Pulmonary Nontuberculous Mycobacterial Disease Prevalence and Clinical Features

An Emerging Public Health Disease

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***Rationale*: Respiratory specimens with nontuberculous mycobacteria (NTM) are increasingly common; however, pulmonary disease prevalence is unknown.**

***Objectives*: To determine the disease prevalence, clinical features, and risk factors for NTM disease, and to examine the predictive value of the microbiologic criteria of the American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA) pulmonary NTM case definition for true NTM disease.**

***Methods*: We identified all Oregon residents during 2005–2006 with at least one respiratory mycobacterial isolate. From a population-based subset of these patients, we collected clinical and radiologic information and used the ATS/IDSA pulmonary NTM disease criteria to define disease.**

***Measurements and Main Results*: In the 2-year time period, 807 Oregonians had one or more respiratory NTM isolates. Four hundred and seven (50%) resided within the Portland metropolitan region, among which 283 (70%) had evaluable clinical records. For those with records, 134 (47%) met ATS/IDSA pulmonary NTM disease criteria for a minimum overall 2-year period prevalence of 8.6/100,000 persons, and 20.4/100,000 in those at least 50 years of age within the Portland region. Case subjects were 66 years of age (median; range, 12–92 yr), frequently female (59%), and most with disease caused by *Mycobacterium avium* complex (88%). Cavitation (24.5%), bronchiectasis (16%), chronic obstructive pulmonary disease (28%), and immunosuppressive therapy (25.5%) were common. Eighty-six percent of patients meeting the ATS/IDSA microbiologic criteria for disease also met the full ATS/IDSA disease criteria.**

***Conclusions*: Respiratory NTM isolates frequently represent disease. Pulmonary NTM disease is not uncommon, particularly among elderly females. The ATS/IDSA microbiologic criteria are highly predictive of disease and could be useful for laboratory-based NTM disease surveillance.**

Keywords: nontuberculous mycobacteria; pulmonary disease; disease prevalence; epidemiology; bronchiectasis

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

There is limited information regarding the epidemiology and prevalence of pulmonary nontuberculous mycobacteria (NTM) disease in the United States.

What This Study Adds to the Field

Respiratory NTM isolates frequently represent disease. Pulmonary NTM disease is not uncommon, particularly among elderly females. The American Thoracic Society/Infectious Diseases Society microbiologic criteria are highly predictive of disease and could be useful for laboratory-based NTM disease surveillance.

Nontuberculous mycobacteria (NTM) cause a variety of infections in humans, including chronic, debilitating pulmonary disease among elderly persons. Although the epidemiology of tuberculosis is well described, the prevalence and epidemiology of NTM disease in the United States is largely unknown. There is widespread belief among experts that pulmonary NTM disease is increasingly prevalent and perhaps more prevalent than tuberculosis, although to date, there have been no large population-based studies that document its prevalence or associated risk factors (1). The clinical characteristics and comorbidities associated with this disease have largely been reported in the form of institutional case series from highly specialized treatment centers. These series suggest that bronchiectasis and other chronic lung disease are prevalent in patients with pulmonary NTM (1). Given the specialized nature of such tertiary referral centers, and the severity of NTM disease often treated in those centers, it is unclear whether their reported patient case characteristics mirror those with disease in the general population.

NTM thrive within the biofilm of municipal water systems and likely infect susceptible hosts via aerosolization (2, 3). In this manner, NTM represent a potential public and environmental health threat to those at risk. Because NTM are environmental organisms capable of contaminating respiratory specimens, patients must meet specific clinical, radiologic, and microbiologic criteria for pulmonary disease, including the following: (*1*) respiratory or constitutional symptoms, (*2*) radiologic findings of reticular, interstitial, nodular infiltrate, or cavitation, and (*3*) at least one bronchoalveolar lavage specimen, or in the case of sputum, repeated (two or more) specimens yielding identical NTM species (1). Accordingly, it is understandable why estimates of pulmonary NTM disease are difficult to obtain in the United States or most nations. Prior studies have reported increasing incidence of NTM isolation within populations, but have not been able to examine the clinical records of such patient to distinguish disease from colonization (1).

We performed a statewide laboratory–based surveillance project for NTM in Oregon, whereby we captured demographic and microbiologic information for every Oregon resident with respiratory NTM isolates during a 2-year time period, 2005–2006 (4). We subsequently undertook the current study to review the clinical records of a population-based subset of these patients; those residing in the Portland Tri-County metropolitan region (n $>$ 1.5 million) (5). We sought to determine the pre-

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valence of NTM disease in this population, define the clinical characteristics of pulmonary NTM disease, evaluate potential disease risk factors, and validate the use of the microbiologic criteria of the American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA) case definition alone to estimate disease prevalence; a potential powerful tool for public health authorities with which to track disease trends by laboratory-based surveillance.

METHODS

After the Oregon Public Health Department approved this public health surveillance project, we identified all Oregon residents during 2005 and 2006 with one or more respiratory NTM isolate(s) (4). From these data, we used resident ZIP codes to identify all such patients living in the Tri-County region of Portland, Oregon, and then sought to review their clinical records. Most patients received care at one of the region's five medical care systems, whereas a small minority received care at county clinics. Because county clinics were geographically widespread, lacked radiologic facilities, and lacked electronic medical records, we chose to review all patient records from the five medical systems (i.e., Oregon Health & Science University, Portland Veteran Affairs Medical Center, Kaiser-Permanente Northwest, Legacy Healthcare, and Providence Healthcare). To better understand trends outside the Portland region, we also reviewed clinical records in a less urban county (Marion) in the central Willamette Valley 50 miles south of Portland.

For each patient, we evaluated electronic clinical, microbiologic, and radiologic records dated within the 2-year study time period. Information from records before or after the study time period was not collected. We collected symptom, treatment, and comorbidity data from physician notes, radiographic findings from radiologist reports, and concomitant medication information from physician notes and medication fields of electronic records from visits associated with each patient's respiratory culture. During record review, some patient medical records lacked recorded symptom or radiologic information. We considered such patients "not clinically evaluable." Patients with clinical records containing symptom, radiographic, and microbiologic information were considered clinically evaluable and defined either as "case" or "noncase" according to the full 2007 ATS/IDSA pulmonary NTM case definition (1). We calculated period prevalence of disease for the Portland Tri-County region, using an age-adjusted population denominator provided by Oregon State census data (5).

All data were entered into an Access Database (Microsoft, Redmond, WA) and analyzed with Epi Info (Centers for Disease Control and Prevention, Atlanta, GA). Univariate comparisons were made to evaluate differences between cases and noncases. We used χ^2 and Fisher P values to evaluate observed differences. Comparison of medians (age) was done by Mann-Whitney/Wilcoxon two-sample test.

RESULTS

Statewide, there were 807 Oregonians with one or more respiratory NTM isolates during the 2-year time period, and 407 (50%) of these patients resided within the Tri-County Portland metropolitan region. Of these 407 patients, 283 (70%) had full clinical records available for review. One hundred and thirty-four (47%) of those with evaluable clinical records met ATS/IDSA criteria for pulmonary NTM. Statewide, including our evaluation of Marion County residents with evaluable clinical records (n = 30) and those patients with records who received medical care within the Tri-County region but who resided elsewhere in the state (n = 58), a total of 184 (50%) of 371 patients with clinically evaluable records met the ATS/IDSA criteria for pulmonary disease. Patients meeting disease criteria who lived within the Tri-County region (n = 134) were similar regarding age, sex, comorbid diseases, therapy, and etiology to those additional 50 patients meeting disease criteria who lived outside the Tri-County region. Accordingly, to simplify presentation of our clinical results, we have reported case-related data for all 184 cases meeting disease criteria.

Patients meeting case criteria (n = 184) were 66 years of age (median; range, 12–92 yr) and 109 (59%) were female. Nearly one-quarter of pulmonary NTM case subjects presented with cavitation, and 31 (17%) had effusions noted on imaging (Table 1). Compared with males, female case subjects were older (median age, 68 vs. 62 yr; $P = 0.01$), significantly less likely to present with pulmonary effusion (12 vs. 24%; relative risk [RR], 0.5; 95% confidence interval [CI], 0.3–0.95; $P = 0.03$), and less likely to present with cavitary disease, although this difference was not statistically significant (20 vs. 31%; $P = 0.07$ [Table 2]). Comorbid conditions were common among case subjects and included chronic obstructive pulmonary disease (COPD), lung cancer, and bronchiectasis (Table 3). Among case subjects, COPD was less common among female case subjects (22 vs. 37%; RR, 0.7; 95% CI, 0.5–1.0; $P = 0.02$), whereas bronchiectasis showed a trend toward being associated with female case subjects (20 vs. 11%; RR, 1.9; 95% CI, 0.9–4.0; $P = 0.06$). One-quarter (n = 47) of patients were taking systemic or inhaled immunosuppressive medication at the time of NTM isolation (Table 3). Oral prednisone alone or in combination with other agents (n = 29) accounted for nearly two-thirds of the immunosuppressive medications noted. There were 14 patients using inhaled corticosteroids, 5 of whom were also taking oral prednisone concomitantly. Smaller numbers of patients were using methotrexate (n = 4), the biologic therapies infliximab, adalimumab, and rituximab (n = 1 each), or chemotherapy (n = 1).

When comparing differences between those patients with evaluable records who met disease criteria versus those who did not, few differences were found. Patients meeting criteria were more likely to be female (RR, 1.3; 95% CI, 1.0–1.5; $P = 0.01$) and to have radiographic evidence of cavitary disease (RR, 2.5; 95% CI, 1.5–4.2; $P < 0.01$) (Table 1), but were otherwise similar regarding age and medical comorbidities (Table 3).

M. avium was etiologic in most cases (n = 161, 87.5%). Patients with disease due to rapidly growing mycobacteria (RGM) most frequently had isolates identified as *M. abscessus* (n = 6) or *M. abscessus/chelonae* (n = 4). A small number of cases were due to unspeciated or other mycobacteria (Figure 1). Patients with pulmonary RGM disease were significantly more likely to have underlying gastroesophageal reflux disease noted (RR, 4.8; 95% CI, 1.8–12.9; $P = 0.01$), There were no other differences regarding sex or comorbidities noted between RGM and *Mycobacterium avium-intracellulare* cases, although we had limited power for such comparisons.

TABLE 1. CHARACTERISTICS OF PATIENTS WITH CLINICALLY EVALUABLE RECORDS THAT MET ATS/IDSA PULMONARY NTM DISEASE CRITERIA IN THE 2-YEAR STUDY TIME PERIOD, COMPARED WITH PATIENTS WITH ONE OR MORE RESPIRATORY NTM ISOLATES WHO DID NOT MEET CRITERIA

	Confirmed Case (*n = 184*)	Did Not Meet ATS/IDSA Criteria (*n = 187*)
Age (median)	66 (12–92)	65 (20–93)
Female	109 (59%)*	88 (47%)*
Cavitary†	45 (24.5%)*	18 (10%)*
Effusion	31 (17%)	44 (23.5%)
NTM therapy	62 (37%)*	14 (8%)*

Definition of abbreviations: ATS/IDSA = American Thoracic Society/Infectious Diseases Society; NTM = nontuberculous mycobacteria.

* Denotes $P \leq 0.05$ for comparison between columns.

† Cavitation noted on either chest radiograph or computed tomography (CT). For cases, cavitation was noted in 18 (10%) and 40 (21.5%) of chest radiograph and CT exams, respectively. For non-cases, cavitation was noted in 8 (4%) and 14 (7.5%) of chest radiographs and CT scans, respectively.

TABLE 2. COMPARISON OF PULMONARY NTM DISEASE CHARACTERISTICS BETWEEN MALE AND FEMALE CASE SUBJECTS

	Female (*n = 109*)	Male (*n = 75*)
Age (median)	68 yr*	62 yr*
Cavitation†	22 (20%)	22 (31%)
Effusion	13 (12%)*	18 (24%)*
COPD	24 (22%)*	28 (37%)*
Bronchiectasis	22 (20%)	8 (11%)
Immunosuppressive Tx	32 (29%)	15 (20%)
Previous TB‡	8 (7%)	9 (12%)

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; TB = tuberculosis; Tx = treatment.

* Denotes $P < 0.05$ for comparison between columns designated male and female.

† Cavitation noted on either chest radiograph or computed tomography.

‡ Previous TB included history of latent TB infection (n = 11), prior active TB disease (n = 3), and history of unknown active versus latent TB (n = 3).

Of all patients with clinically evaluable records (n = 371), there were 214 (58%) patients that met the microbiologic component of the full ATS/IDSA disease criteria. Of these 214 patients, 183 (86%) met the full ATS/IDSA disease criteria, indicating the positive predictive value of the microbiologic component alone to be 86% in patients with records available to review (one additional patient met full disease criteria based on tissue pathology and one positive sputum sample and was therefore not detected on the basis of the microbiologic criteria alone). Among Tri-County residents, where we had a complete denominator of residents and could therefore fully evaluate differences between those residents with and without clinically evaluable records, patients with full clinical records present were significantly older (median age, 66 vs. 56 yr; $P < 0.01$), more likely to be female (55 vs. 48%; RR, 1.2; 95% CI, 0.9–1.4; $P = 0.08$), more likely to meet the ATS microbiologic criteria (56 vs. 39%; RR, 1.5; 95% CI, 1.1–1.8; $P < 0.01$), and much less likely to have a nonspeciated isolate (36 [27%] vs. 19 [67%]; RR, 0.20; 95% CI, 0.1–0.4). One hundred and fifty-nine (77%) of the 206 Tri-County residents who met microbiologic criteria for disease had full clinically evaluable records present.

Disease Prevalence

Using the Portland Tri-County census data for the years 2005–2006, we calculated a minimal estimate of 2-year period prevalence. The average Tri-County population for the 2-year study time period was 1,556,540 residents, among whom we identified 407 potential case subjects. Of these, at minimum, 134 case subjects met the ATS/IDSA case definition for disease, representing a 2-year period prevalence of 8.6/100,000 in the general population. After adjusting for age, the 2-year period prevalence among those at least 50 years old was 20.4/100,000 at minimum. Of the 124 patients for whom clinical records were not available for review, an additional 48 (39%) met the microbiologic criteria of the ATS case definition and could have been cases (35 of these 48 were 50 yr of age or older). If 85% of these were in fact true case subjects, as based on the validated positive predictive value of the ATS microbiologic criteria, then adding these likely case subjects to those confirmed case subjects would give an upper limit 2-year prevalence estimate of 11.2/100,000 in the general population and 25.7/100,000 in those at least 50 years old. By contrast, the 2-year incidence rate for tuberculosis (TB) in those at least 50 years old in the Tri-County area during the study time period was 6.7/100,000.

TABLE 3. MEDICAL COMORBIDITIES AMONG PATIENTS WITH FULLY EVALUABLE CLINICAL RECORDS FOR THOSE WITH CONFIRMED PULMONARY NTM DISEASE (N = 184) COMPARED WITH THOSE WHO DID NOT MEET CASE CRITERIA (N = 187) DURING THE 2-YEAR STUDY TIME PERIOD

	Confirmed Case (*n = 184*)	Did Not Meet ATS/IDSA Criteria (*n = 187*)
Bronchiectasis	30 (16%)*	19 (10%)*
COPD	52 (28%)	53 (28%)
DM	13 (7%)	16 (9%)
Lung cancer	12 (6.5%)	14 (7.5%)
Immunosuppressive Tx	47 (25.5%)	48 (26%)
RA	5 (3%)	5 (3%)
GERD	15 (8%)	13 (7%)

Definition of abbreviations: ATS/IDSA = American Thoracic Society/Infectious Diseases Society; COPD = chronic obstructive pulmonary disease; DM = diabetes mellitus; GERD = gastroesophageal reflux disease; RA = rheumatoid arthritis; Tx = treatment.

* Denotes $P \leq 0.05$ for comparison between columns.

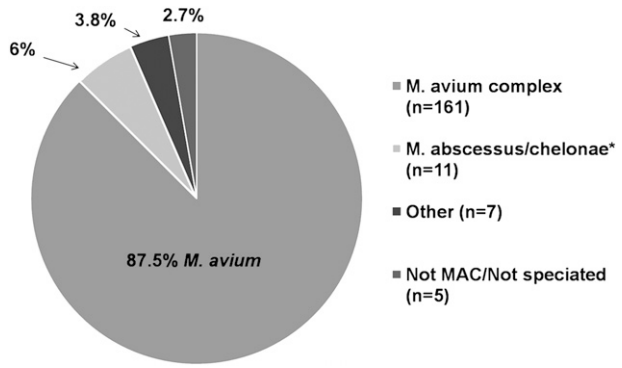

Figure 1. Mycobacterial etiology of confirmed pulmonary nontuberculous mycobacteria (NTM) disease, Oregon 2005–2006 (n = 184). **M. abscessus/chelonae* includes patients with isolates labeled as *M. abscessus* (n = 6), *M. abscessus/chelonae* (n = 4), and *M. chelonae* (n = 1). "Other" includes *M. simiae* (n = 2), *M. goodii* (n = 1), *M. fortuitum* (n = 1), *M. gordonae* (n = 1), *M. xenopi* (n = 1), and *M. kansasii* (n = 1). MAC = *Mycobacterium avium* complex.

DISCUSSION

We have conducted a population-based study of patients with respiratory NTM isolates in Oregon during 2005–2006. To our knowledge, this is the first study to determine pulmonary NTM disease prevalence within a population, and the first to systematically examine the clinic–epidemiologic features of disease from a general population. We have documented a minimal 2-year NTM pulmonary disease prevalence of 8.6/100,000 in the general population and more than 20/100,000 in those at least 50 years of age. Our results establish that elderly women are disproportionately affected by this disease and that they tend to manifest disease differently than do men; further, underlying lung disease and immunosuppressive therapies are common among cases. Importantly, we have validated the use of the microbiologic component of the ATS/IDSA disease criteria as a surveillance tool for pulmonary NTM disease. Overall, between one-third and one-half of all respiratory NTM isolates in Oregon are indicative of NTM disease. Efforts should be made to monitor trends in this emerging disease.

In population-based fashion, we have documented that pulmonary NTM more frequently affect women (6–10). This is contrary to early case series reports of disease from the United States, and contrary to current European studies suggesting that pulmonary NTM is more strongly associated

with males, particularly those with COPD (11, 12). In our study, a high proportion of case subjects had underlying structural lung disease regardless of sex, although COPD was more common among males and bronchiectasis was more common among females. Several notable NTM pulmonary pathogens are missing from Oregon epidemiology, including *Mycobacterium xenopi*, *M. malmoense*, and *M. kansasii*. These pathogens are more prevalent in Europe and perhaps of different pathogenicity, potentially explaining the difference in sex predisposition between the continents (12, 13). Our study also suggests that men and women with NTM often manifest disease differently. Men were more likely to have pleural effusion or COPD, and a trend was observed with female case subjects more likely to be using immunosuppressive drugs or having bronchiectasis. Although we had little power to examine differences between RGM disease and that caused by *Mycobacterium avium-intracellulare* or other slowly growing mycobacteria, we found gastroesophageal reflux disease (GERD) to be significantly associated with RGM disease. Prior institution-based case-series studies have suggested this association (14), although it is unclear whether GERD is causal in RGM or other NTM disease and our findings could be explained by potential diagnostic bias. Some investigators speculate that proton pump inhibitors used to treat GERD might increase the ability of mycobacteria to live in the gut and could predispose to RGM or other NTM disease, although evidence of this for *M. avium* at least *in vitro* is lacking, and proton-pump inhibitor (PPI) use might simply serve as a marker for more severe GERD (15, 16). Further research is necessary to evaluate the potential causal role of GERD and PPI use in promoting RGM and other mycobacterial pulmonary disease.

The pathogenesis of pulmonary NTM is poorly understood. Many female patients with NTM are slender, underweight, and have characteristic features such as scoliosis, pectus defects, hypomastia, or mitral valve prolapse (1, 8). Investigators have described various immune deficits that lead to disseminated, but not pulmonary, NTM disease. These deficiency states are rare and include IFN-γ deficiency or autoantibody states and IL-12 deficiency (6, 17). Cytokines such as tumor necrosis factor (TNF)-α are known to be essential to granuloma formation and maintenance. Cases of pulmonary NTM have been reported among patients taking drugs that inhibit TNF (18–20), and at least one study has suggested that patients with pulmonary NTM have lower levels of TNF expressed by lung immune cells in the presence of NTM challenge as compared with non-diseased control subjects (21). Few patients in our cohort were using anti-TNF drugs; however, a large percentage were using systemic or inhaled corticosteroids, presumably to treat COPD, rheumatoid arthritis, or other chronic diseases commonly noted in our cohort. It is unclear whether prednisone increases the risk of NTM as it does for TB (22), or if the high percentage of immunosuppressive use in this cohort simply reflects the high degree of comorbidities in these patients. Although we could find little background prevalence data for many of these chronic conditions, we believe the rates of COPD and lung cancer observed in our NTM cohort are well above that seen in the general population, even among the elderly. For bronchiectasis, the prevalence in our cohort (16%) far exceeded the background population prevalence in elderly populations (national estimates of 0.27% prevalence among Americans 75 yr or older) (23, 24). It has been hypothesized that the pulmonary architectural defects associated with these conditions impair host response locally and promote the trapping of environmental organisms such as NTM and increase the risk of infection (25, 26).

The estimation of pulmonary NTM disease prevalence has previously been elusive. NTM are not reportable pathogens, and in the case of NTM culture isolation, review of clinical records is necessary to ascertain whether the NTM is clinically meaningful and represents disease. Accordingly, microbiologic criteria for disease have been developed by an expert ATS/IDSA committee (1). These criteria, when present in the context of symptoms and characteristic radiologic abnormalities, suggest that NTM disease is present. We hypothesized that patients meeting the microbiologic criteria would be likely to meet the full disease criteria, given that existing pulmonary symptoms or radiographic abnormalities generally trigger the collection of respiratory specimens. Among patients with clinical records present in our cohort, the microbiologic criteria in fact had high positive predictive value for disease. This may in part be because most of our disease was caused by *Mycobacterium avium* complex, for which the ATS/IDSA disease criteria are most applicable. For the patients with clinical records lacking, however, it is possible that the positive predictive value of the microbiologic criteria could be lower, although there were many fewer such persons who met the microbiologic criteria and it is unlikely that this would affect our overall calculated positive predictive value substantially. Accordingly, we believe our findings suggest that future surveillance efforts could be laboratory-based and rely solely on these microbiologic criteria to estimate disease prevalence and monitor disease trends.

We were not able to systematically access all patient records before the study time period, so we were unable to distinguish between existing and incident cases. For this reason, we chose to calculate a period prevalence for the 2-year study time period. We believe this calculation likely underestimates the true prevalence for several reasons. First, there were a number of persons who failed to meet the ATS/IDSA microbiologic criteria during the 2-year time period, but who were known to the investigators to have had additional positive respiratory cultures collected either before or after the study time period, which would have allowed them to meet disease criteria. However, because we could not look systematically at data before or after the 2-year study time period for all patients, we did not record such persons as case subjects. Second, among many of the patients with only one sputum examination positive for NTM, there was no evidence in the clinical records that subsequent respiratory evaluations had been performed during the study time period such that these patients did not have the "opportunity" to meet the case definition. Third, many patients with NTM disease are unable to produce sputum, particularly after beginning antibiotic therapy. It is likely there were such prevalent cases in the state during this time, but that our laboratory-based case-finding failed to identify them. Last, some patients meeting the microbiologic criteria failed to satisfy the full ATS/IDSA disease criteria, primarily because they either lacked radiographic findings from chest radiographs, a methodology not as sensitive as chest computed tomography, or because they had other conditions (e.g., lung cancer, TB) and it was unclear during our chart review whether they also had NTM disease. In our review of these patients not meeting disease criteria, it is interesting that they were similar in many respects (e.g., age, comorbidities, and underlying lung disease) to their counterparts who satisfied the criteria. It is likely that at least some of these patients truly had disease.

Our study suggests that pulmonary NTM disease is not rare in Oregon, and that it has emerged as a pathogen with important environmental and public health implications. If we apply the 86% predictive value of the ATS/IDSA microbiologic criteria to our statewide microbiology findings, then the 2-year period prevalence for the entire state is 26.7/100,000 in persons more than 50 years of age (4). This indicates that pulmonary NTM disease occurs several-fold more frequently than tuberculosis

(annual incidence rate, 2.5/100,000 during the study time period) (27), and it is likely that at least some of these patients are considered TB suspects before diagnosis, with many undergoing clinical and laboratory assessment within the TB control infrastructure. These county clinics and laboratories are funded for TB control, yet much of their efforts in Oregon, and likely other low-prevalence TB regions, are dominated by NTM. If NTM disease is increasing in prevalence as suggested by the increasing population prevalence of isolates in previous studies (28), then an increasing proportion of TB control dollars are being spent on NTM control. In this regard, NTM represents an important public health issue. Furthermore, and most importantly, NTM appear to represent an environmental health threat for predisposed individuals. These organisms are environmental pathogens not unlike *Legionella* in many respects, a reportable pathogen for which public and environmental health efforts are made to prevent disease (29). Like *Legionella*, NTM live in municipal water supply systems, where they are competitors within pipe biofilm (2, 30). It is likely that persons are exposed in similar ways to both organisms, via the aerosolization and inhalation of such water, and similarly only a small percentage of exposed persons develop subsequent disease. Interestingly, *Legionella* is sensitive to chlorination whereas NTM are not, and it is plausible that the steps taken to disinfect our municipal water supply systems over the last several decades have resulted in decreased *Legionella* concentrations, with corresponding increases in NTM concentrations (31). There are published source exposure investigations of patients with newly diagnosed NTM, whereby NTM isolates from patients and their home or hospital tap water have been found to be genetically identical, suggesting this as the likely source of their infection (32–34). Clearly, efforts should be made to better understand issues of NTM pathogen exposure and routes of transmission, disease risk factors, and methods of mitigating the risk of disease should be developed for those at high risk. At present, most of these questions remain unexplored. These efforts will require significant investment, and will likely require dedicated effort from public and environmental health agencies within this country.

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