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Seasonality of Tuberculosis in the United States, 1993–2008

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Abstract

Background—Although seasonal variation in tuberculosis incidence has been described in several recent studies, the mechanism underlying this seasonality remains unknown. Seasonality of tuberculosis disease may indicate the presence of season-specific risk factors that could potentially be controlled if they were better understood. We conducted this study to determine whether tuberculosis is seasonal in the United States and to describe patterns of seasonality in specific populations.

Methods—We performed a time series decomposition analysis of tuberculosis cases reported to the Centers for Disease Control and Prevention from 1993 through 2008. Seasonal amplitude of tuberculosis disease (the difference between the months with the highest and lowest mean case counts), was calculated for the population as a whole and for populations with select demographic, clinical, and epidemiologic characteristics.

Results—A total of 243 432 laboratory-confirmed tuberculosis cases were reported over a period of 16 years. A mean of 21.4% more cases were diagnosed in March, the peak month, compared with November, the trough month. The magnitude of seasonality did not vary with latitude. The greatest seasonal amplitude was found among children aged <5 years and in cases associated with disease clusters.

Conclusions—Tuberculosis is a seasonal disease in the United States, with a peak in spring and trough in late fall. The latitude independence of seasonality suggests that reduced winter sunlight exposure may not be a strong contributor to tuberculosis risk. Increased seasonality among young children and clustered cases suggests that disease that is the result of recent transmission is more influenced by season than disease resulting from activation of latent infection.

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Tuberculosis is a leading cause of death globally. Although one-third of the global population is estimated to be infected with *Mycobacterium tuberculosis* bacillus, only a minority of people with tuberculosis infection will develop tuberculosis disease [1]. Tuberculosis disease occurs through 1 of 2 pathways. The first is through recent infection that progresses to disease within a short period of time, reflecting ongoing transmission of tuberculosis. Alternatively, after infecting a person, *M. tuberculosis* may enter a state of prolonged latency. Persons with latent tuberculosis are neither ill nor contagious, but a small proportion of them will develop active tuberculosis disease later in life. Latent tuberculosis thus represents infection that was acquired remotely, often years earlier, that can later activate to tuberculosis disease. It is estimated that approximately three-quarters of tuberculosis cases in the United States are attributable to activation of latent infection and one-quarter to recent transmission [2].

Studies in the preantibiotic era [3] and more recent analyses in the United Kingdom [4], Spain [5], Hong Kong [6], India [7], and South Africa [8] have found a seasonality of the incidence of tuberculosis that is highest in late spring or early summer. The mechanisms underlying seasonal variation in tuberculosis disease are unknown. One dominant hypothesis in the literature suggests that spring surges in tuberculosis result from increased activation of latent tuberculosis due to late winter nadirs in vitamin D [9], an immune regulator synthesized in sun-exposed skin that enhances cellular immunity against *M. tuberculosis* in vitro [10]. An alternative hypothesis proposes that springtime peaks in tuberculosis diagnosis are due to increased transmission of tuberculosis rather than an increase in activation of latent disease, perhaps due to wintertime indoor crowding [7, 8].

Understanding the determinants of seasonality can shed light on pathogenesis of disease, identify potentially modifiable risk factors, and suggest new therapeutics. The aims of this study were to determine if seasonality of tuberculosis exists in the United States and to characterize patterns of seasonal variation in tuberculosis diagnoses among specific populations.

Methods

We analyzed laboratory-confirmed tuberculosis cases from all 50 states and the District of Columbia reported to the Centers for Disease Control and Prevention (CDC) National Tuberculosis Surveillance System who started tuberculosis treatment between 1 January 1993 and 30 November 2008. Laboratory confirmation was based on positive *M. tuberculosis* culture or positive acid-fast bacilli smear examination. Covariates examined were sex, age, race and ethnicity (self-designated), reporting state, site of disease, chest radiographic findings, human immunodeficiency virus (HIV) status, origin of birth (US-born or foreign-born), and years in the United States prior to tuberculosis diagnosis among foreign-born persons.

A case was defined as exclusively pulmonary if the only site of disease reported was pulmonary (ie, no additional site of disease was specified) and exclusively extrapulmonary if the reported site(s) of disease was not pulmonary. For analyses based on site of disease, any patient with both pulmonary and extrapulmonary tuberculosis was excluded. Patients with

abnormal chest radiographs were categorized radiologically as having cavitary or noncavitary disease by the reporting health department. US-born persons were defined as those either born in the United States (or its jurisdictions) or those born in a foreign country with at least 1 US citizen parent. Foreign-born persons were categorized into those who were diagnosed with tuberculosis within 1 year vs >1 year after entry into the United States. Time since entry into the United States was calculated by subtracting the month and year of US entry from the month and year the case was reported.

We categorized the 50 states and the District of Columbia into 5 latitude strata by intervals of 4° based on the midpoint latitude of each state and calculated seasonal amplitude for each stratum.

Tuberculosis clusters generally refer to a grouping of cases occurring within a certain geographic region and time frame that are potentially related through a single chain of disease transmission. For analysis of clustered cases, we utilized routinely collected data from the CDC National Tuberculosis Genotyping Service [11] linked to demographic and clinical data on reported tuberculosis cases in the National Tuberculosis Surveillance System. Cases with a treatment start date between 1 January 2005 and 30 November 2008 with the same genotype (based on indistinguishable spoligotype and 12-locus mycobacterial interspersed repetitive units–variable number of tandem repeats results reported within statistically significant geospatial zones determined by a spatial scan statistic [12] using SaTScan version 9.1.0 [13] were defined as clustered cases.

Time Series Analysis

Monthly case counts were analyzed with SAS version 9.2 [14] using a time-series decomposition method (X-11) developed by the US Census Bureau to seasonally adjust census data [15, 16]. The seasonal component was isolated from overall trend and irregular factors (noise) through the multiplicative model, $X_m = T_m \times S_m \times I_m$, where X_m is the observed number of persons starting tuberculosis treatment in month m , T_m is the trend component, S_m represents the seasonal factors, and I_m is the random, or irregular, factors. Figure 1 demonstrates the seasonal decomposition of laboratory-confirmed tuberculosis cases in the United States from 1993 through 2008. This decomposition method uses an iterative procedure that passes through the series data 3 times. First, a preliminary estimate of the trend is obtained by averaging logarithm values in a 13-month moving window. This preliminary trend is removed from the original series, leaving the combined seasonal and irregular components. A moving average applied to this series, with adjustment to reduce the influence of extreme values, gives a preliminary estimate of the separate seasonal and irregular components. This seasonal component is removed from the original series, giving an updated estimate of the combined trend and irregular components. The seasonal component is updated again, and then the trend, yielding the final result after 2 more iterations of this procedure.

A decomposition of monthly case counts was obtained for each population of interest. The presence of seasonality was assessed through the X-11 combined test of identifiable seasonality, which combines the stable and moving F statistics with the Kruskal-Wallis test. We calculated mean peak month, trough month, and annual seasonal amplitude with 95%

confidence intervals (CIs) for populations with identifiable seasonality. Confidence intervals were calculated using the Wald method based on the variance around the mean of the 16 yearly amplitude measurements. Annual seasonal amplitude was calculated from isolated seasonal factors and was defined as the peak-to-trough difference between the months with the highest and the lowest case counts for that year. Annual seasonal amplitude is expressed as a proportion of mean case counts to facilitate comparison between groups.

Results

A total of 243 432 laboratory-confirmed tuberculosis cases were reported to the CDC during the study period, which ranged over 191 months (approximately 16 years). Figure 1A shows monthly case counts with the X-11 seasonal decomposition of the isolated trend (Figure 1B), seasonal (Figure 1C), and irregular (Figure 1D) factors. Examination of the raw data showed a consistent annual periodicity. There was a steadily decreasing trend over the 16-year period. Removal of the trend reveals the seasonal and irregular (random) factors of the time series. From the isolated seasonal factors we found that seasonal amplitude for the United States was 21.4%; that is, an annual mean of 21.4% more cases of tuberculosis were diagnosed in the peak month compared with the trough month. The month with the greatest number of cases fell between March and May in 15 of 16 years; the month with the least number of cases was November or December in all years. Analysis of the isolated seasonal component revealed that mean cases per month peaked in March, with a trough in November.

Table 1 illustrates the peak and trough months with amplitude of seasonal variation for populations of interest. We found no latitude gradient for the seasonality of tuberculosis in the United States. The midpoint latitudes for Hawaii, the southernmost state, and Alaska, the northernmost state, are 21.1° and 61.4°, respectively, a latitude range of 40.3°. Within the 48 contiguous states, the midpoint latitudes of Florida and North Dakota are 27.8° and 47.5°, respectively, a range of 19.7°. We found that inhabitants of the 11 northernmost states, with midpoints above 44° latitude (Alaska, North Dakota, Washington, Montana, Minnesota, Maine, Oregon, South Dakota, Wisconsin, Idaho, and Vermont) exhibited a magnitude of seasonal variation in tuberculosis disease similar to that of inhabitants of the 9 southernmost states, located below 34° (South Carolina, Arizona, Georgia, Alabama, Mississippi, Louisiana, Texas, Florida, and Hawaii).

By contrast, the magnitude of seasonality was strongly associated with age. Among children <5 years, in whom disease likely represents recent transmission with early progression to disease, seasonal amplitude was 55.5%. The amplitude of seasonality declined progressively with increasing age to 19.4% among persons aged ≥ 65 years (Table 1). Cases associated with genotype disease clusters, in whom tuberculosis disease also likely represents recent disease transmission, exhibited a seasonal amplitude of 44.9%, more than twice the value for the overall population. Among nonclustered cases, seasonality was not detected.

Seasonal amplitude was 29.2% among persons of black race, compared with 17.8% for those of white race. Seasonal amplitudes of 23.8% and 26.9%, respectively, were observed for persons self-reporting as Asian or Hispanic. Seasonality analysis limited to those of

black race (Table 2) showed no association with latitude but showed a strong relationship with younger age, consistent with the patterns seen in the broader population. Data for clustered cases were too sparse for meaningful stratified analysis of seasonality by race. We found that 34% of tuberculosis isolates from persons of black race were part of a disease cluster compared with 19% among those of white race.

Seasonal variation was also higher among persons with cavitary disease (28.7%) and among persons with extrapulmonary disease (32.2%) compared with those with either non-cavitary (21.2%) or pulmonary disease (21.0%), respectively. There was no substantial difference in amplitude of seasonality by sex or by HIV status. Foreign-born persons diagnosed with tuberculosis within 1 year of entry into the United States exhibited decreased seasonal amplitude (17.6%) relative to both US-born persons (24.2%) and foreign-born persons diagnosed with tuberculosis >1 year after arrival to the United States (26.1%).

Discussion

Tuberculosis is a seasonal disease in the United States, with a peak in spring and trough in late fall. The seasonal pattern is similar to what has been found in non-US studies. We did not detect greater amplitude of seasonality at higher latitudes, suggesting that latitude-dependent factors, including reduced winter sunlight and its potential effect on vitamin D levels, do not appear to contribute significantly to seasonality in the United States. Instead, we found the degree of seasonality is greater among clustered cases and children, groups in whom disease likely reflects recent transmission of tuberculosis. Our interpretation of this finding is that tuberculosis disease resulting from recent infection with early progression to disease appears to be more influenced by season than disease that results from activation of latent tuberculosis.

Recent Transmission Hypothesis

The amplitude of seasonality was nearly 4-fold higher among children aged <5 years who, as children, must have had relatively recent infection with *M. tuberculosis* compared with persons aged ≥65 years, who may have been infected decades earlier. Clustered cases are likely to be linked through recent transmission, as opposed to nonclustered cases, which more commonly represent genotypically unique isolates and activation of remote infection [17]. We found that there were 45% more clustered cases in the spring peak month than the fall trough month. No seasonal variation among nonclustered cases was detected.

The finding that seasonal amplitude is increased among persons of black race may be attributable to increased disease transmission in this population. An association between black race and tuberculosis disease clustering in the United States has been described [18, 19]. We found persons of black race were nearly twice as likely to be associated with a disease cluster than those of white race (34% vs 19% of cases, respectively). The greatest amplitude of seasonality among populations we analyzed was for children of black race <14 years, with 60% more cases in the spring peak month than the fall trough month.

For patients who develop tuberculosis disease after recent infection, as opposed to entering a state of prolonged latency, the windows between infection and symptom onset and between

symptom onset and diagnosis of tuberculosis are variable. The average period to tuberculosis diagnosis from symptom onset was 47 days in high-income countries in a recent meta-analysis [20]. The antecedent window between infection and development of symptoms is not well described. Thus, March peaks may reflect a window of increased risk of transmission, or vulnerability to infection, that begins in winter, probably in November and/or December.

A peak in March and trough in November indicates a consistently steep upswing in cases, with a more gradual downswing (Figure 1C). The gradual downswing in tuberculosis diagnosis after the spring peak may reflect variations in time from infection to diagnosis following a common period of increased transmission in winter.

Authors of studies of seasonality of tuberculosis in India [7] and South Africa [8] suggest that increased tuberculosis disease transmission in winter may be due to increased indoor crowding in colder winter weather. However, we found that cases peaked in spring for all latitude strata in the United States. Seasonal patterns of indoor congregation are unlikely to be uniform throughout the United States. Thus, if seasonality of tuberculosis in the United States is due to increased transmission in winter, the mechanism may not be as simple as increased indoor crowding.

Vitamin D Hypothesis

It has been postulated that the role of vitamin D in tuberculosis seasonality is mediated through increased risk of activation of latent tuberculosis due to late winter nadirs in vitamin D levels. Latitude is closely associated with ultraviolet light exposure [21], and negligible cutaneous vitamin D synthesis occurs during winter months for people living north of 40° latitude [22]. Seasonal variation in vitamin D (25-hydroxyvitamin D) levels is more pronounced among those living north of 37° [23]. Vitamin D enhances cellular immunity against *M. tuberculosis* in vitro [10]. Wilkinson et al found an association between vitamin D deficiency and tuberculosis disease among Gujarati Asians living in West London [24]. In the United States and England, recent immigrants experience higher rates of tuberculosis disease than immigrants who are long-term residents [25]. Vitamin D deficiency associated with a move into a more northern latitude has been hypothesized to contribute to the increased incidence of tuberculosis disease seen among recent immigrants [9].

On the basis of these studies, investigators have suggested empiric vitamin D supplementation to prevent activation of latent tuberculosis among immigrants moving from equatorial to northern latitudes [9]. Our findings showing the latitude independence of seasonality and decreased seasonality among populations representing activation of latent tuberculosis, including recent arrivals to the United States, suggest that vitamin D supplementation may not prevent most cases among immigrants.

Darker skin pigmentation is independently associated with higher risk of vitamin D deficiency [26, 27]. Cases of tuberculosis among persons of black race exhibited a greater degree of seasonality relative to persons of white race; however, the amplitude of seasonality among persons of black race did not vary by latitude. Additionally, other studies conducted

in the United States show that persons of black race are more likely to be associated with tuberculosis genotype clusters, suggesting recent transmission [18, 19].

If vitamin D does play a role in tuberculosis seasonality, it may be through mechanisms not yet well understood. Although the utility of vitamin D in tuberculosis treatment remains uncertain, some trials have demonstrated success among patients with variants in the vitamin D receptor gene [28, 29]. Vitamin D receptor polymorphisms have also been associated with both increased risk of vitamin D deficiency and tuberculosis disease [30, 31]. It is possible that such individuals represent a subpopulation in whom seasonal variation in vitamin D levels may seasonally affect tuberculosis risk, although in the United States this is likely to be either uncommon or not related to latitude-dependent ultraviolet radiation exposure.

Alternative Hypotheses for Tuberculosis Seasonality

A wide variety of infectious diseases exhibit seasonality [32, 33]. Coinfection with other seasonal pathogens may affect vulnerability to tuberculosis disease. Viral respiratory infection may increase susceptibility to tuberculosis infection and/or progression to disease [34]. Influenza is strongly seasonal in the United States, with a winter peak in both northern and southern latitudes. The effect of respiratory viral pathogens on concomitant pulmonary infection is evidenced by the association between influenza and pneumococcal pneumonia [35]. Helminthic infections, chickenpox, and measles also increase risk of tuberculosis disease [36–38].

Seasonal changes in population susceptibility based on fluctuations of neuroendocrine function and immune response have been proposed to contribute to seasonality of infectious diseases [33]. Glucocorticoid and melatonin levels, which, like vitamin D, influence cellular immune response in vitro, vary seasonally [39]. The clinical manifestation of tuberculosis toward cavitary or extrapulmonary disease is strongly influenced by host immunologic capacity, and these forms of disease are more common among immunosuppressed patients [36]. Our finding of increased seasonality among these forms of tuberculosis may reflect relative seasonal immunosuppression in winter.

It has been suggested that spring surges in tuberculosis cases may be due to delay in diagnosis of wintertime disease [40]. In winter, cough and fever are common seasonal symptoms and are usually reflective of viral upper respiratory infection. Thus, missed diagnosis of tuberculosis early in its course may occur more frequently in winter. This could lead to both longer periods of infectivity and increased transmission during winter, as well as more cases of advanced disease detected in the spring. Although we found greater seasonal variation in cavitary disease, which generally represents more advanced disease than noncavitary disease [34, 36], March was the peak month for both forms of disease.

In conducting an ecologic study, we were unable to address the cause of seasonal variation in disease directly. However, because our study is based on a very large sample size accrued over an extended time frame and includes substantial information regarding patient-level characteristics, we were able to shed some light on the potential determinants of tuberculosis seasonality. We hope these findings help inform the direction of future research regarding factors related to tuberculosis transmission and progression to disease.

In conclusion, tuberculosis is a seasonal disease in the United States, with a peak in spring and trough in late fall. The data suggest that in the United States, latitude-dependent factors, including reduced winter sunlight exposure and its potential effects on vitamin D levels, may not contribute significantly to seasonality. Increased seasonality among children and cases clustered by genotype may be due to increased transmission in winter with progression to disease diagnosed in spring. Further research, including correlation with other seasonally expressed diseases and the role of seasonal immunologic changes, may clarify specific factors leading to the seasonality of tuberculosis in the United States.

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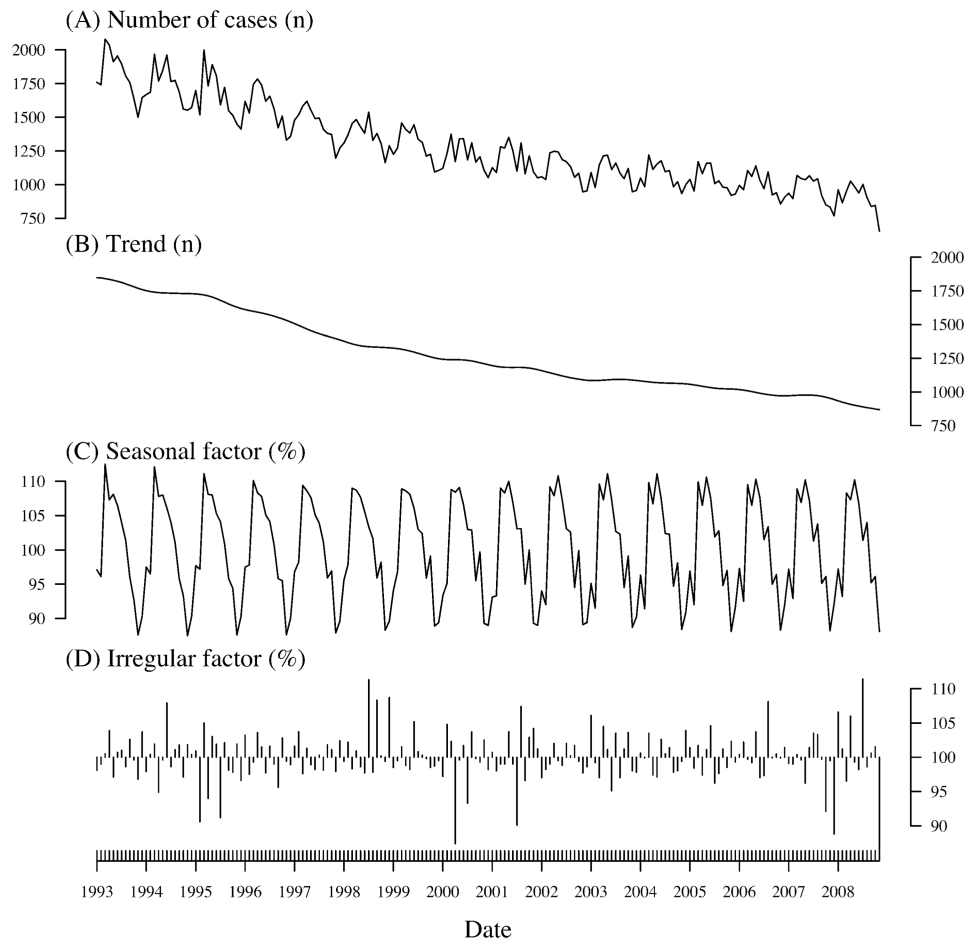


Figure 1. Seasonal decomposition of laboratory-confirmed tuberculosis cases per month, United States, 1993–2008; raw data (*A*) with trend (*B*), seasonal factor (*C*), and irregular (random) factor (*D*).

Table 1
Timing and Amplitude of Seasonality of Laboratory-Confirmed Tuberculosis Cases in the United States, 1993–2008

Characteristic		No. of Cases	Peak/Trough Month	Mean Seasonal Amplitude (95% CI)
All cases		243 432	March/November	21.4 (20.5–22.4)
Latitude	North of 44.0°N	11 849	May/February	25.3 (23.0–27.5)
	40°–43.9°N	47 567	May/December	26.4 (25.2–27.6)
	36°–39.9°N	73 341	May/November	23.7 (21.8–25.5)
	32°–35.9°N	40 490	March/November	28.6 (27.1–29.9)
	South of 32°N	49 515	March/November	23.9 (22.4–25.2)
Age	0–4 y	7351	March/November	55.5 (49.2–61.7)
	5–14 y	5391	March/November	37.1 (34.9–39.4)
	15–24 y	23 643	March/November	33.8 (32.9–34.8)
	25–44 y	88 039	March/November	23.5 (22.3–24.7)
	45–64 y	67 401	June/November	22.5 (21.2–23.7)
	65 y	51 576	June/November	19.4 (18.5–20.2)
Cluster status ^a	Clustered	6013	May/November	44.9 (44.1–45.6)
	Nonclustered	21 593	Seasonality not detected ^b	
Race	Black	75 957	March/November	29.2 (28.4–30.0)
	Hispanic	58 474	May/November	26.9 (25.4–28.3)
	Asian	49 785	April/November	23.8 (23.1–24.5)
	White	53 763	May/November	17.8 (16.3–19.3)
Chest radiograph	Cavitary	54 190	March/November	28.7 (27.8–29.6)
	Noncavitary	139 717	March/November	21.2 (20.5–21.9)
Disease site	Pulmonary only	179 106	March/November	21.0 (19.8–22.2)
	Extrapulmonary only	45 094	May/November	32.2 (31.4–32.9)
HIV status ^c	Positive	21 894	May/November	27.3 (22.9–33.4)
	Negative	92 769	March/November	28.7 (25.9–35.9)
Origin and years in the United States	US born	132 216	March/November	24.3 (22.6–26.1)
	Foreign born	91 481	March/November	22.2 (21.2–23.1)
	Foreign born 1 year in the US	28 305	March/February	17.6 (15.5–19.6)
	Foreign born >1 year in the US	63 176	May/December	26.1 (25.0–27.2)
Sex	Male	152 552	March/November	23.6 (22.8–24.3)
	Female	90 284	May/November	22.8 (22.4–23.4)

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus.

^aCluster analysis is limited to 1 January 2005 through 30 November 2008; clustered cases were defined as cases with indistinguishable tuberculosis genotypes that were statistically significantly geospatially clustered.

^bSeasonality not present according to the X-11 combined test of identifiable seasonality.

^cCalifornia reported state AIDS-registry-matched tuberculosis patients as HIV positive through 2004; all other California tuberculosis patients are missing HIV status. Vermont has not reported HIV status since 2006.

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Table 2
Timing and Amplitude of Seasonality of Laboratory-Confirmed Tuberculosis Among Persons of Black Race in the United States, 1993–2008

Characteristic		No. of Cases	Peak/Trough Month	Mean Seasonal Amplitude (95% Confidence Interval)
All cases, black race		75 957	March/November	29.2 (28.4–30.0)
Latitude	North of 40.0°N ^a	19 075	May/November	29.2 (27.5–30.9)
	36°N–39.9°N	12 528	March/November	28.6 (25.0–32.2)
	32°N–35.9°N	18 908	March/November	33.7 (32.8–34.5)
	South of 32°N	17 243	May/November	31.3 (29.2–33.5)
Age	0–14 y ^a	4241	May/November	60.0 (51.5–68.4)
	15–24 y	6621	May/November	49.9 (47.3–52.4)
	25–44 y	31 241	March/November	30.1 (29.0–32.5)
	45–64 y	22 669	June/November	28.7 (27.2–30.2)
	65 y	11 173	May/November	25.6 (22.6–28.5)
Site of disease	Pulmonary only	55 368	May/November	24.7 (22.5–26.8)
	Extrapulmonary only	13 605	May/November	34.2 (32.3–36.0)
Chest radiograph	Cavitary	18 834	March/November	33.9 (32.8–35.1)
	Noncavitary	45 629	March/November	27.1 (26.4–27.7)

^aLatitude strata north of 40°N and age <14 years were combined to yield sufficient numbers to perform time-series decomposition.