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Epidemiology of human pulmonary infection with nontuberculous mycobacteria

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Nontuberculous have been recognized since the late nineteenth century [1], not long after Robert Koch's discovery of the tubercle bacillus. The recognition of the presence of these organisms in human disease was reported as early as 1893 [2], and numerous reports and reviews supporting their role as a true pathogen appeared subsequently [2–5]. As reviewed by Fogan [6], these organisms had been collectively referred to as atypical [7], anonymous [8], and unclassified [9], with the former moniker still in common use today. In one of these reports, Runyon described a classification scheme based primarily on morphologic colony characteristics [8], which has evolved to include epidemiologic and clinical features to group the numerous recognized species involved in human disease [10]. NTM organisms have been recovered from many environmental sources. These include: *M avium complex* (MAC) and *M malmoense* from waters and soils; *M kansasii, M xenopi*, and *M marinum* from water; and the so-called rapid growers (*M abscessus, M chelonae*, and *M fortuitum*) from many environmental sources [11–13].

Studying the epidemiology of pulmonary NTM disease can be challenging. Reporting of the disease to public health authorities is not required in the United States and many other nations, making regional case registries scarce. The organisms are commonly isolated from environmental sources, so their growth in culture may raise the question of specimen contamination [10]. 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 [14,15]. For this reason, clinical information is required in concert with microbiologic data to assess for the presence of disease in an individual [10] and, correspondingly, to estimate its frequency in a population. In this article, we will use the term infection to refer to the recovery of viable NTM organisms from an uncontaminated clinical specimen in the absence of obvious clinical manifestations. The term disease will be reserved for infections in which there are signs or symptoms suggesting a pathogenic process.

The frequency of NTM pulmonary disease has been reported to be increasing on several continents [10,14,16]. Changing patient populations, most notably from infection with HIV, have greatly increased the numbers of people at risk. A thorough understanding of the overall magnitude of the problem would assist with the planning and execution of research studies, resource allocation, and individual patient care. The purpose of this article is to present the current state of knowledge regarding the frequency of pulmonary NTM infection in different parts of the world, and to assess the evidence for temporal changes in the epidemiology of this infection.

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Studies addressing the epidemiology of NTM infection may be broadly divided into three types. Cutaneous delayed-type hypersensitivity to NTM antigens has been used to study large samples of people in many countries [17–27]. These studies have the strength of providing information regarding simple infection in large groups of people but suffer from the lack of information regarding the prevalence of disease. Another drawback of this study type reflects the relatively poor specificity of the skin test, as well as overlap in reactivity among various Mycobacterial species. Early information on the epidemiology of NTM infection came from skin test studies employing low (standard) and high doses of tuberculosis purified protein derivative (PPD-S), wherein the observation was made that tuberculosis (TB) patients reacted to a wide range of PPD-S doses; a large proportion of people not known to have been in contact with TB patients reacted only to high doses [28]. These and other data [21,24,29] have shown significant overlap in cutaneous hypersensitivity between mycobacterial species. For this reason, only two such studies will be reviewed [17,18], based on their large size and historical importance in shaping the current understanding of the epidemiology of NTM infection.

The second useful type of epidemiologic study of NTM infection includes investigations reviewing consecutive isolates from a mycobacterial laboratory with a known and well-defined catchment area. In the presence of adequate laboratory protocols to avoid contamination with environmental organisms, these studies provide unequivocal evidence of infection but have the obvious shortcoming of a lack of clinical data, preventing the assessment regarding the presence or absence of disease. These studies also are affected by a type of work-up bias, as the criteria for obtaining specimens on individual patients are unknown and likely vary between clinicians. The final and most useful study type combines information from the mycobacterial laboratory and the clinician's assessment. This study type is unique in its ability to provide estimates of disease rates but shares the potential weakness of work-up bias discussed above. Studies based on mycobacterial isolates will also likely suffer from an insensitive measure bias [30], as most patients likely have only spontaneously expectorated sputum obtained, and relatively few would have had more invasive (and potentially more sensitive) investigations including induced sputum, bronchoscopic, or surgical specimens. Also, patients with milder cases would be less likely to have specimens obtained by any method, leading to an underestimate of the prevalence of milder cases. Overall, these biases would tend to underestimate the frequency of NTM infection and to a lesser extent disease. We have reviewed studies of all three categories and present them by geographic regions and in chronologic sequence. All studies had a well-defined underlying population and complete capture of microbiologic data. For studies without rates of infection or disease, we calculated annual rates per 100,000 based on contemporary population data. Information on risk factors was collected from all studies. Studies presenting data regarding at least two of infection rates, disease rates, pathogenic potential (fraction of isolates judged to be causing disease), and relative frequency of TB versus NTM are summarized in Tables 1–4.

When reviewing studies of the epidemiology of NTM pulmonary infection and disease, one must consider the specific population studied. Prince et al divided patients with NTM disease into three groups, HIV-infected, those with "traditional" predisposing conditions (including neoplasms, chronic obstructive pulmonary disease [COPD], and bronchiectasis), and individuals without recognizable predisposing factors [31]. Given the widely differing rates between these groups, this distinction is critical. This article focuses on the epidemiology of NTM in the non-HIV and non-cystic fibrosis (CF) population because these areas are reviewed comprehensively in subsequent articles.

North America

Skin test studies

Two landmark studies of skin testing helped shape our understanding of the epidemiology of NTM. Between 1943 and 1959, Palmer skin-tested over 22,000 students starting their nursing training in the United States [17]. A complete history of geographic residence and TB exposure was taken to classify subjects by area of origin within the United States and as having had close, intermediate, or no known contact with tuberculosis. Skin tests were considered positive if there was at least 5 mm of induration. All were skin-tested with 5 tuberculin units (TU) of PPD-S, and those with negative tests had a repeat test with a 250 TU dose. The high dose was meant to detect infection with organisms other than *M tuberculosis*. Analysis of subjects with a negative 5 TU test showed that those who had lived exclusively in one of the three defined southeast zones (including North and South Carolina, Georgia, Florida, Tennessee, Alabama, Mississippi, Louisiana, Arkansas, Oklahoma,

Table 1
Studies of North American rates of NTM infection and disease

Location and dates	Rates[a] (species frequency)		Pathogenic potential[b]	Relative frequency of TB and NTM disease
	Infection	Disease		
British Columbia 1960–7 [34]	NTM 12.8	Not reported	Not reported	1960: TB 89%, NTM[c] 11%, 1967: TB 93%, NTM[c] 7%
British Columbia 1960–81 [25,37]	MAC, *M scrofulaceum, M. simiae*: 1972–5: 2.1 (∼70%) 1976–9: 2.8 (∼70%) 1980–1: 3.4 (∼70%) *M fortuitum/chelonei* ∼0.6 (15%) *M xenopi* ∼0.2 (5%) *M kansasii* ∼0.2 (4%)	MAC, *M scrofulaceum, M simiae*: 1960–3: 0.1 (∼70%) 1968–71: 0.2 (∼70%) 1976–9: 0.3 (∼70%) 1980–1: 0.6 (∼70%)	MAC, *M scrofulaceum, M simiae*: 1976–9:7% 1980–1:18%	1972–5: TB 79%, NTM 21% 1976–9: TB 74%, NTM 26% 1980–1: TB 62%, NTM 38%
Oklahoma 1966–8 [29]	NTM 6.8 MAC 2.4 (36%) *M scrofulaceum* 2.4(35%) *M kansasii* 1.1 (16%) Rapid growers 0.8 (11%)	NTM 1.3 MAC 0.6 (45%) *M kansasii* 0.5 (43%) *M scrofulaceum* 0.1 (12%)	NTM 19% MAC 25% *M kansasii* 45% *M scrofulaceum* 4%	TB 93%, NTM 7%
Texas 1967–76 [38]	Not reported	*M kansasii* 1.2 MAC 0.6	Not reported	1967–9: TB 97%, NTM 3% 1974–6: TB 88%, NTM 12%
44 U.S. states 1979 [15]	MAC 2.5 (58%) *M fortuitum* 0.7 (15%) *M kansasii* 0.5 (10%)	Not reported	Not reported	TB 68%, NTM[c] 32%
48 U.S. states 1980 [33]	MAC 3.2 (61%) *M kansasii* 0.5 (10%) *M fortuitum* 0.5 (9%)	Not reported	Not reported	TB 65%, NTM[c] 35%
33 U.S. states 1981–3 [14]	NTM 4.5 MAC 2.7 (60%) *M kansasii* 0.4 (9%) *M fortuitum* 0.6 (13%) *M chelonae* 0.2 (4%)	NTM 1.8 MAC 1.3 (72%) *M kansasii* 0.3 (17%) *M fortuitum* 0.1 (6%) *M chelonae* 0.1 (4%)	NTM 40% MAC 47% *M kansasii* 75% *M fortuitum* 18% *M chelonae* 38%	TB 85%, NTM 15%
Massachusetts 1972–83 [35]	1972–1983 MAC: 0.9 (34%)–4.6 (20%) Other NTM: 1.7(66%)–6.8 (80%)	Not reported	Not reported	1972: TB 88%, NTM[a] 12% 1983: TB 30%, NTM[c] 70%
San Francisco 1992–6 [39]	*M kansasii* 2.4 HIV negative 0.75/ positive 115.1/AIDS 646.5	*M kansasii* 2.1 HIV negative 0.62/ positive 105.3	*M kansasii* 88%	Not reported

AIDS, acquired immune deficiency syndrome; HIV, human immunodeficiency virus infection; NTM, nontuberculous mycobacteria TB, tuberculosis

[a] Rates expressed as annual rates per 100,000 population

[b] Proportion of isolates judged to be causing disease

[c] Infection rate

and Texas) had a median reaction of 7 mm to the 250 TU dose, with 65% having a reaction of at least 5 mm. The subjects in this category from other parts of the United States had a median reaction of 0 mm to the 250 TU dose, and only 29% had a reaction of at least 5 mm ($p < 0.0001$, chi-square). Importantly, the degree of TB exposure by history was not related to the reaction to the 250 TU

Table 2
Studies of European rates of NTM infection and disease

Location and dates	Rates[a] (species frequency)		Pathogenic Potential[b]	Relative frequency of TB and NTM disease
	Infection	Disease		
Wales 1952–78 [43]	NTM 0.39 *M kansasii* 0.25 (64%) MAIS 0.11 (28%) Others 0.02 (5%)	NTM 0.30 *M kansasii* 0.21 (70%) MAIS 0.06 (20%) Others 0.02 (7%)	NTM 78% *M kansasii* 84% MAIS 55% Others 100%	1952–78 TB: 99.8–98.2% NTM: 0.2–1.8%
Scotland 1990–3 [45]	National: NTM— 1.7 *M malmoense* 0.7 (40%) MAC 0.5 (32%) Lothian region: NTM 4.8 *M malmoense* 1.8 (38%) MAC 1.6 (33%)	National: not reported Lothian region: *M malmoense* 1.3	Lothian region: *M malmoense* 72%	Not reported
Seine-Saint-Denis, France 1915 [46]	*M kansasii* 1.1	*M kansasii* 0.5	*M kansasii* 45%	Not reported
Zurich, Switzerland 1983–8 [48]	NTM: 1983:5.3, 1988:11.1 Average: NTM 7.6 *M gordonae*—3.4 (45%) MAC 0.9 (20%) *M fortuitum* 0.5 (7%) *M kansasii* 0.5 (7%) *M xenopi* 0.4 (5%)	NTM:1983:0.4,1988:0.9 Average: NTM 0.5 MAC 0.2 (46%) *M kansasii* 0.06 (12%) *M xenopi* 0.06 (12%) *M fortuitum* 0.03 (6%)	NTM: 8% Average: MAC 22% *M kansasii* 12% *M xenopi* 15% *M fortuitum* 6%	1983: TB 98%, NTM 2% 1988: TB 94%, NTM 6%
Karvina, Czech 1968–79 [49]	*M kansasii*: 1968:1,1979:18	*M kansasii*: 1968:1,1979:12	M kansasii: 1968:100%,1979:33%	1968: TB 95%, *M kansasii* 5% 1979: TB 63% *M kansasii* 37%
Karvina, Czech 1984–9 [50]	*M kansasii*: 1984:19,1989:25	*M kansasii*: 1984:14,1989:18	*M kansasii* 73%	Not reported
Netherlands [47]	NTM: 2.9 *M kansasii* 0.2 (7%)	*M kansasii* 0.06	*M kansasii* 32%	Not reported

NTM, nontuberculous mycobacteria; TB, tuberculosis; MATS, Mycobacteria avium, intracellular and scrofulaceum
[a] Rates expressed as annual rates per 100,000 population
[b] Proportion of isolates judged to be causing disease

dose. This argues strongly against the second test detecting TB infection through a booster phenomenon, instead supporting the author's supposition that these subjects were infected with other antigenically related organisms. This important study not only established the 5 TU skin test as the gold standard for TB infection (through analysis of response to the 5 TU dose test) but also helped form the current understanding of the striking geographic differences in the epidemiology of NTM infection in the United States, with particularly high rates in the southeast.

Edwards et al performed a large survey of skin testing in the United States between 1958 and 1965 [18]. They studied over 670,000 male navy recruits, between the ages of 17 and 21, with a battery of skin tests that included 5 TU PPD-S, PPD-B (Battey bacillus extract, MAC), and histoplasmin. The threshold value for a positive reaction to PPD-B was at least 4 mm. For the study of geographic variability, the analysis was restricted to the 275,000 recruits who were lifelong single-county residents in the continental United States. The 56% rate of positivity in recruits who had lived only in the southeastern states was significantly higher than the 15–25% range seen in recruits from other regions ($p < 0.0001$, chi-square).

Although the accuracy of the specific rates of infection can be called into question [21,24,29], the two studies reviewed above, and others of a similar nature [20–27] performed worldwide over many decades, have nearly uniformly shown marked geographic variability in prevalence of sensitivity to NTM preparations.

Table 3
Studies of African, Asian and Australian rates of NTM infection and disease

Location and dates	Rates[a]		Pathogenic potential[b]	Relative frequency of TB and NTM
	Infection	Disease		
KwaZulu region, Natal, South Africa 1974 [54]	1,400	Not reported	Not reported	TB 35%, NTM 65%
Transkei region, South Africa 1977 [55]	6,700	Not reported	Not reported	TB 39%, NTM 61%
South Africa 1993–6 [53]	125	78	*M kansasii* 78% *M scrofulaceum* 75%	TB 40%, NTM 60%
South Africa 1996–7 [52]	174	54	*M kansasii* 41% *M scrofulaceum* 50%	Not reported
Japan 1971–84 [16], 1993 [56]	Not reported	1971–5: 1.2 1976–80: 1.6 1981–4: 1.8	Not reported	1971–5: TB 99%, NTM 1% 1976–80: TB 98%, NTM 2% 1981–4: TB 96%, NTM 4%
Japan 1985–90 [57]	Not reported	1985: 4.2 1990: 6.9	Not reported	1985: TB 91.1%, NTM 8.9% 1990: TB 86.2%, NTM 13.8%
Japan 1985–92 [58,59]	Not reported	1985: 1.5 1991: 2.5 1992: 3	Not reported	1985: TB 91%, NTM 9% 1991: TB 86%, NTM 14% 1992: TB 84%, NTM 16%
Japan 1997 [61]	Not reported	3.5	Not reported	TB 81%, NTM 19%
Hong Kong 1990 [62]	12	2	NTM 17% MAC 22% *M chelonei* 27% *M kansasii* 6% *M terrae* 6%	TB 98%, NTM 2%
Western Australia 1959–68 [63,64]	8.8	1.8	Overall — 20% Runyon Group: 1 — 45% 2 — 35% 3 — 20% 4 — 1%	1959: TB 96%, NTM 4% 1968: TB 89%, NTM 11%
Western Australia 1962–87 [65]	*M kansasii* 1962–82: 0.2 1983–7: 0.7	*M kansasii* 1962–82: 0.1 1983–7: 0.3	*M kansasii* 1962–1982: 50% 1983–1987: 43%	1962: TB 99.6%, *M kansasii* .4% 1987: TB 95.2%, *M kansasii* 4.8%
Northern Australia 1989–97 [66]	Not reported	1989–93: 2.7 1994–7: 4.7	Not reported	1989: TB 92%, NTM 8% 1997: TB 75%, NTM 25%

NTM, nontuberculous mycobacteria; TB, tuberculosis
[a] Rates expressed as annual rates per 100,000 population for all NTM species combined unless otherwise stated
[b] Proportion of isolates judged to be causing disease

Restricted microbiologic studies

A number of useful studies of positive NTM culture results have been performed in North America [15,32–34]. A Centers for Disease Control (CDC) laboratory survey of NTM isolates from 42 of 54 mycobacterial laboratories across the United States was performed in 1979 [15]. Data were reported as total number of isolates rather than patients, so the calculated infection rates could be a significant overestimate if a large number of patients produced several positive samples. Thirty-two per cent of mycobacterial isolates were NTM, comprising a sample of 7,764 positive specimens. Of NTM isolates, 58% were MAC, 15% *M fortuitum*, 10% *M kansasii*, and 9% *M scrofulaceum*. MAC was most common in all regions, followed by *M fortuitum* and *M kansasii* in all regions with the exception of the Midwest, where isolates of *M kansasii* outnumbered those of *M fortuitum*. National rates of infection were 2.5, 0.7, and 0.5 per 100,000 respectively for MAC, *M fortuitum,* and *M kansasii*. Regional data showed MAC to be most common in all areas, ranging from 1.7 in the Midwest to 5.1 per 100,000 in the Southeast. *M fortuitum* was more common than *M kansasii* in all areas except the Midwest. Rates of *M kansasii* infection ranged from 0.2 in the Northeast to 1.1 per 100,000 in the Southeast. These data were

Table 4
Risk factors for NTM infection and disease

Risk Factor	Risk ratio[a]	Disease or Infection
Age, sex and race		
Increasing age, usually >40–70 years [25,29,38,63]	4–26.5 [25,60,66]	Both
Male [14,25,29,38,39,42,44,46,48,51,59,63,65]	1.2–25 [14,25,38,39,42,44,46,48,51,59,65]	Both
"Elderly females," "middle-age males" [38,51]	NR	Both
Caucasian [14,29]	NR	Both
Black [39]	3–4 [39]	Infection
Environment		
Coastal [37]	NR	Both
Warmer climate [16,40,56,57,63]	NR	Disease
Urban, high population density [37–39]	2.5 [38]	Both
Rural [29,38]	2 [38]	Disease
Mining, smelting, dusty, residence in mining areas [37,42,43,47,49,51,63,65]	NR	Both
Other Medical		
Silicosis/pneumoconioses [42,43,50,53,62,64]	NR	Both
COPD [44,46,64]	NR	Both
Bronchiectasis [46,60,62]	NR	Disease
Radiographic changes of previous TB [53,64]	NR	Both
HIV/AIDS [39,46,66]	150–863 [39]	Both
Malignancy [44,48]	NR	Both
Diabetes mellitus [46]	NR	Both
Alcohol abuse [48,66]	NR	Both

NTM, nontuberculous mycobacteria, TB signifies reports not differentiating species-specific risk factors; NR, not reported; COPD, chronic obstructive pulmonary disease; HIV, infection with human immunodeficiency virus; AIDS, acquired immune deficiency syndrome

[a] Risk ratios were not quantified in most studies. Presented values therefore represent a minority of reports.

updated and expanded upon in 1980, again including only the total number of positive isolates rather than patients [33]. A slightly higher proportion of mycobacterial isolates were NTM (35%), but the total number of isolates had increased by more than 3,500 to 11,391. Isolation rates and species frequencies were generally similar. Rates of MAC isolation tended to be highest in states bordering the Atlantic Ocean and Gulf of Mexico (>4.8 per 100,000), as well as the Southwest, several states bordering Canada, and Kansas. Regions with high rates of *M kansasii* isolation were distributed in an inverted "T," with a large cluster in the central United States (>0.75 per 100,000) extending northward and a band across the majority of the southernmost states. Although both of these reports may represent an overestimate regarding infection rates, as data are reported as numbers of isolates rather than patients, they provide worthwhile data on relative frequencies of the common organisms. The isolation rates may also provide a reasonable approximation of infection rates, as they are comparable to those presented in the following studies.

In an eight-year study between 1960 and 1967, Robinson et al reviewed all positive mycobacterial cultures in the Canadian province of British Columbia [34]. Data were collected on total isolates rather than number of patients and may therefore overestimate rates of infection. Over the study period, the proportion of mycobacterial isolates from NTM, as compared with TB, fell slightly from 11% to 7%. The annual rate of NTM isolates remained constant at approximately 12.8 per 100,000 (Table 1). This is far higher than the range of 2–8 calculated from data reported for the bordering US state of Washington a decade later [15,33].

DuMoulin et al performed a study of patients with positive NTM cultures in Massachussetts from 1972 to 1983 [35], observing a rate of infection of 2.6 per 100,000 in 1972, and rising to 11.4 in 1983 for all NTM species combined. Rates of MAC infection increased fivefold (from 0.8 to 4.6) and other NTM fourfold (from 1.7 to 6.8) over the study period. The fraction of mycobacterial cases from NTM exhibited a concomitant rise from 12% to 70%, compared with TB, which decreased from 88% to 30% (see Table 1).

This study documented a tremendous increase in rates of NTM infection over a very short period of time, with most cases occurring in urban communities. The number of HIV-infected patients was not provided, and no compelling hypothesis to explain these findings was offered. Worth noting is that the estimates based on the number of isolates by Good [15,33] are very similar to the rates based on the number of patients by DuMoulin. Both report an annual rate of MAC infection of approximately 4 per 100,000 in Massachusetts around 1980.

A Canadian study of positive NTM isolates in the province of Manitoba calculated annual infection rates based on number of patients with positive cultures from 1988 to 1990 [32]. Given that 438 patients had positive cultures, and a population of 1.5 million, the mean annual rate of infection over the 2-year study period was an astonishing 14.6 per 100,000. This is far higher than 5–6 in the bordering state of Minnesota, based on data reported 10 years previously by Good [33]. The limited data presented limits conclusions that may be drawn from this study.

Studies with clinical correlation

The group of studies reviewing both microbiologic and clinical data on the rates of NTM disease in North America span nearly 4 decades [14,25,29,36–39]. A study of all cases of mycobacterial disease from the province of Newfoundland between 1957 and 1960 reported that 2% were caused by NTM [36]. Two thirds of NTM cases were pulmonary, and all isolates were classified as chromogens. Based on the presented data, the average annual rate of NTM disease was 2.0 per 100,000 overall and 1.3 for pulmonary disease. As the methods of ensuring a truly comprehensive sample were not explicit, the calculated rates may be significant underestimates.

Data on all mycobacterial isolates from the province of British Columbia from 1960–1981 were reported in two publications [25,37]. Data were presented on new infections and the fraction of patients with disease. The annual incidence rate of disease per 100,000 rose at a near exponential rate, from 0.08 in 1960 to 0.60 in 1980 (see Table 1). MAC was the most commonly isolated species, followed by rapid growers, *M xenopi*, and *M kansasii* [37]. These two reports present a thorough analysis and suggest a steadily increasing rate of NTM infection and disease over more than 2 decades.

From 1966 to 1968 in the state of Oklahoma, all NTM isolates were reported to the health department. Fogan reported on the 240 patients identified during this 17-month period [29]. Approximately one fifth of patients with infection were classified as having disease. Overall mean annual rates of infection and disease, calculated from the reported data, were 6.8 and 1.3 per 100,000, respectively. Although *M kansasii* was the third most commonly isolated species (less than half the number of isolates of Battey bacillus, and scotochromogens), it was the second most common cause of NTM disease, with a rate nearly identical to that of MAC (see Table 1). A full 50% of *M kansasii* isolates were felt to be causing disease, compared with 23% of Battey organisms and 6% of scotochromogens. This report underscores the high pathogenic potential of *M kansasii* and its importance in this geographic region, and it provides an accurate estimate of diagnosed NTM infection and disease.

Ahn et al reported on microbiologic and clinical data based on all reported NTM isolates in the state of Texas between 1967 and 1976 [38]. Although only state-supported hospitals were required to report these data, the authors made the assumption that other hospitals and private physicians would do the same but provide no assurances in this regard. Bearing this in mind, the rates provided by this study may well be a significant underestimate. The authors presented data only on patients classified as having disease with either MAC or *M kansasii*. The annual rates of disease with *M kansasii* and MAC were estimated at 1.2 and 0.6 per 100,000 respectively (see Table 1). Over the 10-year study period, the fraction of cases of mycobacterial disease caused by NTM rose from 2% to 11%. Barring an increase in rate of reporting among private hospitals over the study period, it is unlikely that the potential for incomplete sampling would have caused an artifactual increase in rate. Thus, there is reasonable evidence for an increase in disease over this period. The authors postulated that the increase may have been secondary to the decrease in TB, with less cross-immunity to the NTM organisms.

O'Brien et al performed a survey of 26 U.S. state and 22 city health departments from a total of 33 states, recording laboratory and clinical information on patients with NTM positive specimens between 1982 and 1983 [14]. They found MAC was the most common NTM isolated and causing disease. Overall infection and disease rates were 4.5 and 1.8 per 100,000, and more than 80% were pulmonary (see Table 1). This study was limited in its ability to generalize given the incomplete sampling, especially because of the absence of data from at least four centers with over one million people. Despite this, the investigators have provided some of the most useful and recent nationwide estimates of rates of NTM disease in the United States.

Bloch et al performed a rigorous study of the epidemiology of *M kansasii* in the San Francisco Bay area from 1992 to 1996 [39]. In addition to ensuring all isolates were recorded, they obtained information on HIV status and other important clinical factors. They observed that 92% of all cases were pulmonary, and of the 270 patients with positive specimens, 69% were infected with HIV. Some 88% of all patients were judged to have manifestations of disease from their infection. The mean annual incidence of infection and disease were 2.4 and 2.1 per 100,000, respectively (see Table 1). Incidence rates for infection were analyzed in specific groups (see Table 1) and found to be as high as 647/100,000 in people with AIDS. This study provides useful data in at least three important areas: accurate infection and disease rates for *M kansasii* in a defined geographic area, rates in patient groups with different risk factors, and further evidence for the high pathogenicity of *M kansasii* consistently observed to cause disease in the majority of patients from whom it is recovered.

In summary, the data from North America present a useful, if somewhat patchy, collection of infection and disease rate estimates. Although it is inappropriate to compare rates directly between different studies, as differing methodologies will lead to differing biases, looking across the studies does provide interesting observations. Some of the recent Canadian reports [32,34] observed rates of infection as high as 12.8 and 14.6 per 100,000 but did not provide accompanying clinical information. Others [25,37] failed to find similarly high rates and reported levels of 2–4 per 100,000. Studies from the United States have shown tremendous geographic variability. The highest rates of MAC are observed in southeastern Atlantic states and several states along the U.S.-Canadian border. *M kansasii* is most commonly found in some Midwestern and several southernmost states. Rates for infection and disease in the United States have generally been reported at approximately 4 and 2 per 100,000, respectively, for NTM overall, with 50–60% of cases caused by MAC, 20% caused by *M kansasii*, and approximately 10% rapid growers. *M kansasii* has consistently been reported to cause disease in the majority of cases with a positive isolate. Finally, of the few reports that have presented data on disease rates over time, most [25,35,37] have found a profound increase.

Central and South America

Data on the epidemiology of NTM infection in Central and South America are limited. Barrera surveyed laboratories in Argentina to review mycobacterial isolates and related clinical information between 1982 and 1984 [40]. NTM disease was defined by the presence of symptoms, repeated isolation with quantitative culture, and the lack of response to standard anti-TB therapy. Over three-year study period, the authors found that 3% of all mycobacterial isolates were NTM, and only 6% were classified as causing disease. Rates were reported as 3.2 and 0.2 per 100,000 for infection and disease, respectively. MAC was the cause in 25 of 27 cases of disease, and 1 each was caused by *M scrofulaceum* and *M chelonei*. Some important limitations of this study deserve mention. As only 15 of 26 surveyed laboratories provided adequate data, a high level of geographic variability could have led to inaccurate estimates of disease rates. Requiring that someone fail traditional anti-TB therapy before being classified as having disease is probably inappropriate. Given that disease from several NTM species may respond to such treatment, this stipulation could significantly underestimate the proportion of infected patients with disease. Based on this study, NTM infection does not appear to be a significant problem in Argentina, but its limitations preclude definite conclusions.

Europe and the United Kingdom

Restricted microbiologic studies

Tala and Viljanen published a brief report of the mycobacterial isolates in Finland between 1991 and 1993 [41]. With the aid of national compulsory reporting for all mycobacterial infections, they found NTM rates remaining relatively stable, with a mean annual isolation rate of 6.6/100,000; 55% of isolates were MAC, with rapid growers (*M chelonei* and *M fortuitum*) making up 20%, *M gordonae* 15%, and *M malmoense* 10%. No data were provided on the clinical significance of these isolates, and the calculated rates of infection may well represent an overestimate, given that they reflect the total number of isolates, more than one of which could come from a single patient.

Studies with clinical correlation

Numerous reports on the epidemiology of NTM in the United Kingdom (UK) have been published. Two reports from Wales present data from 1953 to 1978 [42,43]. In one study, the authors apparently report only cases with NTM disease, but the definition is not explicit [42]. This study found a greater than twofold

increase in rates of disease over a decade (from 0.2 to 0.5 per 100,000 from 1953–7 to 1963–1967). *M kansasii* was the most common cause of disease (67%), followed by MAC (28%) and *M xenopi* (4%). The other study reported that incidence rates peaked around 1968 and then decreased somewhat [43]. They also concluded 84% of *M kansasii* and 40% of MAC isolates were causing disease, similar to findings of other groups. Data from Scotland suggest high rates of infection and disease with *M malmoense* [44,45]. A limited report on all the cases of *M malmoense* pulmonary disease between 1982 and 1984 provided data to calculate a national annual incidence rate of 0.1 per 100,000 [44]. A subsequent study between 1990 and 1993 reported a disease rate of 1.3 per 100,000 for *M malmoense* pulmonary disease in the Lothian region [45]. Rates of infection for the nation as a whole and Lothian were also presented, reporting *M malmoense* as the most common isolate, followed closely by MAC (Table 2). Taken together, these studies highlight the important geographic variability in NTM infections in the UK.

A study from France between 1991 and 1995, limited to *M kansasii* in a Paris suburb with a high prevalence of HIV, reported rates of infection and disease of 1.1 and 0.5 per 100,000, respectively (see Table 2) [46]. One third of patients were HIV-positive, and all had a history of some pulmonary disease within the past 2 years. The remaining patients all had a chronic (>2 year) history of pulmonary disease, with 48% having a documented history of previous TB. These rates of *M kansasii* infection and disease are somewhat lower than estimates from the demographically similar but geographically remote jurisdiction of the San Francisco Bay area [39].

M kansasii infection and disease rates were reported from the Netherlands for a 1-year period over 1978–1979 [47]. The presented data suggest rates of infection and disease of 0.2 and 0.1 per 100,000, respectively (see Table 2). Most isolates were from the mining province of Limburg, and the authors speculate that this reflects a particular susceptibility of miners, probably caused by high rates of underlying lung disease.

Debrunner et al reported on a 6-year study of all NTM isolates from the Zurich area of switzerland, excluding patients with known HIV infection. [48] They report that 34/513 (7%) patients with positive cultures had clinical disease. Of note, only 26% of patients with *M kansasii* infection were judged to have clinical disease, just slightly higher than the 21% seen in MAC. The most common disease-causing species were found to be MAC followed by *M kansasii*, *M xenopi*, and *M fortuitum* (see Table 2). Overall rates of NTM infection and disease doubled between 1983 and 1988 to reach 11.1 and 0.9 per 100,000, respectively.

Several studies from the Czech Republic have reviewed the experience with *M kansasii* in the Karvina district of North Moravia, where mining is a major industry [49–51]. Over a 12-year period ending in 1979, one study reported a greater than 10-fold increase in rates of both infection and disease, measured at 17 and 12 per 100,000, respectively (see Table 2), with a simultaneous decrease in the rate of TB from 30 to 20 per 100,000. [49] Similar rates were reported by Kaustova et al [50] (see Table 2) and Chobot et al [50,51] These studies highlight the great regional variation in rates of infection, and the high pathogenicity of *M kansasii* reported to be 70% or greater in two of these studies. [49,50] The population under study may also bear some similarities to others in mining communities [47,52,53] likewise reported to have high rates of *M kansasii* infection and disease.

Africa

Restricted microbiologic studies

A number of studies of the epidemiology of NTM have been performed in South Africa. These have generally been limited to select populations, providing accurate population-specific information, but no national averages to generalize to the population as a whole. Two studies reported on the results of mycobacterial studies of sputum cultures from large random samples of South African native peoples [54,55]. Arabin et al obtained sputum from 1,196 Zulus in Natal, South Africa [54]. No clinical information was provided. Sputum was obtained either spontaneously or induced by mechanical irritation of the epiglottis. Nine samples grew *M tuberculosis* and 17 grew NTM, translating into prevalence rates of 750 and 1,400 per 100,000, respectively (Table 3). Fourie et al obtained aerosol-induced sputum from 2,230 Xhosa people in the Transkei region in 1977 [55]. Ninety-six specimens grew *M tuberculosis* and 150 grew NTM, yielding prevalence rates of 4,300 and 6,700 per 100,000, respectively. Both studies utilized population-based methods to determine prevalence of pulmonary mycobacterial infection in specific groups and reported alarmingly high rates of NTM infection and TB disease. The results cannot be generalized to other populations, however, and do not provide information about NTM disease.

Studies with clinical correlation

Investigations in Africa that present clinical and microbiologic data include two South African studies focusing on a population of gold miners [52,53]. The records of a cohort of HIV negative gold miners, investigated for suspected pulmonary mycobacterial disease between 1993 and 1996, were reviewed [53]. Annual rates of NTM infection were measured at 101 per 100,000 and rates of disease with the 2 most common organisms were 66 (*M kansasii*) and 12 (*M scrofulaceum*) per 100,000, respectively (see Table 3). Interestingly, MAC made up only 6% of all isolates and the rate of MAC disease was not reported, presumably because of its scarcity. The same group subsequently presented data on another cohort of gold miners, this time including HIV-positive patients [52]. Rates of NTM disease were somewhat lower than the earlier report (see Table 3) but still higher than reports from all others reviewed herein. Of HIV patients who developed NTM infection and disease, the relative species frequency and clinical course were similar to HIV-negative patients. The investigations from Africa reported extremely high rates of infection and disease but studied very select populations in a single country.

Asia

Studies with clinical correlation

There has been a proliferation of studies on the epidemiology of NTM in Japan over the past two decades. Data for these studies come from patients investigated for suspected mycobacterial disease, who by public health law, are admitted to TB hospitals for investigations. These methods may lead to an underestimate of infection rates and an overestimate of the proportion of patients who have NTM disease rather than colonization, as patients with lower levels of symptoms may not reach medical attention, hospitalization and intense investigation. Two publications providing complementary data on rates of NTM disease were first reviewed together [16,56]. Between 1971 and 1984, records from a sample of hospitals from across Japan were reviewed, and the results were extrapolated to the entire nation. The investigators reported a steady increase of NTM rates, with MAC disease comprising the vast majority, followed by a much lower rate of disease from *M kansasii* (see Table 3). Other organisms were relatively uncommon, causing on average, less than 5% of cases. A marked geographic variability was noted, with a near 10-fold difference between lowest (0.47 per 100,000) and highest (4.64 per 100,000) incidence areas. The increase in *M kansasii* rates was most marked and was postulated to be related to a concomitant decrease in TB rates, with NTM organism filling a niche left vacant by *M tuberculosis* [56]. A subsequent study of NTM from 1985 to 1990 [57] reported rates of disease nearly fourfold higher than previously described (see Table 3) [16,56]. The explanation for this discrepancy is unclear, but may relate to reporting cases of infection rather than disease, or different sampling methods, given that the latter study reviewed records from all sanitoria in Japan. Estimates in this study were probably not accurate reflections of NTM disease at that time, given the same group reported updated data one year later [58] and a report for 1991 [59] presenting rates that were similar to those reported by others. In this latter study, they found average annual rates of NTM, MAC, and *M kansasii* to be 3.0, 2.4, and 0.3 per 100,000, respectively (see Table 3). A report on cases from Hiroshima prefecture in 1993 [60] observed similar overall rates but less *M kansasii* (0.1 per 100,000) than in contemporary nationwide reports. A final report from Japan presented data from 1997 and compared it with rates dating back to 1971 [61]. Over the 27-year period, a progressive increase in rates of NTM disease, (from 0.8 to 3.5 per 100,000) accompanied by a drop in TB rates (133 to 15 per 100,000) was observed. Taken together, studies from Japan have shown rising rates of NTM disease from approximately 1 per 100,000 in 1971 to greater than 3 per 100,000 by the late 1990s, with a simultaneous precipitous drop in the rates of TB. Generally, MAC was the isolate in 75–80%, *M kansasii* in up to about 20%, and there were few rapid growers.

Hosker reported data from Hong Kong based on respiratory NTM isolates from 1985 and 1989–1991 [62]. Clinical information was available to estimate rates of NTM disease for 1990, whereas data from other years were limited to total numbers of isolates from which we calculated rates of infection based on contemporary population data. Rates of infection varied widely, from as low as 0.7 per 100,000 in 1989 to a high of 12.0 in 1990 (see Table 3). Using a sample of approximately 25% of culture-positive patients in 1990, and American Thoracic Society (ATS) criteria for the diagnosis of NTM disease, disease rates were estimated as 2.0 per 100,000. Given the widely varying estimates of infection over the study period, it is difficult to know if the results provide an accurate reflection of rates, or if other biases were acting.

Australia

Studies with clinical correlation

Mycobacterial epidemiologists in Australia have enjoyed a system of screening for TB that requires reporting of all cases of mycobacterial disease, facilitating several thorough studies of rates of NTM infection and disease. Two studies presenting overlapping data on the epidemiology of NTM in Western Australia between 1959 and 1968 are reviewed together [63,64]. Data reflected all positive NTM cultures over the study period and were correlated with clinical information. Disease was defined by the presence of clinical or radiographic progression, or by histologic evidence of invasive infection. The annual incidence of NTM infection and disease was stable at 8.8 and 1.8 per 100,000, respectively, with Runyon Group 3 organisms most commonly isolated and causing disease responsible for approximately 75% of either condition. Runyon Group 2 organisms were next most common in causing disease but were isolated slightly less frequently than the rapid growers, which rarely caused disease (see Table 3). Noteworthy are the findings of pulmonary versus nonpulmonary disease almost exclusively in adults versus children, respectively, as well as the significant geographic variability. Of interest also is the decline in TB rates from 40 to 15 per 100,000 over the same period without any significant coincident change in rates of NTM. In an overlapping time period, from 1962 to 1987, Pang reported on the epidemiology of *M kansasii* in the same territory [65]. The definition of disease was the presence of a tissue diagnosis, a notified case, or treated infection, and it was determined that approximately 50% of isolates were disease-causing. The rates increased threefold from the first period (1962–1982) to the second (1983–1987), with a concomitant drop in TB rates from 24 to 6 per 100,000 (see Table 3). Rates were comparable between this study and the previous two, and *M kansasii* was infrequently isolated, making up a small proportion of NTM infection.

Rates of NTM disease in Northern Australia were studied from 1989 to 1997 [66]. The authors compared laboratory data with clinical information and used ATS criteria to define cases. There was an increase from 2.7 to 4.7 per 100,000 between the first and second half of the study period, which was modestly attenuated after removing HIV-associated cases; 62% of cases were pulmonary, and 78% overall were caused by MAC, followed by rapid growers at 12% (see Table 3). There was a simultaneous drop in TB rates from 40 to 17 per 100,000. There was a conspicuous absence of *M kansasii*, an organism seen at a low but regular frequency in the Western Territory (see Table 3). The authors speculate that the increase in incidence may be caused by a combination of factors: increased exposure from changing bathing habits (showering) and increases in the numbers of organisms in the environment, decreased resistance from an aging population and immune deficient states such as HIV, and increased awareness and testing.

Risk factors

Reviewing well-defined surveys of NTM infection and disease permits a relatively unbiased assessment of risk factors. These factors, summarized in Table 4, may be divided, in decreasing order of importance, into coexisting medical conditions, living and work environment, and patient demographics. Less well-studied is the magnitude of risk associated with these factors, and whether a factor increases the risk of infection, disease, or both. When available, these data are presented in Table 4, but generally reflect a minority of studies.

Coexisting medical conditions likely provide the most powerful risk factors for NTM infection and disease. These risk factors may be divided into impairment of local pulmonary defenses and generalized immune defects, with examples including cystic fibrosis (CF) and HIV, respectively. CF apparently has not been studied in population-based reports of NTM, making quantification of this risk factor difficult. HIV and AIDS have been found to be associated with risk ratios of 150 and 863, respectively, for *M kansasii* [39]. Pre-existing lung disease, including silicosis and other pneumoconioses [42,43,50,53,62,64], chronic obstructive pulmonary disease [44,46,48,50,64], bronchiectasis [46,50,60,62], and other radiographic changes consistent with previous TB [53,64] have been identified by studies throughout the world as important risk factors (see Table 4). Alcohol abuse [48,66], diabetes mellitus [48], malignancy [44,48], and smoking [44,66] also have been associated with NTM.

Living and work environment has consistently been identified as an important risk factor in NTM. Studies covering large geographic areas have generally found an increased risk of NTM in people living in warmer regions [16,40,56,57,63]. This may be confounded by coexisting industrialization, as identified in the Japanese studies [16,56,57]. This finding is consistent with skin test surveys concluding that rates of sensitization in the United States were

highest in the warmer southern states, especially in the Southeast [17,18]. One study also found higher rates of infection in coastal versus inland residents in the Canadian province of British Columbia [37]. Living in an urban versus rural setting has been associated with altered rates and patterns of NTM in several studies. Overall rates of NTM were reported to be higher in urban residents in the United States [14] and British Columbia [37]. Two studies have reported living in an area of higher population density to be associated with *M kansasii* [38,39], whereas MAC has been associated with rural living [29,38]. The most commonly cited environmental risk factor for NTM is work environment, specifically mining, associated heavy industry such as smelting, and residence in areas where these industries dominate. This has been reported in North America [37], the United Kingdom [42,43], continental Europe [47,49–51], and Australia [63,65]. Studies of South African coal miners have described tremendous rates of NTM but did not compare this to nonminers, so its ascertainment as a risk factor was not possible [52,53]. Mining has been described as a risk factor for NTM in general, *M kansasii*, MAC, and *M xenopi*. It has been hypothesized that the reason for the association between mining and NTM infection is related to the high rates of pneumoconiosis that miners have traditionally developed. This is a plausible explanation, especially in light of the data that approximately half of South African gold miners with NTM had previous silicosis identified on chest radiography [53], but the frequency of silicosis in the entire cohort was not reported.

Certain demographic features have been identified as risk factors for NTM, including age, sex, or combinations of the two. Increasing age has almost universally been identified as a risk factor for NTM in general [25,48,60,63], MAC [14,29,38,66], and *M kansasii* [14,29,38,49]. Male sex has generally been considered to be a risk factor as well [14,25, 29,38,39,42–44,48,63,66]. Studies also have documented observations regarding the patient-profiles of ''elderly females'' and ''middle-aged males'' being at increased risk for MAC [14,38] and *M kansasii* [51]. Data regarding race are conflicting, with higher rates observed in whites in three studies [14,29,66] and blacks in one [39].

Summary

A great deal of study has gone into the assessment of the epidemiology of NTM infection and disease in many different parts of the world. Review of the available studies provides insight into the frequency of this clinical problem as well as important limitations in current data. Study methods have varied greatly, undoubtedly leading to differing biases. In general, reported rates of infection and disease are likely underestimates, with the former probably less accurate than the latter, given that people without significant symptoms are not likely to have intensive investigations to detect infection.

Pulmonary NTM is a problem with differing rates in various parts of the world. North American rates of infection and disease have been reported to range from approximately 1–15 per 100,000 and 0.1–2 per 100,000, respectively (see Table 1). Rates have been observed to increase with coincident decreases in TB. MAC has been reported most commonly, followed by rapid growers and *M kansasii*. Generally similar rates have been reported in European studies, with the exception of extremely high rates in an area of the Czech Republic where mining is the dominant industry (see Table 2). These studies have also shown marked geographic variability in prevalence. The only available population-based studies have been in South Africa and report extremely high rates of infection, three orders of magnitude greater than studies from other parts of the world (see Table 3). This undoubtedly reflects the select population with an extremely high rate of TB and resultant bronchiectasis leading to NTM infection. Rates in Japan and Australia were similar to those reported in Europe and North America and also show significant increases over time (see Table 3).

Specific risk factors have been identified in several studies. CF and HIV, mentioned above, are two important high-risk groups. Other important factors include underlying chronic lung disease, work in the mining industry, warm climate, advancing age, and male sex. Aside from HIV and CF, mining with associated high rates of pneumoconiosis and previous TB may be the most important historically, reported in studies worldwide [63].

A recurring observation is the increase in rates of infection and disease. The reason for this is unclear but may be caused by any of several contributing factors. The possibility exists that the apparent increase is either spurious or less significant than studies would suggest. Changes in clinician awareness leading to increased investigations, or laboratory methods leading to isolation and identification of previously unnoticed organisms, could play a role in this trend, and studies have been published that support [67] and refute [31] this argument. We believe such factors may contribute to but do not explain the significant increases that have been observed.

A true increase could be related to the host, the pathogen, or some interaction between the two. Host changes leading to increased susceptibility could play an important role, with increased numbers of patients with inadequate defenses from diseases such as HIV infection, malignancy, or simply advanced age [31]. An increase in susceptibility could also relate to the decrease in infection with two other mycobacteria. It has been speculated that infection with TB [29,38] and Bacillus Calmette-Guerin (BCG) [19,68] may provide cross-immunity protecting against NTM infection. Many investigations have observed decreasing rates of TB concomitant with the increases in NTM. In addition, studies from Sweden [68] and the Czech Republic [19] have found that children who were not vaccinated with BCG had a far higher rate of extrapulmonary NTM infection. Potential changes in the pathogens include increases in NTM virulence, and it has been argued that this should be considered as a possible contributing factor [69]. Finally, an interaction between the host and pathogen could involve a major increase in pathogen exposure or potential inoculum size. This may be occurring secondary to the increase in popularity of showering as a form of bathing [66], a habit that greatly increases respiratory exposure to water contaminants.

Several limitations of our review should be noted. We reviewed English-language reports and abstracts, probably leading to fewer data from non-English speaking regions, which may explain the paucity of studies from Africa, Eastern Europe, and most Asian nations. The heterogeneity of study methods in identifying cases and the lack of a uniformly applied definition of disease makes it difficult to compare rates between studies. Finally, the lack of systematic reporting of NTM infection in most nations limits the ability to derive accurate estimates of infection and disease. Regardless, there are more than adequate data to conclude that NTM disease rates vary widely depending on population and geographic location. NTM disease is clearly a major problem in certain groups, including patients with underlying lung disease and also in individuals with impaired immunity. The rates of NTM infection and disease are increasing, so the problem will likely continue to grow and become a far more important issue than current rates suggest.

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