Pulmonary nontuberculous mycobacterial (pNTM) disease is clinically challenging. Therapy entails complex antimycobacterial drug combinations, typically for 18 months (1), often with poor tolerability (2) and limited success (3). pNTM disease is increasingly common in Canada (4) and the United States (5–7), but its prevalence is not well understood. Determining the epidemiology of pNTM disease is difficult for several reasons. It is generally not reportable, so population-level data are not routinely compiled. The diagnosis requires clinical and radiologic information in addition to microbiological examination (≥2 positive sputum cultures or 1 bronchoscopic or biopsy culture) (1). Finally, the chronic nature of pNTM disease dictates longitudinal study, illustrated by considering that only a minority with pNTM disease appear to be treated (18% in 1 study) (6), treatment succeeds in only 56% (3), and disease recurs in >30% of patients (2,8). These data indicate that most pNTM cases are expected to be chronic. Cases detected by isolation of nontuberculous Mycobacterium spp. in 1 year, generally remain prevalent over several subsequent years, regardless of the reliable appearance of subsequent isolates, with a disease duration that may depend primarily on patient survival.

The traditional method of identifying cases for NTM disease epidemiology studies by using mycobacterial laboratory databases and measuring annual prevalence is not ideal. Such studies assume that, in patients with pNTM disease, the organism is isolated during every year of disease, an invalid assumption (6). Recent investigators have focused on prevalence within a defined period (period prevalence) as an improved estimate of pNTM disease, including a 2-year study in Oregon (5), 3-year sampling of 4 US health care delivery systems (6), and ≥11-year US-wide sample of Medicare beneficiaries (7). Important limitations of these studies included the patient populations and geographic regions selected and the limited data about temporal prevalence changes. Expanding on methods of previous studies to overcome some prior limitations, we performed a population-based study of pNTM disease in Ontario, Canada, using 5-year periods for prevalence calculations and compared prevalence from 1998–2002 to 2006–2010.

The Study

We performed a retrospective cohort study of all Ontario residents who had pulmonary nontuberculous Mycobacterium spp. isolated during 1998–2010, identified from the records of the Public Health Ontario Laboratory, capturing ≥95% of NTM disease in Ontario. Culture was performed by using Bactec 460 TB system until 2000 and thereafter with BACTEC MGIT 960 (Becton Dickinson, Baltimore, MD, USA). Before 2008, speciation was performed by using a combination of DNA probes (AccuProbe, Gen-Probe, San Diego, CA, USA) for Mycobacterium avium complex (MAC) and M. gordonae and high-performance liquid chromatography for other species and thereafter solely by DNA probes (AccuProbe, Gen-Probe) or line-probe assays (GenoType, Hain Lifescience, Germany). Because MAC was not identified to individual species for most of our study, we present data only for MAC.

Full criteria for pNTM disease include the presence of all clinical (symptoms and radiology) and microbiological components (1). We defined surrogate criteria as microbiological criteria only (1), (≥2 positive sputum cultures or 1 bronchoscopic or lung biopsy culture), which has a positive predictive value of 70%–100% (5,6,9,10). Period prevalence of disease was calculated as the number of persons who fulfilled the disease criteria during a 5-year period (1998–2002 or 2006–2010), divided by the Ontario population at the period midpoint. We left a 3-year gap (2003–2005) between periods to minimize patient overlap. We excluded M. gordonae from period prevalence because it is rarely pathogenic (1). We selected a conservative 5-year period on the assumption that the median survival with pNTM disease is 5–10 years (10,11), using the low end of the survival range based on assumptions that a small
The 5-year prevalence of pNTM disease was substantial and increased significantly during our population-based assessment in Ontario, Canada. Our measurements of period prevalence (29.3 and 41.3 cases/100,000 persons) were substantially higher than observed in Oregon (8.6/100,000), probably partially because of the shorter period (2 years) and more stringent definition for disease (medical records review) used in the Oregon study (5). Other studies did not present period prevalence for the entire study populations, only by age strata, and used durations of 3 years (6,7) or ≤11 years (7). We selected a 5-year period assuming it would provide the most accurate estimate of disease prevalence based on the chronic nature of pNTM disease. Prior studies provided age-stratified data, with high period prevalence in older patients (20.4/100,000 to >200/100,000, depending on period length and specific age range) (5–7), as expected, because pNTM disease is a disease of the elderly (1,4,6,12). Although age data were unavailable for our study, annual disease prevalence of pulmonary MAC in Ontario has a strong age association, with an average increase of 14/100,000 per decade increase during 50–80 years (4).

Changes in microbiological methods and the number of samples submitted annually did not account for the increases in pulmonary nontuberculous Mycobacterium isolation (13). The attenuation in the rate of increase in isolation prevalence around the middle of the study corresponded with a previously reported plateau in the annual number of specimens submitted (13). However, the annual

| Year | Isolation prevalence† | Disease prevalence‡ |
|------|-----------------------|---------------------|
| 1998 | 11.4                  | 4.9                 |
| 1999 | 14.3                  | 6.3                 |
| 2000 | 15.1                  | 6.1                 |
| 2001 | 18.7                  | 7.6                 |
| 2002 | 21.0                  | 8.1                 |
| 2003 | 18.9                  | 7.3                 |
| 2004 | 22.8                  | 8.6                 |
| 2005 | 22.6                  | 9.1                 |
| 2006 | 23.4                  | 9.7                 |
| 2007 | 24.0                  | 10.3                |
| 2008 | 24.5                  | 10.4                |
| 2009 | 24.9                  | 10.7                |
| 2010 | 22.2                  | 9.8                 |

*Annual (1-year) prevalence, per 100,000 population, in a calendar year.
†Prevalence of ≥1 pulmonary nontuberculous Mycobacterium isolate.
‡Prevalence of ≥2 sputum nontuberculous Mycobacterium isolates or 1 bronchoscopic or biopsy nontuberculous Mycobacterium isolate. Mean annual increase: 6.5% (p<0.0001).
isolation prevalence continued to rise, and the annual disease prevalence rose steadily throughout the study period. We suspect a multifactorial explanation for the increase in pNTM disease: an increase in susceptible hosts (aging, chronic lung disease) contributes (4); decades-old increases in water aerosol exposure could cause recent increases in pNTM disease, given the potential latency of pNTM disease; more computed tomographic scanning probably leads to sampling patients with previously unidentified abnormalities; and reduced tuberculosis, with an associated reduction in cross-immunity, may play a role. The latter is supported by observations of increased extrapulmonary NTM infection in children not vaccinated with M. bovis BCG (14,15). pNTM disease in Ontario is substantial and increased greatly from early (1998–2002) to recent (2006–2010) periods.

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Table 2. Five-year prevalence of pulmonary nontuberculous mycobacterial disease, Ontario, Canada, 1998–2002 and 2006–2010*  

| Isolate                      | 1998–2002 | 2006–2010 | p value |
|-----------------------------|----------|----------|---------|
| M. avium complex            | 18.0     | 26.5     | <0.0001 |
| M. xenopi                   | 7.4      | 9.5      | <0.0001 |
| M. fortuitum                | 0.63     | 1.2      | 0.01    |
| M. abscessus                | 0.63     | 1.2      | <0.0001 |
| Other nontuberculous        | 1.8      | 3.0      |         |
| Mycobacterium spp.          |          |          |         |
| All nontuberculous          | 29.3     | 41.3     | <0.0001 |

*Period prevalence of disease excludes Mycobacterium gordonae (a rarely pathogenic species) and is calculated as the total number of persons whose illness fulfilled disease criteria (≥2 sputum nontuberculous Mycobacterium isolates or 1 bronchoscopy or biopsy nontuberculous Mycobacterium isolate) during 1 of the 5-year periods of interest (1998–2002 and 2006–2010), divided by the Ontario population at the midpoints of the periods (2000 for 1998–2002 and 2008 for 2006–2010).