Prevalence of Nontuberculous Mycobacterial Lung Disease in U.S. Medicare Beneficiaries

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Rationale: Pulmonary nontuberculous mycobacteria (PNTM) are an important cause of morbidity among older adults in the United States, but national prevalence estimates are lacking.

Objectives: To describe the prevalence and trends of PNTM disease among adults aged 65 years or older throughout the United States.

Methods: A nationally representative 5% sample of Medicare Part B beneficiaries was analyzed from 1997 to 2007. Demographic and medical claims data were compiled and prevalence estimates for PNTM and selected comorbidities were calculated and trends over time evaluated. Logistic regression was used to identify demographic and geographic factors associated with PNTM.

Measurements and Main Results: From 1997 to 2007, the annual prevalence significantly increased from 20 to 47 cases/100,000 persons, or 8.2% per year. The period prevalence was 112 cases/100,000 persons, although prevalence was twofold higher among Asians/Pacific Islanders than among whites (228 vs. 116 cases/100,000 persons).

Western states had the highest period prevalence at 149 cases/100,000 persons, with Hawaii having the highest prevalence at 396 cases/100,000 persons, followed by southeastern states, which had a period prevalence of 131 cases/100,000 persons. PNTM cases had more comorbid conditions than noncases and were 40% more likely to die than noncases. Women were 1.4 times more likely to be a PNTM case than men. Relative to whites, Asians/Pacific Islanders were twice as likely to be a case, whereas blacks were half as likely.

Conclusions: The prevalence of PNTM is increasing across all regions of the United States and among both men and women. Significant racial/ethnic and geographic differences suggest important gene–environment interactions.

Keywords: nontuberculous mycobacteria; pulmonary; epidemiology; prevalence; United States

Nontuberculous mycobacteria (NTM) have been increasingly recognized as an important cause of morbidity in the United States. NTM are ubiquitous in the environment, frequently detected in soil and water samples as well as in biofilms that form in municipal water sources (1). Exposure is typically believed to originate from exposure to environmental sources (2). Although severe infection can affect the lymph nodes, skin, soft tissues, bones, and joints, the vast majority of disease is pulmonary (3). More than 140 NTM species have been identified, although approximately 80% of pulmonary NTM (PNTM) infections in the United States are associated with Mycobacterium avium complex, and prevalence varies by geographic region (4).

Recent studies suggest that the prevalence of pulmonary nontuberculous mycobacteria (PNTM) disease is increasing throughout the United States, especially among older adults; however, disease prevalence estimates vary widely by geographic region.

What This Study Adds to the Field

Using a data set of 2.3 million Medicare beneficiaries, this study found that the prevalence of PNTM is increasing significantly across all regions of the United States and among both men and women. Additionally, significant racial/ethnic differences exist that are independent of region.

METHODS

Data were compiled from the Centers for Medicare and Medicaid’s Carrier Standard Analytic File using a 5% sample of all Medicare Part B beneficiaries enrolled from 1997 to 2007. Beneficiaries were excluded if they were less than 65 years old, enrolled in a health maintenance organization (HMO), enrolled in Medicare Part B for less than 1 month, or resided outside of the United States. For each individual, sex, self-reported race/ethnicity, age, and county and state of residence were available. Individuals with race listed as “unknown” were excluded from analyses by race/ethnicity. Demographic data were summarized and compared with the general population using year 2000 U.S. Census Bureau data. Any deaths that occurred were also recorded.

All medical claims submitted for beneficiaries from noninstitutional outpatient care providers were scanned for the International Classification of Diseases, 9th revision (ICD-9) code associated with PNTM disease (031.0). Claims were also evaluated for the most frequently occurring comorbidities and for others known to be associated with PNTM. The occurrence of ICD-9 codes on claims was used to estimate the prevalence of PNTM disease and of comorbidities for individuals with and without PNTM. PNTM disease prevalence estimates and 95% confidence intervals (CIs) were calculated by dividing the total number of unique individuals for whom a PNTM-associated claim was submitted

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(termed a PNTM case) by the total number of beneficiaries during the time period evaluated. Annual prevalence (AP) estimates were calculated for each year and period prevalence (PP) estimates for the total 11-year time period. Prevalence estimates were stratified by sex, race/ethnicity, age group, state of residence, and geographic region, and were mapped by states using ArcGIS Desktop 9.3.1 (Environmental Systems Research Institute, Inc., Redlands, CA).

Poisson regression models with allowance for overdispersion were used to calculate the annual percent change in prevalence over time. Logistic regression was used to estimate the risk of death in PNTM cases and to identify significant demographic and geographic factors associated with being a PNTM case. Racial/ethnic groups with 20 or fewer PNTM cases were excluded from these analyses. Variables with significant \( P < 0.05 \) odds ratios (OR) in univariate regression analyses were included in a multivariate model built using backward stepwise selection procedures to calculate adjusted odds ratios (AOR) (9). Statistical analyses were conducted using SAS 9.2 (SAS Institute Inc., Cary, NC).

RESULTS

Medicare Part B Population

Nearly 2.3 million individuals were included from the sample of Medicare Part B beneficiaries. The demographic and geographic distribution of this sample did not differ from that of the general population (10, 11). Fifty-eight percent of beneficiaries were women, and the annual average age distribution was as follows: 50% were aged 65 to 74 years, 36% aged 75 to 84 years, and 13% aged 85 years or older. Approximately 86.7% of beneficiaries were white, 8.4% black, 1.7% Hispanic, 1.6% Asian/Pacific Islander, and 0.3% North American Native; race was unspecified for 1.2%. Beneficiaries came from all 50 states and the District of Columbia.

PNTM PP

Overall, 2,548 cases were identified from all 50 states and the District of Columbia (Figure 1). Cases were 65% women and 90% white. The overall PP was 112 (95% CI, 108–116) cases/100,000 persons, and was higher among women than men (127 [95% CI, 121–133] vs. 93 [95% CI, 86–98] cases/100,000 persons). Prevalence also varied by race/ethnicity (Figure 2). Asians/Pacific Islanders had a twofold increased prevalence relative to whites (228 [95% CI, 179–277] vs. 116 [95% CI, 111–121] cases/100,000 persons). Among Asians/Pacific Islanders, men had a higher prevalence than women (263 [95% CI, 182–343] vs. 201 [95% CI, 141–262] cases/100,000 persons), whereas among whites, women had a higher prevalence than men (135 [95% CI, 129–142] vs. 89 [95% CI, 44–135] cases/100,000 persons). Among blacks, the PP of men was twofold that for black women (79 [95% CI, 59–98] vs. 40 [95% CI, 28–51] cases/100,000 persons).

Prevalence also varied geographically (Figure 1). One-third of PNTM cases resided in the Southeast, which had an overall PP of 131 (95% CI, 122–140) cases/100,000 persons. However, the highest PP was observed in the West at 149 (95% CI, 136–163) cases/100,000 persons. This was largely related to the very high PP in Hawaii (396 [95% CI, 170–211] cases/100,000 persons) and California (191 [95% CI, 170–211] cases/100,000 persons), which combined included 67% of Asian/Pacific Islander PNTM cases. When Asians/Pacific Islanders were excluded from analyses for these states, PP estimates remained high, though they dropped to 205 (95% CI, 166–485) and 168 (95% CI, 164–206) cases/100,000 persons for Hawaii and California, respectively. The Midwest had the lowest PP at 78 (95% CI, 71–86) cases/100,000 persons.

AP. The average AP from 1997 to 2007 was 31 (95% CI, 28–34) cases/100,000 persons. During this time period, the AP increased significantly by 8.2% (95% CI, 7.2–9.2) per year, from 20 (95% CI, 18–23) to 47 (95% CI, 44–51) cases/100,000 persons (Figure 3). The annual percent change for women was greater than for men (9.1% [95% CI, 6.5–11.7%] vs. 6.4% [95% CI, 3.7–9.2%]) per year, respectively. All regions also showed a significant increase in prevalence over time, ranging from 1.7% (95% CI, 1.0–3.8%) per year in the West to 11.9% (95% CI, 9.5–14.8%) per year in the Northeast.

Comorbidity analysis. The majority of comorbidities evaluated were more frequent among PNTM cases than noncases, especially bronchiectasis, which occurred in 44% of PNTM cases compared with 1% of noncases (Table 1). On average, PNTM cases had four comorbidities, whereas noncases averaged only two. When evaluated by sex, among PNTM cases, 1.5 and 1.7 times more women had claims for rheumatoid arthritis and bronchiectasis, respectively, than men, whereas 1.5 times more men had claims for diabetes and lung cancer than women. The prevalence of chronic obstructive pulmonary disease (COPD), which included ICD-9 codes for COPD, emphysema, and chronic obstructive pulmonary disease (COPD), was significantly higher among PNTM cases than noncases. Among PNTM cases, 1.5 times more women had claims for rheumatoid arthritis and bronchiectasis, respectively, than men (95% CI, 1.0–3.8%) per year in the West to 11.9% (95% CI, 9.5–14.8%) per year in the Northeast.

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Figure 1. Prevalence of pulmonary non-tuberculous mycobacteria cases among a sample of U.S. Medicare Part B enrollees aged 65 and older, 1997 to 2007. NTM = nontuberculous mycobacteria.
bronchitis, was 87% among PNTM cases and 44% among non-cases; estimates did not vary significantly by sex or region. ICD-9 codes for pulmonary tuberculosis were also identified among 3.6% of the PNTM cases and 0.09% of non-cases.

**Mortality analysis.** PNTM cases were 40% more likely to die over the period of study than noncases (OR, 1.4; 95% CI, 1.3–1.6). Among PNTM cases, the risk of death was greater in men (OR, 1.8; 95% CI, 1.6–2.2) than women, and relative to whites, was greater among blacks (OR, 2.1; 95% CI, 1.4–3.1) and Hispanics (OR, 2.4; 95% CI, 1.2–4.7). PNTM cases were more likely to die if they had three or more comorbidities (OR, 1.3; 95% CI, 1.0–1.6) or if they also had lung cancer (OR, 1.7; 95% CI, 1.4–2.1), asthma (OR, 1.7; 95% CI, 1.1–2.7), or pneumonia (OR, 2.9; 95% CI, 2.3–3.6). In contrast, PNTM cases with bronchiectasis, regardless of other comorbidities reported, were half as likely to die (OR, 0.5; 95% CI, 0.4–0.6) than cases without this diagnosis.

**Demographic/geographic risk factor analysis.** Significant regional differences in prevalence were observed, with the West (AOR, 1.8; 95% CI, 1.6–2.1) and Southeast (AOR, 1.8; 95% CI, 1.6–2.0) at similarly higher risk relative to the Midwest, followed closely by the Southwest (AOR, 1.7; 95% CI, 1.5–2.0). Women were 40% more likely to be PNTM cases than men (OR, 1.4; 95% CI, 1.3–1.5), and relative to whites, Asians/Pacific Islanders were twice as likely to be cases (OR, 2.0; 95% CI, 1.6–2.5), whereas blacks were half as likely to be cases (OR, 0.5; 95% CI, 0.4–0.6). In a multivariate model looking at both sex and race/ethnicity, a significant interaction was observed ($P < 0.0001$): among both men and women, Asians/Pacific Islanders were more likely to have PNTM than whites, although the risk was greater among men (AOR, 2.9; 95% CI, 2.2–4.0) than women (AOR, 1.5; 95% CI, 1.1–2.0). When region was included in the multivariate model, Asian/Pacific Islander men remained at significantly greater risk for PNTM than white men (AOR, 2.6; 95% CI, 1.9–3.6). Although an increased risk among women was still observed, it was no longer statistically significant (AOR, 1.3; 95% CI, 0.95–1.8).

**DISCUSSION**

Using a nationally representative population-based sample of Medicare beneficiaries, we found that the prevalence of PNTM, as estimated from diagnostic codes on medical claims, is increasing significantly across all regions of the United States and among both men and women. Additionally, we identified significant racial/ethnic differences that are independent of region. Although other studies have estimated the prevalence of PNTM within specific geographic areas in the United States (4–6), this is the first study to provide nationally representative estimates among older adults from all 50 states plus the District of Columbia and across various racial/ethnic groups. The ability to
define the burden of PNTM across an 11-year period is important given the often chronic nature of this disease (12, 13).

Although clinic-based reports have suggested that the prevalence of PNTM has increased (14), few population-based studies have documented this (4, 15). du Moulin and colleagues (15) demonstrated a fivefold increase in the number of patients with M. avium complex isolates in Massachusetts from 1972 to 1983, suggesting that this trend of an increasing prevalence has been occurring before our study period, at least in some areas. More recently, an isolate-based study in four HMOs using American Thoracic Society (ATS) microbiologic criteria found an average annual prevalence of 30 and 23 cases/100,000 persons in women and men, respectively, which is similar to our average annual prevalence among women and men of 37 and 23 cases/100,000 persons, respectively (4). Although some individuals in our data set may have received a PNTM ICD-9 code without having met ATS criteria, our results most likely represent an underestimate of true disease prevalence, because using ICD-9 codes to identify PNTM cases meeting ATS criteria has been shown to miss at least some of the observed increase is likely true and beyond the contribution of potential surveillance and diagnostic biases. Numerous hypotheses have been advanced for the increase in NTM prevalence, such as the Clean Water Act in 1970, which led to widespread disinfection of drinking water that may have increased NTM prevalence by selection due to increased resistance to chlorination relative to competing microorganisms (1). Additionally, therapies that inhibit tumor necrosis factor-α (TNF-α), a cytokine that mediates host immune defense against opportunistic pathogens, have become widely used within the last decade to treat autoimmune inflammatory conditions such as rheumatoid arthritis, increasing the risk of NTM infection in these patients and perhaps contributing to its increasing prevalence (16, 29). However, TNF-α inhibitor exposure is unlikely to account for the overall increases that we found.

Prior clinic-based studies in the United States have identified an increase in PNTM among white women with no identified risk factors (7). Although more than 90% of the PNTM cases in this study were white, Asians/Pacific Islanders were at significantly greater risk for disease, with a prevalence twofold that of whites. Additionally, whereas white women had a 50% higher prevalence than white men, among Asians/Pacific Islanders, men were more affected than women. In fact, Asian/Pacific Islander men were twice as likely as white men to have PNTM. The difference in risk between Asian/Pacific Islander men and women is notable, and may be attributed to behavioral or cultural factors associated with

### TABLE 1. FREQUENCY OF SELECTED MEDICAL CONDITIONS REPORTED THROUGH MEDICARE CLAIMS AMONG PULMONARY NONTUBERCULOUS MYCOBACTERIA AND NON—PULMONARY NONTUBERCULOUS MYCOBACTERIA CASES FROM A SAMPLE OF U.S. MEDICARE PART B ENROLLEES FROM 1997–2007

<table>
<thead>
<tr>
<th>Medical Condition</th>
<th>ICD-9 Code(s)</th>
<th>PNTM Cases (%)</th>
<th>Non-PNTM Cases (%)</th>
<th>Relative Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td>480 (480.0-480.3, 480.8, 480.9), 481, 482 (482.0-482.32, 482.4-482.42, 482.49, 482.8, 482.9), 483 (483.0, 483.1, 483.8), 484 (484.1, 484.3, 484.5-484.8), 485-487 (487.0, 487.1, 487.8)</td>
<td>82</td>
<td>33</td>
<td>2.5</td>
</tr>
<tr>
<td>Acute bronchitis</td>
<td>466 (466.0, 466.1, 466.11, 466.19)</td>
<td>66</td>
<td>32</td>
<td>2.1</td>
</tr>
<tr>
<td>Bronchietasis</td>
<td>494 (494.0, 494.1)</td>
<td>44</td>
<td>1</td>
<td>44.0</td>
</tr>
<tr>
<td>Mitral valve disorder</td>
<td>424.0</td>
<td>37</td>
<td>21</td>
<td>1.8</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>250.00-250.03, 250.09</td>
<td>26</td>
<td>9</td>
<td>0.9</td>
</tr>
<tr>
<td>Cancer of the trachea, bronchus, and lung</td>
<td>162 (162.0, 162.2-162.5, 162.8, 162.9)</td>
<td>17</td>
<td>5</td>
<td>3.4</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>416.8</td>
<td>7</td>
<td>2</td>
<td>3.5</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>714, 714.0</td>
<td>13</td>
<td>6</td>
<td>2.2</td>
</tr>
<tr>
<td>Asthma</td>
<td>493 (493.0-493.2, 493.8, 493.81, 493.82, 493.9)</td>
<td>4</td>
<td>1</td>
<td>4.0</td>
</tr>
<tr>
<td>Aspergillosis</td>
<td>117.3</td>
<td>2</td>
<td>0.1</td>
<td>20</td>
</tr>
<tr>
<td>Anomalies of the larynx, trachea, and bronchus</td>
<td>748.3</td>
<td>0.4</td>
<td>0.05</td>
<td>8.0</td>
</tr>
<tr>
<td>HIV</td>
<td>042</td>
<td>0</td>
<td>0.0004</td>
<td>0.0</td>
</tr>
</tbody>
</table>

*Definition of abbreviations: ICD-9 = International Classification of Diseases, 9th revision; PNTM = pulmonary nontuberculous mycobacteria.*
increased risk, such as frequent tobacco use, which among Asian/Pacific Islanders is higher in men than women (30, 31).

Assessing the role of race/ethnicity in disease can be complex, as racial/ethnic categorizations may be a surrogate measure for behavioral, cultural, and biological factors. Furthermore, the lack of clearly defined and consistently applied categorizations for racial/ethnic groups limits the ability to compare results across studies (32). In particular, the Asian/Pacific Islander category comprises a variety of subgroups that have significant health-related and demographic differences. Pacific Islanders are more likely than Asian Americans to be smokers, overweight, have lower income and education levels, and have higher chronic disease and mortality rates, despite no differences reported in access to care (33). It is also possible that some subgroups within the Asian/Pacific Islander population may share a common genetic ancestry and have increased susceptibility to PNTM disease. For instance, among patients in Japan with pulmonary M. avium complex infection, human leukocyte antigen–A33 and human leukocyte antigen–DR6 antigens, which have been linked to a role in host-defense mechanisms, were significantly more frequent than in the control population (34). PNTM disease dynamics are most likely driven by complex interactions among behavioral, cultural, genetic, and environmental factors.

In this study, the majority of Asian/Pacific Islander PNTM cases resided in Hawaii, which also had the highest PP at 396 cases/100,000 persons. However, even when Asians/Pacific Islanders were excluded, Hawaii still had the highest PP in the United States, suggesting that the regional exposure was dominant over the ethnic issues. Similarly, in 1979, a nationwide survey of state public health laboratories found Hawaii had the highest isolation rate of M. avium complex in the United States (35). Environmental conditions unique to Hawaii may contribute to greater levels of NTM exposure. For example, the soils of Hawaii are high in polycyclic aromatic hydrocarbons, environmental contaminants produced by fossil fuel combustion and human industry, but also by volcanic activity. Some mycobacteria have the unique property of being able to readily degrade polycyclic aromatic hydrocarbons, enabling them to thrive in this environment (36).

The higher prevalence of disease among older adults living in southeastern and western states is consistent with prior reports of higher human exposure and observed prevalence (5, 37, 38) and with studies isolating greater numbers of mycobacteria from southeastern states than from other locations surveyed (39). Although regional variation in medicare practices relevant to PNTM may exist, the strength of our findings indicates that these results are unlikely to be explained by differences in regional practices alone. PNTM is prevalent throughout the United States, and exposure may often occur through drinking water distribution systems (40). Households with average water heater temperatures 50°C or lower have higher rates of NTM recovery, but it is unclear whether their inhabitants are at higher risk (41). Therefore, regional factors, individual behaviors, and local exposures likely contribute to the true risk of infection.

PNTM cases identified here had more reported comorbidities than noncases. Almost all PNTM cases were diagnosed with at least one other lung-associated condition, including 44% with bronchiectasis, an otherwise uncommon condition. This frequency is much higher than what was previously reported. Among Oregon residents with PNTM, only 16% had bronchiectasis (42), and in a study of non-AIDS PNTM-associated hospitalizations, 15% also had bronchiectasis (5), although these studies both included patients less than 65 years old. Among patients in Canada more than 56 years old meeting ATS criteria for NTM infection, 62% had nodular bronchiectasis (43). Although bronchiectasis may increase susceptibility to NTM infection, infection with NTM likely also exacerbates bronchiectasis. Similarly, rheumatoid arthritis, which was twice as prevalent among PNTM cases as noncases, especially among women, may be associated with NTM infection, and this association may be increased by anti–TNF-α therapies (29). COPD is associated with PNTM, but this relationship could not be adequately assessed here due to identified challenges associated with its definition and subsequent coding (44). COPD is typically defined to include emphysema and chronic bronchitis, though other conditions, such as asthma and bronchiectasis, are also sometimes categorized as COPD by physicians (44) and may have been coded as such in some Medicare claims analyzed here, resulting in inflated estimates.

PNTM cases had higher mortality, especially among men and in those with greater numbers of comorbidities. Surprisingly, PNTM cases with bronchiectasis were half as likely to die as those without it. It is possible that those patients without bronchiectasis may be more likely to have fibrocavitary disease, which has been noted to have a worse prognosis (45). Black and Hispanic PNTM cases were more than twice as likely to die as whites, which may reflect racial/ethnic differences in the use of services among Medicare beneficiaries (46). Elderly white Medicare beneficiaries were more likely than blacks and Hispanics to receive care and seek out more services (46–48), regardless of urban or rural residence (46). Whites were also more likely to seek out care from private physicians, whereas blacks more frequently used community health centers (46), possibly resulting in barriers to access of specialized care, which may be more difficult to obtain in low-income areas. This might also account for the higher observed prevalence of bronchiectasis and PNTM in whites compared with blacks and Hispanics, as well as the lower death rate among those with a diagnosis of bronchiectasis, as whites might be more likely to obtain specialized testing, such as computerized tomography scans or X-rays, and to receive more intensive care and follow-up. In contrast, differences in use of Medicare services between whites and Asians/Pacific Islanders have not been consistently demonstrated (48–52).

Because PNTM is not a nationally notifiable disease, systematic monitoring of temporal trends for disease across all regions is difficult. However, with PNTM increasing among adults aged 65 years or older, a population that is expected to nearly double by 2030 (11), it is critical that this condition is recognized as an important public health issue with potentially significant consequences for affected patients.

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