Epidemiology of Human Pulmonary Infection with Nontuberculous Mycobacteria
A Review

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KEYWORDS

• Epidemiology • Nontuberculous mycobacteria • Pulmonary disease • Global

KEY POINTS

- Population-based data from North America, Europe, and Australia show that the prevalence of nontuberculous mycobacteria (NTM)-related pulmonary disease (NTM PD) continues to increase, and that prevalence is lower in Europe than in North America and Australia.
- Large tertiary care facility–based studies in East Asia (Japan, South Korea, Taiwan) also suggest high and increasing prevalence of NTM PD.
- In selected African countries, NTM were identified in 4.2% to 15% of suspected tuberculosis (TB) cases and in 18% to 20% of persons with "chronic" suspected multidrug-resistant TB.
- Improved surveillance for NTM is needed, including population-based surveillance and sentinel studies.
- Host and environmental factors interact in disease risk; host factors include neoplasms, preexisting lung disease, and more recently identified factors such as thoracic skeletal abnormalities, rheumatoid arthritis, and immunomodulatory drugs. Environmental risk factors for disease clustering include high vapor pressure such as is found in warm, humid environments.

INTRODUCTION

This article reviews approaches to studying the epidemiology of nontuberculous mycobacteria (NTM)-related pulmonary disease (NTM PD), and updates in the field since the last review published in 2002.[1]

Methodologic Challenges

Studying the epidemiology of NTM PD presents several methodologic challenges that affect the measures obtained. First, with a few exceptions,[2] in most countries NTM PD is not a reportable condition, such that describing the burden, trends, and associated risk factors for this condition depend on special studies, surveys, and sentinel surveillance efforts described later in this article. Second, isolation from an uncontaminated clinical specimen is insufficient to document disease, because respiratory secretions from patients with underlying lung disease may be colonized with these organisms without overt untoward manifestations For this reason, clinical information is required in concert with microbiological data to

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be certain whether disease is present in an individual, although reliance on solely microbiological information has recently been shown to provide a reasonable approximation.[3–5] The diagnosis comprises 3 components to include microbiological, radiographic, and clinical criteria.[6] These criteria require that a patient with symptoms seeks health care, that the health care provider suspects a diagnosis, that appropriate samples are obtained (sputum or lung biopsy), and that radiographic imaging is performed. Finally, the disease is often indolent (slowly progressive) and chronic, and patients may not be routinely evaluated with appropriate samples throughout their disease course. Often patients may have difficulty producing sputum samples, which limits the ability to obtain appropriate samples. In one study of NTM, 40% to 70% of patients were cultured in only a single year during a study period spanning from 5 to beyond 10 years.[3]

Measures of Disease Burden

For a chronic disease such as NTM PD, prevalence is the best measure of disease burden in a population. Incidence is a measure of the frequency of new infections and is the best measure for identifying risk factors for disease. Defining incidence, that is, the frequency of new cases occurring in a defined population over a specified time period, requires definition of a time period when patients were disease-free. Because the disease is often indolent and samples for microbiological analysis may not be taken, this disease-free risk window may not be clear.

Prevalence is a measure of the frequency of all cases existent in a defined population, newly or previously diagnosed. Two measures of prevalence have been used to define the NTM PD burden in a population: average annual prevalence and period prevalence.[3,4,7,8] The average annual prevalence is defined by averaging the annual number of cases over a defined period and dividing by the average annual population over that time period. The period prevalence is defined as the total number of cases existent over a defined period divided by the population in that time period. For a longer time period, for example over 5 to 10 years, the period prevalence estimates will always be greater than an average annual population estimate because for the former, cases are summed over multiple years so that cases that are identified only once during a period of interest whereas for annual prevalence, the same case occurring over multiple years would be counted only in years in which multiple isolates are obtained, despite ongoing chronic disease.

Although mortality data are suboptimal given the uncertain validity of death certificate coding for NTM PD as a cause of death, such data have been used in 2 instances to provide a national picture of the epidemiology of NTM. In the United States, mortality patterns mirrored prevalence data with respect to time, place, and person.[9] In Japan, mortality data were useful for providing insight into patterns by age, sex, and region, and for estimating prevalence.[10]

Risk Factors: Approaches

To more fully understand the population patterns and trends for NTM PD, both host and environmental risk factors must be considered, as both contribute to disease patterns. Because these organisms are widespread in soil and water in most countries and yet disease is rare, host susceptibility likely plays a key role. The role of inherited genetic factors can be studied by both traditional and modern genetic methods. Traditional methods include pedigree analysis to indicate clustering of NTM PD and related traits within families.[11,12] Future studies can include approaches such as whole-exome sequencing or candidate gene approaches to identify variants associated with disease or severe disease, similar to the work that has been done for cystic fibrosis (CF) to identify genetic modifiers of disease.[13] For studies involving genetic sequencing, as with any control group, the comparison population should be as similar as possible to the case group except with respect to the factor under study. Characterization of human leukocyte antigen types has also been used to identify genetic variants associated with NTM disease.[14,15]

An area of great concern has been the role of specific environmental exposures to soil and water, and particularly to water aerosols from showers and baths.[16] One approach to studying this has been to design case-control studies with detailed ascertainment of these exposures. However, the measurement of individual behaviors is limited by recall bias and the unknown incubation period (time between exposure and disease onset). In addition, these studies are limited to some degree by the lack of knowledge regarding infectious dose for NTM PD, which would help guide the detail needed for exposure ascertainment. An alternative and more recent approach has been to study these factors using spatial analysis, which allows detection of disease clusters and analysis of the association of these clusters with atmospheric and other environmental conditions.[17,18] Because NTM are environmental organisms, an analytical approach that seeks to relate population patterns