Nontuberculous Mycobacterial Disease Prevalence and Risk Factors: A Changing Epidemiology

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Background. Nontuberculous mycobacteria (NTM) are important human pathogens, yet little is known about disease prevalence in the United States. Reports suggest prevalence has increased, particularly in women, but population-based data to substantiate this are lacking. We sought to estimate NTM disease prevalence in Oregon, and describe disease by site, species, and patient demographic characteristics.

Methods. We contacted laboratories that performed mycobacterial cultures on Oregon residents in 2005–2006. For each isolate, we obtained source, collection date, species, and patient demographics. We used the microbiologic component of the American Thoracic Society/Infectious Diseases Society of America's pulmonary NTM disease criteria to define cases of pulmonary NTM, and patients with isolates from a normally sterile site were classified as having extrapulmonary disease.

Results. We identified 933 patients with ≥1 NTM isolate. Of these, 527 (56%) met the case definition (annualized prevalence, 7.2 cases per 100,000 persons). Pulmonary cases predominated (5.6 cases per 100,000 persons), followed by skin/soft-tissue cases (0.9 cases per 100,000 persons). *Mycobacterium avium* complex was the most common species identified in pulmonary cases (4.7 cases per 100,000 persons). Pulmonary disease prevalence was significantly higher in women (6.4 cases per 100,000 persons) than men (4.7 cases per 100,000 persons) and was highest in persons aged >50 years (15.5 cases per 100,000 persons).

Conclusions. NTM are frequently isolated from Oregon residents; more than one-half of all isolates likely represent true disease. Pulmonary NTM is most common among elderly women, and *M. avium* causes most disease. Future efforts to monitor disease trends should be undertaken, and efforts made to validate the use of the ATS/IDSA microbiologic criteria alone to predict pulmonary NTM disease.

Nontuberculous mycobacteria (NTM) are an important cause of morbidity and mortality, often in the form of progressive lung disease [1]. Despite this, few data are available on NTM disease prevalence in the United States. Experts believe prevalence is increasing [2]; however, population-based data to substantiate these reports are lacking because in most jurisdictions, neither laboratory isolation of, nor disease due to, NTM is reportable to public health authorities.

NTM are environmental organisms found in soil and water throughout the world [3, 4]. They are considered opportunistic pathogens, and several species are associated with human disease which is typically pulmo-

nary, skin/soft tissue, lymphatic, or disseminated in presentation [5]. Pulmonary disease is often chronic and occurs in older women [6, 7] or those with underlying lung disease [8, 9]. NTM also cause skin/soft-tissue infections of varying severity in both sporadic and epidemic form. They have been linked to nosocomial infections after surgery [10], and outbreaks in nail salons [11]. Disseminated disease due to NTM is primarily associated with AIDS and other forms of severe immunosuppression [12].

There are numerous species of NTM and because of recently developed molecular methods more are being recognized [13]. Although regional variation in species isolation has been shown [2], the NTM most frequently isolated, and thought to be associated with disease in the United States, are those of the *Mycobacterium avium* complex (MAC). Other important human pathogens include the rapidly growing mycobacterium (RGM); *Mycobacterium abscessus, Mycobacterium chelonae,* and *Mycobacterium fortuitum.* Additional NTM frequently associated with disease in the United States are

Mycobacterium kansasii and *Mycobacterium marinum,* while those that commonly cause disease in other parts of the world are *Mycobacterium malmoense, Mycobacterium xenopi, Mycobacterium scrofulaceum,* and *Mycobacterium ulcerans* [2].

Few population-based studies have examined NTM disease trends in the United States. Because NTM are environmental and opportunistic organisms, the American Thoracic Society (ATS) and Infectious Diseases Society of America (IDSA) have jointly developed guidelines for disease determination, including symptom, radiographic, and microbiologic criteria. However, because patient chart review is labor intensive, laboratory-based surveillance may be the most cost-effective method of estimating and tracking NTM prevalence over time. To our knowledge, no studies have been published to date using the 2007 ATS/IDSA microbiologic criteria alone to estimate disease prevalence.

We conducted this study to estimate the population-based prevalence of pulmonary and extrapulmonary NTM disease in Oregon, and describe the microbiologic and demographic features of these cases. We conducted this project under the authority of the Oregon Administrative Rules for special studies, OAR 333-019-0005 [14].

METHODS

Study design. We conducted a retrospective cohort study using laboratory data for all Oregon residents with NTM isolated by culture during years 2005 and 2006.

Data collection. Through the Oregon State Public Health Laboratory Quality Assurance Program we identified 19 Oregon laboratories accredited to do mycobacterial testing in 2005 and 2006. Six out-of-state reference laboratories performing culture or identification of mycobacteria on Oregon patients were identified through queries of Oregon laboratories. Because some patients had numerous isolates, a maximum of 3 isolates per patient were recorded.

Variables. For each isolate, laboratories supplied patient name, referring physician, birth date, sex, zip code, specimen collection date and source, and species of mycobacteria isolated. Zip codes were used to establish state and county of residence and non-Oregon residents were excluded. Patient ages were divided into the following age groups: ≤5 years, 6–21 years, 22–50 years, and ≥51 years.

Census data from the Center for Population Research and Census at Portland State University (PSU), in Portland Oregon, which included population by county and sex, was used for rate calculations. The average population of Oregon during the 2-year study period was 3,660,972 [15]. The age group populations were calculated using the PSU population data with the United States population census data age-group proportions applied [16].

Pulmonary NTM case definition. We used the microbio-logical criteria of the ATS/IDSA NTM disease definition [2] to establish a laboratory-based case definition. We defined a pulmonary case as a patient with at least two positive sputum cultures with the same species of NTM isolated within the 2-year period, or one positive bronchial wash or lavage, brush, or a lung biopsy. Because we did not have access to clinical or radiological information, we relied on these microbiologic criteria alone to estimate disease burden.

Extrapulmonary NTM. We categorized extrapulmonary NTM disease cases as: skin/soft tissue; disseminated; or lymphadenitis. We defined a case of skin/soft-tissue disease as one or more isolates from tissue samples labeled as, "furuncles," "abscesses," "skin," "wound," or "incisions." We defined a disseminated case as NTM isolation from a normally sterile site: blood, bone marrow or other sterile site body fluids such as spinal or abdominal fluid, and a case of lymphadenitis as isolation of NTM from a lymph node biopsy or aspirate. The category of "other" was used for positive urine cultures or other presumably sterile sites (eg, peritoneal, pelvic fluid, and others). *M. gordonae* isolates were considered contaminates and excluded from analysis.

Geographic designations and prevalence. We divided the state of Oregon into 2 regions on the basis of geography and climate. The categories included those counties west and east of the Cascade Mountains. West of the Cascade Mountains, where 87% of the population lived during 2006–2006, is temperate and wet, relative to the high desert and arid climate found east of the mountains.

Data analysis. Laboratory data were imported or entered into a Microsoft Access database. Frequencies, percentages, median age, and age ranges were determined using SPSS 15. Rates were calculated using Microsoft Excel, and 95% Fishers exact confidence intervals (CIs) for rates were calculated using WinPepi [17]. CIs were calculated for the prevalence rates assuming that 1 year in time was a representative sample of the population for all years. Rates were considered significantly different if 95% CIs did not overlap.

RESULTS

During 2005 through 2006, laboratories identified 1301 NTM isolates from 933 Oregonians for an annualized isolation rate for all NTM species of 17.8 cases per 100,000 persons, and 16.4 cases per 100,000 persons after exclusion of *M. gordonae* isolates. Of the 933 patients, 527 (56%) met the ATS/IDSA microbiologic criteria for NTM disease (Table 1). The annualized case rate of NTM disease was 7.2 cases per 100,000 persons (95% CI, 6.6–7.8 cases per 100,000 persons). Pulmonary cases predominated with a case rate of 5.6 cases per 100,000 persons (95% CI, 5.0–6.1 cases per 100,000 persons), followed by skin/soft tissue cases, with a rate of 0.9 per 100,000 (95% CI, 0.7–1.1 cases per 100,000 persons). The rates of disseminated and

Table 1. Nontuberculous Mycobacteria (NTM) Isolates and Estimated Rates of NTM Disease, Oregon, 2005–2006

Species	No. (%) of study isolates	No. (%) of NTM disease cases	Rate[a]
Mycobacterium avium complex	901 (69.3)	397 (74.2)	5.4
Mycobacterium abscessus/chelonae	34 (2.6)	17v (3.3)	.2
Mycobacterium abscessus	19 (1.5)	14 (2.6)	.2
Mycobacterium chelonae	14 (1.1)	11 (2.0)	.2
Mycobacterium fortuitum	18 (1.4)	10 (1.8)	.1
M. fortuitum group	10 (0.7)	4 (0.7)	…
Mycobacterium marinum	17 (1.3)	13 (2.4)	.2
Mycobacterium gordonae	101 (7.8)	…	…
Mycobacterium kansasii	8 (0.6)	3 (0.6)	…
Mycobacterium mucogenicum	6 (0.5)	3 (0.6)	…
Mycobacterium xenopi	4 (0.3)	3 (0.6)	…
Mycobacterium szulgai	3 (0.2)	2 (0.4)	…
Mycobacterium goodi	3 (0.2)	2 (0.4)	…
M. fortuitum complex	4 (0.3)	1 (0.2)	…
Mycobacterium florentinum	1 (<.1)	1 (0.2)	…
Mycobacterium heckeshornense	1 (<.1)	1 (0.2)	…
Mycobacterium immunogenicum	1 (<.1)	…	…
Mycobacterium mageritense	1 (<.1)	1 (0.2)	…
Mycobacterium phlei	1 (<.1)	…	…
Mycobacterium simiae	2 (0.2)	1 (0.2)	…
M. simiae complex	3 (0.2)	1 (0.2)	…
Mycobacterium scrofulaceum	1 (<.1)	1 (0.2)	…
Mycobacterium terrae	1 (<.1)	1 (0.2)	…
Mycobacterium vaccae	3 (0.2)	1 (0.2)	…
Mycobacterium bolletti	1 (<.1)	…	…
Mycobacterium interjectum	2 (0.2)	…	…
Mycobacterium smegmatis	1 (<.1)	…	…
Not *M. avium* or *M. tuberculosis*	138 (10.7)	38 (7.2)	…
Rapid grower	1 (<.1)	1 (0.2)	…
Pigmented mycobacteria	1 (<.1)	…	…
Total	1301	527	7.2

NOTE. Represents isolates recovered from 933 Oregonians. The total isolates may be underreported; a maximum of 3 isolates per person were entered in the database. Estimated rates of disease include both pulmonary and extrapulmonary disease.

[a] Rate is annualized period prevalence of disease per 100,000 Oregon residents.

lymphadenitis cases were both 0.3 cases per 100,000 persons (Table 2).

Pulmonary disease. Pulmonary cases represented 77.2% of all NTM cases. There were 1132 total pulmonary isolates from 804 patients. Of these patients, 407 (51%) met the case criteria. *Mycobacterium avium* complex (MAC) was the most frequent isolate. Pulmonary MAC cases were similar in demographics to other types of pulmonary cases in (Table 3). Three hundred (87.2%) of the pulmonary MAC cases were in the ≥51-year age group, with a rate of 13.5 cases per 100,000 persons (95% CI, 12.0–15.1 cases per 100,000 persons). Females accounted for 60.5% of the pulmonary MAC cases, with a rate of 5.7 cases per 100,000 persons (95% CI, 4.9–6.5 cases per 100,000 per-

sons), compared with 3.7 cases per 100,000 persons (95% CI, 3.1–4.4 cases per 100,000 persons) among males. Most pulmonary MAC cases, 322 (93.6%) were residents of western Oregon with a rate of 5.1 cases per 100,000 persons (95% CI, 4.5–5.6 cases per 100,000 persons), compared with a rate of 2.3 cases per 100,000 persons (95% CI, 1.5–3.5 cases per 100,000 persons) in the east (Table 3).

Extrapulmonary NTM disease. Skin and soft-tissue infection was the most common form of extrapulmonary NTM disease documented, accounting for 12.0% (*n* = 63) of all NTM disease in the 2-year period. Most (57.1%) were due to RGM followed by *M. marinum* (20.6%). Disseminated cases were 4.7% (*n* = 25) of the total Oregon NTM cases. Most cases,

Table 2. Cases of Nontuberculous Mycobacterial Disease (*n* = 527), by Disease Site, Oregon, 2005–2006

Species	Pulmonary		Skin or soft tissue		Disseminated		Lymphadenitis		Other site(s)	
	No. of cases	Rate[a]	No. of cases	Rate[a]	No. of cases	Rate[a]	No. of cases	Rate[a]	No. of cases	Rate[a]
Mycobacterium avium complex	344	4.7	7	0.1	18	0.3	21	0.3	7	0.1
Mycobacterium abscessus/chelonae	8	0.1	7	0.1	2	…	0	…	0	…
M. abscessus	5	0.1	9	0.1	0	…	0	…	0	…
M. chelonae	1	…	8	0.1	1	…	0	…	1	…
Mycobacterium marinum	0	…	13	0.2	0	…	0	…	0	…
Mycobacterium fortuitum	2	…	8	0.1	0	…	0	…	0	…
M. fortuitum group	1	…	3	…	0	…	0	…	0	…
Mycobacterium kansasii	1	…	0	…	1	…	0	…	1	…
Mycobacterium mucogenicum	1	…	0	…	2	…	0	…	0	…
Mycobacterium xenopi	3	…	0	…	0	…	0	…	0	…
Mycobacterium szulgai	1	…	1	…	0	…	0	…	0	…
Mycobacterium goodi	2	…	0	…	0	…	0	…	0	…
Not *M. avium* or *M. tuberculosis*	33	…	4	…	0	…	0	…	1	…
Others	5	…	3	…	1	…	1	…	0	…
Total	407	5.6	63	0.9	25	0.3	22	0.3	10	0.1

[a] Rate is annualized per 100,000 population and was calculated if the numerator was ≥5.

18 (72.0%), were due to MAC and 19 (76%) were male. The median age was 39 years (range, 4–78 years), and all but 1 (92%) lived in Western Oregon, although the rates were similar in urban zip codes (0.37 cases per 100,000 persons; 95% CI, 0.22–0.58 cases per 100,000 persons) and rural zip codes (0.29 cases per 100,000 persons; 95% CI, 0.12–0.61 cases per 100,000 persons). Twenty-two cases of lymphadenitis (4.2% of the total cases) were identified with 21 (95.5%) due to MAC. NTM lymphadenitis mostly occurred in children, with the median age of lymphadenitis cases being 2 years (range, 1–65 years).

DISCUSSION

This is the first study in the United States to estimate a statewide disease rate of NTM through the use of comprehensive laboratory data. Our study estimates a current annualized population based prevalence of NTM disease in Oregon at 7.2 cases per 100,000 persons. Using the ATS/IDSA microbiologic component of the pulmonary NTM disease definition, we estimate an annualized pulmonary disease prevalence of 5.6 cases per 100,000 persons with most disease due to MAC. In comparison, Oregon's rate of tuberculosis (TB) was 2.8 and 2.2 cases per 100,000 persons for 2005 and 2006, respectively [18], suggesting NTM disease causes higher morbidity than TB in the state.

There have been few other population-based studies done in the United States that ascertained NTM prevalence. These had notable methodological differences from our study but provide some comparison. O'Brien et al [19] surveyed public health labs throughout the US in 1981–1983 through state tuberculosis controllers by asking them to provide information for patients in which isolates were thought to represent disease. From this information, they estimated NTM disease prevalence in the United States as 1.8 per 100,000 and disease due to MAC as 1.3 cases per 100,000 persons, which are rates much lower than ours 23 years later. Du Moulin et al [20] used Massachusetts Mycobacteria Reference Laboratory data from 1972–1983 to look at rates for isolation of MAC and found increasing rates over the years and a rate of 4.6 cases per 100,000 persons

Table 3. Demographic Characteristics of Persons with Pulmonary Nontuberculous Mycobacterial Cases, Oregon, 2005–2006

Characteristic	Value	Rate[a] (95% CI)
All persons	407 (77.2)	5.6 (5.0–6.1)
Sex		
Female	235 (57.7)	6.4 (5.6–7.3)[b]
Male	172 (42.7)	4.7 (4.0–5.5)[b]
Age		
Median years	68	…
0–5 years	0 (0)	…
6–21 years	9 (2.2)	0.7 (0.3–1.1)[b]
22–50 years	52 (12.8)	1.7 (1.3–2.3)[b]
≥51 years	346 (85.0)	15.5 (13.9–17.2)[b]
Geographic location		
West	381 (93.6)	6.0 (5.4–6.6)[b]
East	26 (6.4)	2.7 (1.8–4.0)[b]

NOTE. Data are no. (%) of patients, unless otherwise indicated. CI, confidence interval.

[a] Rate is annualized period prevalence of disease per 100,000 Oregon residents.

[b] *P* < .05.

in 1983. However, that study only evaluated isolation rates and did not use the ATS microbiological definition to estimate disease. Furthermore, we believe our evaluation of both private and public laboratory data allowed for a much more complete capture of NTM isolates as compared to these previous US studies which relied solely on public health laboratory data. Although practices might vary by state, and could be different than three decades ago, most private laboratories in Oregon do not send isolates to the public health laboratory for speciation of NTM. In addition, many public health laboratories do not speciate mycobacteria beyond MAC or tuberculosis, therefore leaving a number of isolates identified only as "not TB/not MAC." Accordingly, relying on public health laboratory data alone for surveillance purposes may no longer be relevant.

We found that most NTM disease in Oregon is pulmonary in nature and caused by MAC. While MAC accounted for 85% of pulmonary cases within the state, most other cases were due to rapidly growing mycobacteria such as *M. abscessus* and *M. chelonae.* This is consistent with other North American studies suggesting MAC to be the most common cause of pulmonary NTM disease [19, 21, 22]. Notably, there was only 1 *M. kansasii* case and 3 *M. xenopi* cases in Oregon over the 2-year study time-period. *M. kansasii* disease is frequently found in the southern states of the United States [23], while *M. xenopi* cases are relatively concentrated along and north of the Canadian border [24]. A population-based study of NTM isolates in Ontario, Canada in 1997–2003 found similar isolation rates of NTM as our study; 14.1 cases per 100,000 persons in 2003, compared with our 16.4 cases per 100,000 persons in 2005–2006. That study also found a similarly high proportion of NTM isolates (93% compared to our 87%) were from pulmonary sources [24]. In addition, they found MAC to be the most common NTM isolated among respiratory samples, although notably, they had a high percentage of patients (25%–30%) with *M. xenopi* isolates.

Pulmonary disease in Oregon appears to be strongly associated with advanced age and occurs more frequently in women than men. The population-based study by O'Brien et al [19] found a similar age distribution for cases in that older patients were overrepresented; however, their data suggested that MAC lung disease was more common among males. Our study suggests a female predominance for disease and, to our knowledge, is the first to document this in a population-based fashion in the United States. Our findings are in line with published reports from institutional cases series and experts who believe the epidemiology of this disease has changed during the last several decades to affect women more frequently than men [2, 25]. A recent study from New Zealand, using similar methodology as ours but relying solely on mycobacterial reference labs, estimated pulmonary NTM disease incidence to be 1.2 cases per 100,000 persons and found a majority (79%) of cases

to be females [26]. In the last several decades, "Lady Windermere" forms of NTM lung disease have become increasingly recognized [27] in otherwise healthy, thin, elderly women.

Notably, we found a significantly higher prevalence of disease in the western, more urban portion of Oregon even after adjusting for differences in age and sex distribution within the background population throughout the state. It is possible that persons at risk for NTM might be more likely to be exposed to NTM in Western Oregon where urban areas are more likely to rely on large, municipal water systems. Water in municipal systems may be stored for long periods of time in pipes and reservoirs providing opportunity for biofilm formation that promote NTM growth. This hypothesis was used to explain the higher incidence of MAC found in the population living in urban communities including Boston in the 1970s and 1980s [20]. It is also possible that our findings are influenced by a diagnostic bias, in that persons living in urban areas might be more likely to seek medical care and be diagnosed with mycobacterial disease. Similarly, patients with chronic lung disease, which predisposes to NTM infection, might more commonly live in urban areas where medical care is easier to access. Additional explanations for our findings might also include climatic factors. Western Oregon is wetter and more temperate than the more rural eastern portion of the state; factors that might promote greater NTM survival within the environment [28,29]. Some or all of these factors could explain the difference in disease geography that we observed in our study, and further research is necessary to understand these findings.

In this study, we were limited in our ability to precisely determine NTM disease because we did not have access to clinical information. However, we believe it is reasonable to assume that most patients undergoing sputum or bronchoscopic assessment likely have symptoms and radiological findings present to trigger such evaluation. We recognize that this assumption could cause an overestimation of disease if some of these cases in fact lacked such criteria. On the other hand, we believe our current methodology might underestimate actual prevalence. For example, there were instances where a patient failed to meet disease criteria because of having only 1 positive sputum, but where we were aware of additional positive culture results being present either before or after the study time-period such that they did actually meet the case definition for pulmonary disease. This occurred when the laboratory reported additional culture data outside the study time-period. However, given that we did not collect information from outside the study time-period systematically, we ignored this information and such patients were not counted as cases. Lastly, because we were not able to systematically look before the year 2005, we were unable to distinguish between incident and prevalent cases. Further efforts should be made to distinguish be-

tween such cases in order to better understand the magnitude of NTM disease burden on a population level.

This study demonstrates that Oregon has, until now, unappreciated rates of NTM disease that are several-fold higher than tuberculosis. It is unclear how Oregon NTM prevalence compares to other regions in the United States, but Oregon is not dissimilar in demographics than many other low prevalence TB regions. It is speculated that NTM disease is more common in warmer, moister Southeastern US states [2,3], so it is possible our estimates are lower than these or other areas of the country. Regardless, we have established a baseline estimate for the burden of NTM disease in Oregon, and with using a laboratory-based case definition, have shown that most disease is pulmonary, with higher rates in women and those >50 years old, and that geography affects risk of disease. Rates for skin and soft-tissue infection were the second highest and also occurred primarily in women.

Further studies should be done to validate the use of the ATS/IDSA microbiologic criteria alone to estimate pulmonary NTM disease. NTM are environmental pathogens that deserve further examination as important causes of public health morbidity, and we believe our methods could prove useful in estimating disease prevalence and monitoring disease trends over time. Additional such studies should be conducted in other regions of the United States in order to develop national estimates of NTM disease burden.

Acknowledgments

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