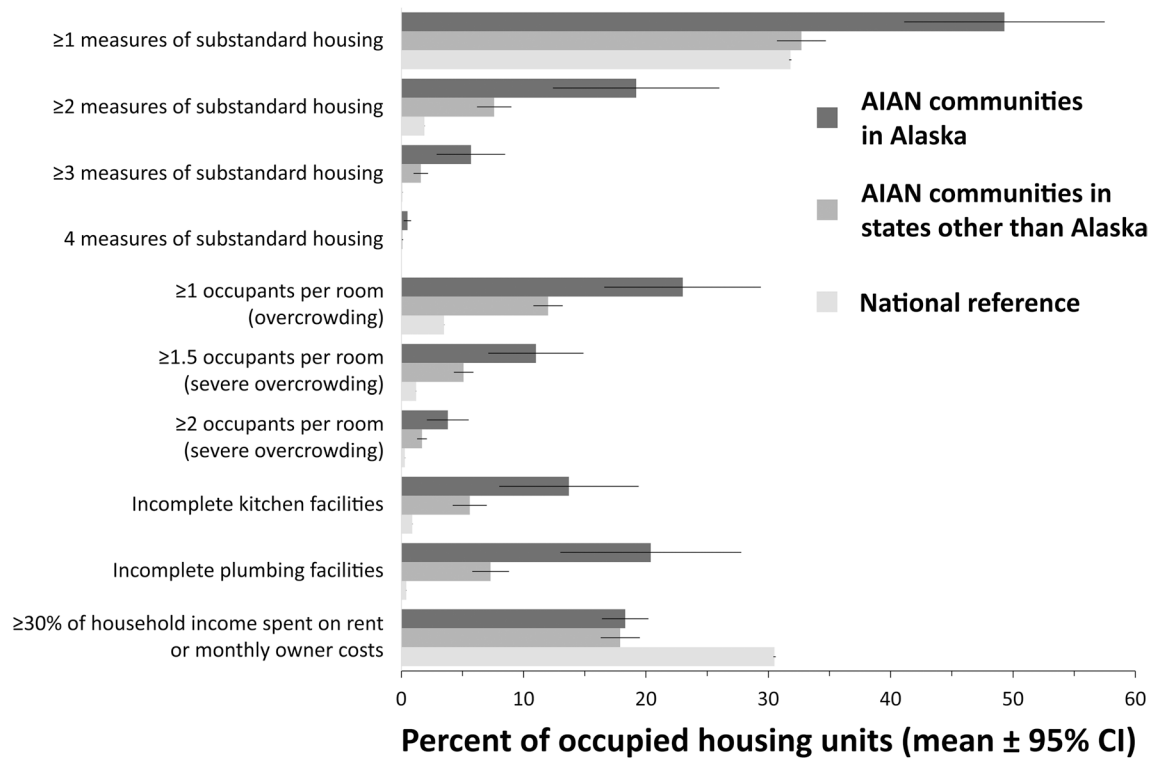
Age-adjusted annual tuberculosis (TB) incidence (cases per 100,000 persons) and associated incidence rate ratios (IRR) for the AIAN Alaska, AIAN other states, AIAN US and White US race/geography groups: USA, 2010–2020. **A** and **B** Incidence for all four groups and for only the AIAN other states, AIAN US, and White US groups, respectively. **C** IRRs for the AIAN Alaska, AIAN other states, and AIAN US race/geography groups compared to the White US group. **D** IRRs for the AIAN Alaska race/geography group compared to the AIAN other states group. AIAN: American Indian and Alaska Native. Case counts based on self-reported race/ethnicity and reflect the number of cases in patients reporting AIAN race and counted in Alaska (AIAN Alaska), counted in a state other than Alaska (including the District of Columbia (DC); AIAN other states), counted in any of the 50 states or DC (AIAN US), or in patients reporting non-Hispanic ethnicity and White race alone (i.e., not multiracial) and counted in any of the 50 states or DC (White US). Analyses restricted to cases in patients who were US-born (i.e., born in the USA or a US-affiliated jurisdiction, or outside the USA to at least one parent with US citizenship) and who self-reported their country of birth as the USA (or for whom no country of birth was recorded). Age-adjusted incidence calculated using population estimates from the USA. Census Bureau's American Community Survey (ACS) 5-year public use microdata sample (PUMS) dataset [22] and direct standardization to the 2010 US population [23]. Associated 95% confidence intervals (CIs) calculated using the log Student's *t* method [24] with a variance of incidence based on PUMS person-weights. IRR 95% CIs calculated using the normal approximation (Wald) method

**Fig. 2.**

Prevalence ratios comparing characteristics of tuberculosis (TB) patients associated with cases assigned to the AIAN Alaska, AIAN other states, and AIAN US race/geography groups compared to the White US group: USA, 2010–2020. Note that prevalence ratios are plotted on a log scale. AIAN: American Indian and Alaska Native. Case counts based on self-reported race/ethnicity and reflect the number of cases in patients reporting AIAN race and counted in Alaska (AIAN Alaska), counted in a state other than Alaska (including the District of Columbia (DC); AIAN other states), counted in any of the 50 states or DC (AIAN US), or in patients reporting non-Hispanic ethnicity and White race alone (i.e., not multiracial) and counted in any of the 50 states or DC (White US). Analyses restricted to cases in patients who were US-born (i.e., born in the USA or a US-affiliated jurisdiction, or outside the USA to at least one parent with US citizenship) and who self-reported their country of birth as the USA (or for whom no country of birth was recorded). Prevalence ratio (PR) 95% confidence intervals (CI) calculated using the normal approximation (Wald) method when the numerator for the nonreference group PR was > 10 and otherwise using a bootstrap method with 10,000 replicates. Black points denote statistically significant PRs ( $P < 0.05$ ); gray points denote non-significant PRs. PR and associated CI values are provided to the left of the data points. For details about the data categories compared for each characteristic, see Sup Table 3 and 4. \*Cases among TB patients 15 years of age only. <sup>1</sup>During 2011–2020 only. <sup>2</sup>Using the plausible source-case method [25] and molecular surveillance data generated using spoligotyping and 24 locus mycobacterial interspersed repetitive units variable number of tandem repeats (MIRU-VNTR) molecular typing methods to identify TB cases attributable to recent transmission. <sup>3</sup>During 2010–2020 only. <sup>4</sup>During 2001–2018 only. <sup>5</sup>ESRD, end-stage renal disease; CRF, chronic renal failure

**Fig. 3.**

Prevalence ratios comparing characteristics of tuberculosis (TB) patients associated with cases assigned to the AIAN Alaska race/geography group compared to the AIAN other states group: USA, 2010–2020. Note that prevalence ratios are plotted on a log scale. AIAN: American Indian and Alaska Native. Case counts based on self-reported race/ethnicity and reflect the number of cases in patients reporting AIAN race and counted in Alaska (AIAN Alaska) or counted in a state other than Alaska (including the District of Columbia (DC); AIAN other states). Analyses restricted to cases in patients who were US-born (i.e., born in the USA or a US-affiliated jurisdiction, or outside the USA to at least one parent with US citizenship) and who self-reported their country of birth as the USA (or for whom no country of birth was recorded). Prevalence ratio (PR) 95% confidence intervals (CI) calculated using the normal approximation (Wald) method when the numerator for the nonreference group PR was > 10 and otherwise using a bootstrap method with 10,000 replicates. Black points denote statistically significant PRs ( $P < 0.05$ ); gray points denote non-significant PRs. PR and associated CI values are provided to the left of the data points. For details about the data categories compared for each characteristic, see Sup Table 3 and 4. \*Cases among TB patients 15 years of age only. <sup>1</sup>During 2011–2020 only. <sup>2</sup>Using the plausible source-case method [25] and molecular surveillance data generated using spoligotyping and 24 locus mycobacterial interspersed repetitive units variable number of tandem repeats (MIRU-VNTR) molecular typing methods to identify TB cases attributable to recent transmission. <sup>3</sup>During 2010–2020 only. <sup>4</sup>During 2001–2018 only. <sup>5</sup>ESRD, end-stage renal disease; CRF, chronic renal failure

**Fig. 4.**

Mean percentage of occupied housing units in AIAN communities in Alaska, AIAN communities in states other than Alaska, and nationally that were associated with various measures of substandard housing conditions as defined by the US Census American Community Survey: USA, 2016–2020. AIAN, American Indian and Alaska Native; CI, confidence interval. Based on data from the 2020 US Census American Community Survey 5-year estimates dataset [12]. AIAN communities in Alaska, and in states other than Alaska (including the District of Columbia), defined by identifying all census within these two geographic areas in which AIAN persons constituted 50% of the resident population; national reference includes all census tracts in the USA. Percentages represent the mean percent of occupied housing units associated with each measure of substandard housing averaged across census tracts within geographic areas. CIs calculated using the normal approximation (Wald) method