Prevention of Tuberculosis in Older Adults in the United States: Obstacles and Opportunities

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Background. Persons ≥65 are a growing proportion of the US population and are at increased risk for tuberculosis disease. The objective of the study was to examine rates and identify risk factors for tuberculosis among older adults in the United States.

Methods. Average rates and rate ratios for tuberculosis by age group, race/ethnicity, country of birth, calendar year, and long-term care facility residence were calculated using Centers for Disease Control and Prevention tuberculosis case reports and Census Bureau data.

Results. Older adults accounted for 21.9% of tuberculosis cases in the United States between 1993 and 2008. Average yearly tuberculosis rates over sixteen years were 10.9 per 100 000 (95% confidence interval [CI], 10.8–11.0) in older adults compared with 7.3 per 100 000 (95% CI, 7.3–7.4) in persons aged 21–64 (rate ratio [RR], 1.5; 95% CI, 1.5–1.5). Among older adults, tuberculosis rates increased with age from 9.6 per 100 000 in persons aged 65–74 to 14.2 per 100 000 in persons aged ≥85 years. Older persons at higher risk for tuberculosis include men (RR, 2.1; 95% CI, 2.1–2.2), American Indians/Alaska Natives (RR 3.6; 95% CI, 3.4–3.9), those in long-term care facilities (RR 2.3; 95% CI, 2.2–2.3), and the foreign-born (RR 5.1; 95% CI, 5.0–5.2).

Conclusions. Elimination of tuberculosis in the United States will require addressing the substantial burden of disease among older persons, especially men, non-whites, long-term care facility residents, and foreign-born persons. Use of interferon-γ release assay testing may help prioritize persons with greatest need for treatment of latent tuberculosis infection, as new shorter and less toxic regimens make latent tuberculosis treatment in older adults more attractive.

Keywords. tuberculosis; aged; surveillance; diagnosis; nursing homes.

An estimated 32% of the world’s population, or 1.86 billion people, is infected with Mycobacterium tuberculosis, and >8 million new cases of tuberculosis disease occur annually [1]. Older adults (persons ≥65 years of age) comprise the fastest-growing sector of the global population, and represent 12% of the current US population, a proportion that is expected to increase to 20% by the year 2050 [2].

Molecular studies of tuberculosis patients in Florida found that compared to younger persons, older adults were significantly less likely to be part of a case cluster; this suggests that their tuberculosis disease was due to reactivation of latent tuberculosis infection [3]. Some researchers have theorized that waning immunity in older adults predisposes to an increased rate of progression from latent tuberculosis infection to reactivation tuberculosis disease [4], but such declines in immunocompetence with age have not been convincingly demonstrated [5].

Older adults living in long-term care facilities have historically had higher rates of tuberculosis disease than those living in the community [4, 6]. In 1984–1985 in 29 US states, the incidence rate was 39.2 per 100 000 persons for older adults in long-term care
facilities and 21.5 per 100,000 for older adults in the community, compared with 9.2 per 100,000 for all age groups in 1984 [7, 8]. In Arkansas at that time, 20% of the tuberculosis disease cases in older adults occurred in the 5% of older adults in long-term care facilities [5]. In the United States, approximately 5% of older adults reside in long-term care facilities [7, 9]. Because the resident population of older adults in such facilities is at increased risk of reactivation tuberculosis disease, other residents in this setting are therefore at risk for outbreaks of primary tuberculosis disease that is the consequence of transmission from a source case with reactivation tuberculosis disease [4, 10].

Tuberculosis disease in older adults is of particular concern given the high tuberculosis mortality rates in this group. In Hong Kong, reported mortality rates ranged from 4.8% in those aged 60–69 years (compared with 0.2% in those 20–39 years of age) up to 19.9% in those ≥80 years; others report rates of 50% in those ≥80 years [11, 12]. In the United States in 1979 and 1998 alike, death rates from tuberculosis disease for persons aged ≥85 years were 10 times higher than for the population as a whole [13]. Between 1993 and 2008, 7% of younger persons and 21% of older persons (including 42% of older persons in long-term care facilities) died while receiving tuberculosis disease therapy [10]. This increased mortality underscores the importance of preventing tuberculosis disease in older adults.

The population of older adults in need of long-term care is predicted to rise from 8 million in 2000 to 19 million in 2050 [14]. Although there is a decreasing risk of latent tuberculosis infection in successive birth cohorts, the need to prevent tuberculosis disease in older adults and in older adults living in long-term care facilities in particular, will remain important over the coming decades [15]. In this report, we calculate rates and ratios of tuberculosis disease in subgroups of older adults in the United States and examine trends over time to gain a clearer understanding of risk factors for tuberculosis disease in this population and to elucidate potential intervention strategies.

**METHODS**

Using tuberculosis disease case reports from the Centers for Disease Control and Prevention (CDC) National Tuberculosis Surveillance System from 1993 to 2008 [10, 16] and US Census Bureau population statistics [17–19], we calculated the average rates and rate ratios for tuberculosis disease by age group, race/ethnicity, birthplace, and residence in a long-term care facility. Except for when we calculated yearly rates (in which case we used population data for that year), we used US Census data from 2000 as this was the midpoint of the collection of incidence data and the proportion of older persons remained relatively constant over the time period studied [17]. Long-term care facility population data from 1997 were collected from the CDC National Center for Health Statistics (NCHS) [20]. Tuberculosis disease incidence data reported persons in long-term care facilities, whereas the NCHS data reported numbers for nursing home residents; those terms were considered synonymous for this analysis.

We used Microsoft Office Excel 2007 to calculate rates, rate ratios, and 95% confidence intervals (CIs), and performed significance testing for incidence density (person-time) data using Episheet Software, version 6 (www.us.oup.com/us/companion/websites/0195135547/downloads/).

This study did not require institutional review board approval as it made use of publicly available, aggregated data.

**RESULTS**

**Rates and Proportions**

From 1993 to 2008, persons ≥65 years of age accounted for 61,124 of 279,378 (21.9%) persons with tuberculosis disease reported to the CDC for whom age was reported [16]. The average yearly rate of tuberculosis disease in the United States over these 16 years was 10.9 per 100,000 (95% CI, 10.8–11.0) in older adults compared with 7.3 per 100,000 (95% CI, 7.3–7.4) in persons aged 21–64 (rate ratio [RR], 1.5; 95% CI, 1.5–1.5). Among older adults, tuberculosis disease rates increased progressively with age from 9.6 per 100,000 in those aged 65–74 years up to 14.2 per 100,000 in those ≥85 years of age (Table 1).

**Trends Over Time**

The proportion of persons with tuberculosis disease who were older adults decreased gradually over the period 1993 to 2008, from 23.2% in 1993 to 19.4% in 2008. The absolute rate of tuberculosis disease among older adults declined from 1993 to 2008 (from 18.4/100,000 to 6.8/100,000), mirroring the decline in the population of persons <65 years of age (from 8.1/100,000 to 4.0/100,000). The rate ratio comparing older adults to persons <65 years of age changed little (2.1 in 1993 to 1.7 in 2008; Figure 1).

**Sex**

Older men have higher tuberculosis disease rates than older women; using cumulative data from 1993 to 2008, the rate ratio was 2.1 (95% CI, 2.1–2.2) comparing older men (15.8/100,000) to older women (7.5/100,000; Table 1). Rates in men increased with age from 13.4 per 100,000 among men aged 65–74 to 25.6 per 100,000 among men ≥85 years of age; in comparison, among women, the rates were 6.5 per 100,000 and 9.5 per 100,000, respectively. The rate ratio comparing men to women was 1.9 among persons aged 21–64, 2.1 in those aged 65–74, and 2.7 in those aged ≥85 years.
Among older adults, Asian Americans had the highest tuberculosis disease rate between 1993 and 2008 (94.6/100,000; 95% CI, 92.9–96.2) followed by American Indians/Alaska Natives (35.9; 95% CI, 33.4–38.3), Hispanics (31.2; 95% CI, 30.5–31.9), non-Hispanic blacks (29.5; 95% CI, 29.0–30.0), and non-Hispanic whites (5.4; 95% CI, 5.3–5.5; Table 2). We found that the rates increased with increasing age among all racial/ethnic groups.

Among those ≥65 years, the rate ratio comparing Asian/Pacific Islanders to non-Hispanic whites was 17.6 (95% CI, 17.2–17.9), American Indians to non-Hispanic whites 6.7 (95% CI, 6.2–7.1), Hispanics to non-Hispanic whites 5.8 (95% CI, 5.6–5.9), and blacks to non-Hispanic whites 5.5 (95% CI, 5.4–5.6).

### Birth Outside the United States

Between 1993 and 2008, 17.3% of tuberculosis disease cases among foreign-born persons occurred in older adults compared with 25.5% of cases among the US-born; 35.1% of older adults with tuberculosis disease were foreign-born compared with 46.9% of younger persons with tuberculosis disease who were foreign-born [10]. Comparing the foreign-born to US-born, the rate ratio was 5.9 (95% CI, 5.8–5.9) in persons 21–64 years of age and 5.1 (95% CI, 5.0–5.2) in older adults (Table 2). Among foreign-born older persons, the majority (57%) were non-Hispanic Asian and 27% were Hispanic [10]. The proportion of older tuberculosis case patients who were foreign-born increased from 23.6% in 1993 to 53.1% in 2008 (Figure 2); however, the rates of tuberculosis disease in older adults declined among the US-born and foreign-born during

### Figure 1.

Rate of tuberculosis disease per 100,000 persons in population ≥65 years of age, and rate ratio comparing population ≥65 years of age to population <65 years of age, 1994–2008. Abbreviation: TB, tuberculosis.
the 16 years of study (Figure 3). Among foreign-born persons, the rate ratio comparing older adults with persons <65 years of age remained relatively constant (Figure 4). The rate ratio for tuberculosis disease among foreign-born older adults increased with increasing age up to 1.8 (95% CI, 1.8–1.9) for those 75–84 years of age (Table 2).

### Long-term Care Facilities

Between 1993 and 2008, 9% of older tuberculosis disease patients were long-term care facility residents; the tuberculosis disease rate in this subgroup was 23.0 per 100 000 (95% CI, 22.4–23.6) compared with 10.2 per 100 000 (95% CI, 10.1–10.3) in older adults not living in long-term care facilities (RR, 2.3; 95% CI, 2.2–2.3). In older men, the rate was 48.9 (95% CI, 47.1–50.7) in long-term care residents and 14.1 (95% CI, 13.9–14.2) in those living in the community; in older women, these rates were 14.2 (95% CI, 13.6–14.7) and 7.1 (95% CI, 7.0–7.2), respectively. The rate ratio comparing men to women in long-term care facilities was 3.5 (95% CI, 3.3–3.6).

### Table 2. Rates and Rate Ratios of Tuberculosis Disease in Older Adults Per 100 000 Persons, by Age Group, Race/Ethnicity, and Foreign-Born Status, 1993–2008

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>21–64</th>
<th>≥65</th>
<th>65–74</th>
<th>75–84</th>
<th>≥85</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asian/Pacific Islander</td>
<td>36.0 (35.6–36.3)</td>
<td>94.6</td>
<td>81.6</td>
<td>111.2</td>
<td>132.7</td>
</tr>
<tr>
<td>Rate Ratioa (95% CI)</td>
<td>1</td>
<td>2.6 (2.6–2.7)</td>
<td>2.3 (2.2–2.3)</td>
<td>3.1 (3.0–3.2)</td>
<td>3.7 (3.5–3.9)</td>
</tr>
<tr>
<td>Non-Hispanic black</td>
<td>21.2 (21.1–21.4)</td>
<td>29.5</td>
<td>25.3</td>
<td>33.4</td>
<td>40.2</td>
</tr>
<tr>
<td>Rate Ratioa (95% CI)</td>
<td>1</td>
<td>1.4 (1.4–1.4)</td>
<td>1.2 (1.2–1.2)</td>
<td>1.6 (1.5–1.6)</td>
<td>1.9 (1.8–2.0)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>15.4 (15.2–15.5)</td>
<td>31.2</td>
<td>27.2</td>
<td>36.6</td>
<td>41.3</td>
</tr>
<tr>
<td>Rate Ratioa (95% CI)</td>
<td>1</td>
<td>2.0 (2.0–2.1)</td>
<td>1.8 (1.7–1.8)</td>
<td>2.4 (2.3–2.5)</td>
<td>2.7 (2.5–2.9)</td>
</tr>
<tr>
<td>American Indian/Alaska Native</td>
<td>9.9 (9.5–10.3)</td>
<td>35.9</td>
<td>29.7</td>
<td>40.1</td>
<td>65.5</td>
</tr>
<tr>
<td>Rate Ratioa (95% CI)</td>
<td>1</td>
<td>3.6 (3.4–3.9)</td>
<td>3.0 (2.7–3.3)</td>
<td>4.1 (3.6–4.6)</td>
<td>6.6 (5.6–7.9)</td>
</tr>
<tr>
<td>Non-Hispanic white</td>
<td>1.9 (1.9–1.9)</td>
<td>5.4</td>
<td>4.0</td>
<td>6.2</td>
<td>8.1</td>
</tr>
<tr>
<td>Rate Ratioa (95% CI)</td>
<td>1</td>
<td>2.8 (2.8–2.9)</td>
<td>2.1 (2.0–2.1)</td>
<td>3.2 (3.2–3.3)</td>
<td>4.4 (4.3–4.6)</td>
</tr>
<tr>
<td>Foreign-born</td>
<td>26.7 (26.5–26.9)</td>
<td>43.1</td>
<td>39.9</td>
<td>49.1</td>
<td>43.1</td>
</tr>
<tr>
<td>Rate Ratioa (95% CI)</td>
<td>1.6 (1.6–1.6)</td>
<td>1.6 (1.5–1.5)</td>
<td>1.8 (1.8–1.9)</td>
<td>1.6 (1.6–1.7)</td>
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</tr>
<tr>
<td>US-born</td>
<td>4.5 (4.5–4.6)</td>
<td>8.4</td>
<td>6.5</td>
<td>9.1</td>
<td>15.7</td>
</tr>
<tr>
<td>Rate Ratioa (95% CI)</td>
<td>1.8 (1.8–1.9)</td>
<td>1.4 (1.4–1.5)</td>
<td>2.0 (2.0–2.0)</td>
<td>3.5 (3.4–3.5)</td>
<td></td>
</tr>
<tr>
<td>Foreign-born:US-born Rate Ratiob</td>
<td>5.9 (5.8–5.9)</td>
<td>5.1</td>
<td>6.1</td>
<td>5.4</td>
<td>2.7</td>
</tr>
<tr>
<td>Rate Ratios compared to persons of same age group.</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Abbreviation: CI, confidence interval.</td>
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</table>

Figure 2. Proportion of tuberculosis cases in persons ≥65 years of age who are foreign-born and US-born 1993–2008.
DISCUSSION

Older adults account for approximately one-fifth of tuberculosis disease cases in the United States, and the risk of tuberculosis disease among older adults is 50% greater than that of persons aged 21–64 years. Particular subgroups of older persons with increased risk include men, persons of non-white race, and residents of long-term care facilities. Foreign-born older persons accounted for an increasing proportion of older persons with tuberculosis disease over time between 1993 and 2008. These data provide the rationale to continue to direct attention and resources to prevention of tuberculosis disease in older persons, as they represent a high-risk group for tuberculosis disease in the United States. Because the vast majority of tuberculosis disease in older adults arises from reactivation of previously contained infection, enhanced testing and treatment of latent tuberculosis infection in subgroups of older persons may be required to decrease the incidence of tuberculosis disease in the United States.

The high rates of tuberculosis disease in older adults are, as expected, paralleled by high rates of latent tuberculosis infection in the same group [15]. Over the past century, older adults have consistently had the highest rates of latent tuberculosis infection; these high rates reflect higher annual risks of infection earlier in life [15]. As the annual risk of infection declined over the course of the century, latent tuberculosis infection rates were lower in each successive birth cohort, ranging from 22.3% among persons born between 1917 and 1926.
1921 to 5.1% among those born between 1942 and 1946, based on National Health and Nutrition Examination Survey data in 1971–1972 [15]. In the 1950s, 44% of persons aged 60–69 years had evidence of infection. Although the overall prevalence of latent tuberculosis infection in the United States is decreasing over time, among those born in the United States, it remains highest in older adults [21]. Among persons with latent tuberculosis infection, older persons may also have an increased rate of progression to disease; in one community, persons >50 years of age with latent tuberculosis infection had an increased risk of reactivation compared to those ≤50 years [3]. A similar trend was seen in US national data, where the rate ratio was 1.6 (95% CI, 1.5–1.7) when comparing persons aged ≥65 to persons aged 0–14 years [22].

Other countries also have a high burden of tuberculosis disease in older adults. In the United Kingdom, the proportion of tuberculosis disease cases in persons >65 years of age increased from 13% in 1991 to 16% in 2001, and this proportion is projected to rise to 23% by 2031 [12]. Similarly, in Hong Kong, the proportion of cases in those aged >60 years increased from 32% to 45% from 1989 to 2004, an increase disproportionately greater than the rise in the number of older persons [23]. In Mexico, the 1994 incidence rate of pulmonary tuberculosis disease was 14.9 per 100 000 for the general population and 45.8 per 100 000 for older adults [24]. With increasing longevity, there is the potential for a relative increase in the proportion of cases in older adults, as persons who previously might have died of another cause earlier in life may now live long enough to reactivate their previously acquired latent tuberculosis infection and progress to tuberculosis disease, although the effect of birth cohorts may balance any increase associated with longevity.

Some of this increased risk for tuberculosis disease may be attributed to the higher prevalence of medical comorbidities associated with tuberculosis disease among older adults. Such comorbidities include diabetes mellitus, renal failure, a history of gastrectomy, and malignancy [24]. In addition, increased reactivation of latent tuberculosis infection in older adults has been thought to occur because of higher rates of underlying malnutrition, poor immunity, and smoking [6, 25]. Others have found that compared to younger persons with tuberculosis disease, older adults are more likely to have silicosis [11, 26] and low body mass index, additional factors associated with an increased risk of latent tuberculosis infection reactivation [27].

Other risk factors for tuberculosis among older adults are similar to those among all adults: men [28], non-white racial groups [4], and persons living in long-term care facilities [4–7]. As with younger persons, foreign birth is a significant and increasing risk factor for tuberculosis disease in older persons. Increased tuberculosis among residents of long-term care facilities has also been observed in other countries. In Taiwan, between 2004 and 2006, the annual tuberculosis disease incidence among persons in “senior centers” was 15.5 times higher than that of the overall population and 3.7 times that reported for older persons in the community [25]. Such persons may have higher rates than other older adults because they are at risk for exposure and primary disease, in addition to being at risk for reactivation.

Over time, even as the absolute number of tuberculosis disease cases has declined, the risk ratio for tuberculosis disease among older to younger persons has remained elevated (Figure 1). In the future, rates will likely remain high particularly among foreign-born older adults, who have been accounting for an increasing proportion of tuberculosis disease cases among older adults. Additional analyses examining this trend while controlling for duration of residence in the United States of older foreign-born tuberculosis patients would provide valuable insight, but this information was not available in the data we used. This study was also limited by the lack of additional risk factor information (eg, comorbid conditions) among persons with tuberculosis disease. Moreover, without individual-level data, we were unable to perform multivariate analyses to identify interactions between different risk factors.

In order to address latent tuberculosis infection and tuberculosis disease in older adults, practitioners must face the limitations of diagnostic testing. The diagnosis of latent tuberculosis infection in older adults is more difficult than in younger persons, because waning immunity may lead to false-negative tuberculin skin test (TST) results [23, 29–31]. However, the data suggest that for the most part, negative TST results in older adults represent self-cure [6, 30–32]. Although debilitated older persons may have a decreased immune response, studies of anergy testing have demonstrated that most older persons retain an adequate immune response [32]. Despite the recommendation to perform boosted TSTs for long-term care facility residents, interpreting boosted results is challenging, and studies from Hong Kong suggest that boosted results are not predictive of tuberculosis disease [33].

Few data exist on the use of interferon-γ release assays (IGRAs) for latent tuberculosis infection diagnosis in older adults, but the limited data suggest that IGRA results may be less affected by age than are TST results. One study in persons prior to renal transplant found an association between increased age and increased Quantiferon Gold-in-Tube (QFT-GIT, Cellestis [Carnegie, Australia]) positivity (odds ratio, 1.1; 95% CI, 1.0–1.1) but not with TST results [34]. Gautam et al found a positive association between increasing age and T. SPOT-TB (Oxford Immunotec [Oxford, United Kingdom]) results (odds ratio, 5.3; 95% CI, 2.9–9.8) [35], and others have found that persons >60 years of age with radiographic evidence of old healed tuberculosis disease showed waning TST reactivity, but their QFT-GIT results were not affected by age.
Future research could further explore the utility of IGRAs and whether they are able to distinguish between old and recent latent tuberculosis infection. Understanding these factors will allow for more effective targeting of latent tuberculosis infection diagnosis and treatment both to prevent tuberculosis disease in older adults and to prevent secondary spread to the community.

Preventing the development of tuberculosis disease by latent tuberculosis infection treatment in older persons is limited by medication toxicities and interactions. Rates of isoniazid-induced hepatotoxicity increase with age from 0.44% in those aged <35 years to 2.08% for those >49 years; the severity has also been reported to increase with age (with a higher mortality in those >50 years of age) [37]. Rifampin and rifapentine have effects on the cytochrome p450 enzymes that lead to interactions with other medications including oral hypoglycemics, corticosteroids, and warfarin [38]. Perhaps as a result of these adverse reactions and interactions, older adults have low latent tuberculosis infection treatment acceptance; only 24% of older adults and 35% of residents of long-term care facilities accepted latent tuberculosis infection treatment in a recent report [39]. Treatment completion is poor as well; long-term care facility residents were nearly 3 times as likely to fail to complete latent tuberculosis infection treatment as nonresidents [39].

New, shorter and less toxic regimens have recently been identified [40]. These regimens may alter the cost-benefit ratio, increase the likelihood of treatment completion, and make latent tuberculosis infection treatment in older adults more appealing [26]. Furthermore, the use of IGRAs in older persons may help address some of the questions that arise when interpreting TST results in this population, particularly with regard to immunosenescence, boosting, and anergy. Continued progress toward elimination of tuberculosis disease in the United States will require addressing the substantial burden of tuberculosis disease in older adults. New tools for diagnosis and treatment of latent tuberculosis infection will help in developing strategies for reducing this burden.

Notes

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Potential conflicts of interest. All authors: No reported conflicts.

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