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# Epidemiology of non tuberculous mycobacteria in India: A review

**Khushboo Jethva, Dhara Bhatt and Maitreyi Zaveri**

## Abstract
Mycobacteria which are ubiquitous in nature residing in various environmental niche having pathogenic, non-pathogenic and zoonotic characters. The term Non Tuberculous Mycobacteria (NTM) and Mycobacteria Other Than Tuberculosis (MOTT) originated from the concept that they comprise of *Mycobacterium spp.* which are not members of *Mycobacterium tuberculosis* complex. Most reports are from developed countries that have low rates of TB. However, in countries with high burden of TB, including India, NTM pulmonary disease often goes unrecognized and is misdiagnosed as pulmonary TB because clinical presentation of NTM and *Mycobacterium tuberculosis* (MTB) diseases are indistinguishable from each other. Not everyone with NTM pulmonary disease has symptoms, but most have a combination of lung and other symptoms. Non Ttuberculos Mycobacteria were isolated from tap water, industrial polluted water, sewage, domestic garbage and drainage water and also from drinking water. *M. marinum, M. ulcerans and M. vaccae* have been reported to cause skin infections. *M. fortuitum, M. gordonae, and M. chelonae* were also described as potential fish pathogens causing ulceration in skin, parenchimal tissue and internal organs of ornamental and food fishes. With respect to environmental exposures to water and soil aerosols, very few individual exposures have been identified, but new analytic approaches have highlighted the important of climatic factors such as warm, humid environments with high atmospheric vapour pressure as contributing to population risk. Additional research is needed to more specifically identify additional climatic and soil factors, and their contribution to microbial growth. Further, the interaction of human populations with these environments will be key to understanding the interaction of host and environmental factors.

**Keywords:** Non Tuberculos mycobacteria, *Mycobacterium tuberculosis*, epidemiology, Global burden, risk factor

## Introduction
Non Tuberculous Mycobacteria (NTM) considered mostly as colonizers or ignored as environmental contaminants in the past, is now increasingly recognized as important pulmonary pathogens in both immunocompromised and immunocompetent population [1]. NTM are widely distributed in the environment, particularly in wet soil, marshland, streams, rivers and estuaries. Different species of NTM prefer different types of environment [2]. Human disease is believed to be acquired from environmental exposures, and unlike tuberculosis and leprosy, there has been no evidence of animal-to-human or human-to-human transmission of NTM, hence the alternative label "environmental bacteria" [3].

Mycobacteria which are ubiquitous in nature residing in various environmental niche having pathogenic, non-pathogenic and zoonotic characters [4, 5]. The term Non Tuberculous Mycobacteria (NTM) and Mycobacteria Other Than Tuberculosis (MOTT) originated from the concept that they comprise of *Mycobacterium spp.* which are not members of *Mycobacterium tuberculosis* complex. Earlier they were named as 'atypical mycobacterium' from the conviction that they are unusual and mostly non-pathogenic in comparison to *Mycobacterium tuberculosis* and *Mycobacterium laprae* strains. Recent investigations have recognized NTMs as potential causative agents for diseases in animals as well as human beings, especially in Immuno compromised people [6].

Besides, NTM infections have been documented having zoonotic implications with its spread from fishes, birds and animals to human hosts, causing epidemics in nature. Environmental NTMs like *M. fortuitum*, *M. gordonae*, and *M. chelonae* has been screened from infected fishes and aquatic systems of Northern, Eastern and South Eastern Parts of India and most of them have been identified as human pathogens [7-9]. Apart from the eminent trouble of drug resistant tuberculosis (MTB) infections, NTM infections are now showing an elevated trend in India [10].

Specific risk factors identified are HIV infection, cystic fibrosis, underlying chronic lung disease, previous tuberculosis (TB), and work in the mining industry [11].

These are also reported to cause surgical-site infections, post-injection abscesses, osteomyelitis, catheter-related blood-stream infections, and central nervous system infections [12]. Non Tuberculous Mycobacteria rates of infection and disease has significantly increased in recent years and rates vary widely depending on population and geographic location [13]. Most reports are from developed countries that have low rates of TB. However, in countries with high burden of TB, including India, NTM pulmonary disease often goes unrecognized and is misdiagnosed as pulmonary TB because clinical presentation of NTM and *Mycobacterium tuberculosis* (MTB) diseases are indistinguishable from each other.

Most reports are from developed countries that have low rates of TB. However, in countries with high burden of TB, including India, NTM pulmonary disease often goes unrecognized and is misdiagnosed as pulmonary TB because clinical presentation of NTM and *Mycobacterium tuberculosis* (MTB) diseases are indistinguishable from each other. Prevalence of NTM is unknown in India as NTM disease is not a reportable condition and there is lack of awareness among clinicians coupled with lack of laboratory capacity to diagnose these infections [14]. Among few reports available, NTM isolation rates are reported to range from 0.5 to 8.6% in India [15].

Clinical signs and symptoms of both NTM and MTB are related to granulomatous inflammations, which are quite similar and thus often go unrecognized and cannot be discriminated based on the common identification protocols of ATS (American Thoracic Society). Thus, NTM is easily misdiagnosed as *M. tuberculosis*, and Multi Drug Resistant (MDR), XDR (Extreme drug resistant) TB, though the infection might be of multiple etiology. Several reports have come up in Indian context where NTMs have been reported in lung infections in patients thought to have tuberculosis [16, 17]. Infections involving various pathogenic NTMs like *M. marinum, M. fortuitum, M.chelonae* have been reported in India. NTM represent over 150 different species, most of which do not seem to cause human disease except in individuals with a weak immune system.

There are about 50,000 to 90,000 people with NTM pulmonary disease in the United States, with a much higher frequency in older adults. However, NTM can affect any age group. In some people NTM infections can become chronic and require ongoing treatment. Severe NTM lung disease can have a significant impact on quality of life. Death directly related to NTM lung disease is rare. The symptoms caused by NTM infection can vary from no symptoms to severe cough, fatigue, and weight loss. NTM disease is more common in individuals with underlying lung disease or weak immune systems.

**What Are the Symptoms of NTM Lung Infections? [18]**

Not everyone with NTM pulmonary disease has symptoms, but most have a combination of lung and other symptoms. The more severe the infection, the more likely you will have symptoms. Symptoms of NTM lung disease can be classified into two categories: symptoms that mainly affect the lungs and symptoms that affect the whole body.

The most common respiratory symptoms of NTM lung disease are:

- Cough that won't go away
- Coughing up blood (hemoptysis)
- Shortness of breath when active

Other symptoms of NTM lung disease include:

- Fatigue
- Low-grade fever
- Night sweats
- Weight loss

Similar to the reports worldwide, this shows the emerging trend of the *Mycobacteria* which were earlier neglected. With the rising incidences of antibiotic resistance in pathogens from environment and nosocomial habitats, these under documented microorganism needs limelight, as India is still fighting to overcome the Tuberculosis scenario. Resistance to multiple drug therapy was thought to be limited among Mycobacterium tuberculosis complex where MDR-TB is considered to be resistant to Isoniazid. In recent years, Non Tuberculous Mycobacterial infections and diseases have significantly increased with treatment strategies involving administration of the single or mixture of standard anti-tubercular drugs such as Rifampin, Isoniazid, Ethambutol, Streptomycin, Moxifloxacin, Telithromycin, Quinupristin and Dalfopristin [19].

Most of the clinical studies showed the NTMs to be remarkably resistant or only partially susceptible to these anti-tubercular drugs. The Multi Drug Resistance of Non Tuberculous Mycobacteria has now become a globally challenging health issue. NTMs encompass extensive diversity in phenotypic features depending on environmental distribution, growth rate, survival to environmental stress, colony morphology and coloration, biochemical characteristics and pathogenecity to eukaryotic hosts [20].

Non Tuberculos Mycobacteria were isolated from tap water, industrial polluted water, sewage, domestic garbage and drainage water and also from drinking water [21, 22]. *M. marinum, M. ulcerans and M. vaccae* have been reported to cause skin infections [23]. *M. fortuitum, M. gordonae, and M. chelonae* were also described as potential fish pathogens causing ulceration in skin, parenchimal tissue and internal organs of ornamental and food fishes [24-27].

**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, 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 microbiologic 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 [28-31]. 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 average population in that time period. For a longer time period, for example over 5–10 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 are included, whereas for an 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, nonetheless, such data have been used in two 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 [32]. In Japan, mortality data were useful for providing insight into patterns by age, sex, and region, and for to estimating prevalence [33].

**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 [34, 35]. Future studies can include approaches such as whole exude sequencing or candidate gene approaches to identify variants associated with disease or severe disease, similar to the work that has been done for CF to identify genetic modifiers of disease [36]. 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 HLA types has also been used to identify genetic variants associated with NTM disease [37, 38].

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 [39]. One approach to studying this has been to design case-control studies with detailed ascertainment of these exposures. However, the measurement of individual behaviours is limited by recall bias as well as 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 [40]. Because NTM are environmental organisms, an analytic approach that seeks to relate population patterns to environmental conditions may be a better approach, as these factors act beyond the individual (i.e. influencing mycobacterial grown in and near bodies of water), in a truly ecologic fashion.

**Epidemiology of NTM Isolation and Disease by Global Region**

Ideal studies comprise population-based investigations including both clinical and microbiologic data, and encompassing an adequate temporal period to best capture the burden of infection in the population. We present reviews of the best available studies by global region.

**Middle East and South Asia**

No recent population-based studies of pulmonary NTM were identified from this region. A number of studies, generally performed in single institutions, provide information regarding species distribution among patients with NTM PD in this region. At a single centre in Turkey, during 2004–2009, among 53 patients with pulmonary NTM isolation, 60% were judged to have disease. The mean age of patients with disease was 54 years and 87.1% were males [41].

In a single institution in Israel, among 215 patients identified with pulmonary NTM isolation over 2004–2010, 21% were judged to have definite or probable disease, but clinical information was not detailed [42]. From various laboratories in Saudi Arabia, a sample of 95 patients with NTM isolation was identified during 2009–2010, including 73 patients with pulmonary isolation, 67% of whom were judged to have pulmonary disease but clinical information was not detailed [43]. In Oman, over 2006–2007, a random sample of 13 NTM isolates from the Central Public Health Laboratory in Muscat, was selected for case review [44]. Eleven isolates were pulmonary, and ATS disease criteria were fulfilled in 63.6%. Among patients with NTM PD, the mean age was 46.3 years and 57.1% were males. At a single institution in Mumbai, India, during 2005–2008, 103 patients had pulmonary NTM isolates, with 65.0% judged to have either “definite” or “probable” disease, but clinical information was not detailed [45].

**East Asia**

No population-based studies of pulmonary NTM epidemiology in East Asia were identified. A number of studies have been done from single institutions and are described below. We generally excluded studies that presented exclusively isolate-level data (lacking patient-level data) and studies which focused on specific patient groups (critical care unit patients, cancer patients, etc.). A number of South Korean studies offer insight into NTM PD species distribution and patient characteristics, and suggest that NTM PD is becoming increasingly common. At one institution in Seoul, over 2002–2003, 794 patients with pulmonary NTM isolates were classified according to disease status [46], using the 1997 American Thoracic Society criteria [47] and the 2000 British Thoracic Society criteria [48] ascertained by full review of medical records. Definite disease was defined by fulfilling both ATS and BTS criteria, probable disease cases fulfilled only the BTS (less stringent) criteria, and unlikely disease comprised the remainder. Of 195 patients judged to have either definite (n= 131) or possible (n=64) disease, the mean age was 63 years, and 55% were women.

Recent Japanese studies provide insight into the prevalence of NTM PD, species distribution, and patient features. A recent study used the mortality rate, among patients with NTM PD, as a way to derive estimates of prevalence of NTM PD (10). The authors estimated a national prevalence of NTM PD in Japan in 2005 at 33–65/100,000, and report that most cases are caused by MAC (10). A single-institution study in Tokyo, describing 273 newly-diagnosed patients with MAC lung disease during 1996–2002, reported an average age of 64 years, and a predominance of females (70%) [49]. The authors divided the disease into radiographic type according to the presence of cavitation, and observed that 30% of females had cavitation, compared with 65–70% of males. Two additional studies of MAC PD patients from Japan provide interesting insights [50-52]. Among 634 HIV-negative patients diagnosed with MAC PD over 1995–2005 in Saitama, the mean age at cohort entry was 68.9 years, 58.5% were women, and 38.3% had pre-existing respiratory disease (including 5.8% with emphysema). Another group presented data on a cohort of 164 patients identified with MAC PD over 1999–2005 in

Kyoto, wherein the mean age was 66 years, 56.7% were women, and 61.6% had COPD [53]. These studies support the notion that MAC PD patients in Japan are generally older and mostly women, although the presence of COPD was variable. However, referral bias may affect cohort characteristics in studies from single institutions [54].

A number of studies from single institutions in Taiwan provide insights into species distribution and suggest that NTM PD is increasingly common. At an institution in Kaohsiung City, Southern Taiwan, it was observed during 2004–2005, that among the 67 patients with NTM PD identified, the average age was 67 years, 70% were males, and 88.1% had pre-existing lung disease, including 61.2% with COPD [55].At a hospital in Taipei City, Northern Taiwan, the annual prevalence of NTM PD increased from 1.28/100,000 in 2000, to 7.94/100,000 in 2008 [56]. From the same institution, 252 NTM PD patients with classifiable radiographic patterns (cavitary, bronchiectatic, or consolidative) were identified over 2007–2009. The mean age was 63.7 years and 50.8% were men [57]. The studies from Taiwan identified NTM PD patients as being in the same age range as most other studies. However, in contrast to work from Japan and Korea, Taiwanese studies described a slight male predominance.

Two recent studies from China reported on the frequency of NTM isolation among patients with mycobacterial isolates. From a single institution in Shanghai over 2005–2008, 5.1% of positive mycobacterial cultures were NTM, increasing from 4.3% in 2005 to 6.4% in 2008. In several counties in rural Shandong Province, of 2,949 specimens that were culturepositive for mycobacteria, 64 were NTM (1.6%) [57].

**Summary and Research Gaps**

Population-based data for prevalence and trends estimation are available primarily from North America, Europe, as well as for New Zealand and Australia, where NTM PD is a reportable condition; these data have documented a continued increase in NTM prevalence since 2000. Annual prevalence in North American and Australia, ranging from 3.2–9.8, is generally higher than in Europe, where available estimates are all below 2 per 100,000. Tertiary care-based studies of NTM PD from South Korea, Japan, and Taiwan, also suggest increasing prevalence of NTM PD. In South America, Africa, and the Middle East, studies among patients with suspected TB and MDR have documented a previously unappreciated prevalence of NTM in this population, ranging from 4–15% for suspected TB and 18–20% for suspected multi-drug resistant TB (MDR TB).

Clinical data available from several regions have allowed better characterization of the affected populations. Across regions, the majority of cases occur among persons aged >50 years, with a mean age of 54–70 years. In North America and East Asia, most NTM PD cases are among women whereas in Europe men predominate among NTM PD cases, with varying proportions of preexisting lung disease across regions. The species distribution also varies by region, with MAC predominant in North America and East Asia, whereas in Europe MAC is less predominant and M. kansasii, M. xenopi, and M. malmoense are found with greater frequency. In addition, species vary by patient sex and the presence of preexisting lung disease.

The available data highlight data needs and research gaps. To more fully characterize prevalence and trends for NTM PD, population-based data on NTM isolates with species information linked to clinical data and patient characteristics (age, sex, geographic location) are needed from more geographic areas of the world. These data could be obtained by linking NTM surveillance to existing TB surveillance, with reporting of all AFB isolates linked to the above clinical and demographic information. In areas where such data are not feasible to obtain, sentinel surveillance could be established at tertiary care centers serving a large population. In particular, to advance the understanding of the influence of species and subspecies type on disease type and progression, as well as the influence of environmental reservoirs on disease presentation, more detailed information related to both patient and demographic factors are needed. Standard microbiologic and clinical data collection will allow assessment of trends. The detection of important proportions of patients with NTM isolates among patients screened for TB and MDR TB highlights the need for enhanced mycobacterial laboratory capacity to discriminate between cases of TB and NTM, ensuring correct diagnosis and management, as well as identifying the burden of NTM in these settings.

With respect to risk factors for NTM, host and environmental factors interact to influence disease risk. Beyond previously described structural abnormalities and immunosuppressive conditions, host factors important to the current epidemiology of NTM PD include thoracic skeletal abnormalities, rheumatoid arthritis, immunomodulatory drugs such as TNF-alpha inhibitors (particularly in the RA population), steroid use, and GERD. Clustering of disease within families suggests a heritable genetic predisposition to disease susceptibility, and additional research is needed to identify these genetic factors. With respect to environmental exposures to water and soil aerosols, very few individual exposures have been identified, but new analytic approaches have highlighted the important of climatic factors such as warm, humid environments with high atmospheric vapor pressure as contributing to population risk. Additional research is needed to more specifically identify additional climatic and soil factors, and their contribution to microbial growth. Further, the interaction of human populations with these environments will be key to understanding the interaction of host and environmental factors.

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