Nontuberculous mycobacteria: incidence in Southwest Ireland from 1987 to 2000

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Abstract  Setting: The Southwest of Ireland (Counties Cork and Kerry) 1987–2000, average population 549 500. Objective: Nontuberculous mycobacteria (NTM) cause significant morbidity worldwide and the study of epidemiology and characteristics helps in their prevention and treatment. This study was performed to determine the incidence of NTM disease in comparison to Mycobacterium tuberculosis (M. tuberculosis) and Mycobacterium bovis (M. bovis) in Southwest Ireland, over the above time period. Design: A retrospective study was carried out in all human isolates of NTM, M. tuberculosis and M. bovis between 1987 and 2000, in the Southwest Region of Ireland. Results: The mean incidence of NTM (0.4/100 000 population) has risen since 1995, principally of pulmonary Mycobacterium avium intracellulare complex (MAC). The annual incidence of M. tuberculosis in humans over 14 years in the same region was 97/100 000 population with a significant reduction since 1994 and M. bovis remained constant at 0.5/100 000 population. Conclusion: The increasing incidence of disease causing NTM noted in Southwest Ireland reflects global data and is surmised to be due to an ageing population, increased incidence related to chronic fibrotic lung disease, and environmental mycobacterial factors.

Keywords nontuberculous mycobacteria; mycobacteria other than tuberculosis; atypical mycobacteria; immunocompromised; human immunodeficiency virus.

INTRODUCTION

Nontuberculous mycobacteria (NTM) have been recognised, since the early 1950s in the U.S.A. (I) as causing disease in humans. These organisms are variously referred to as opportunistic, environmental, and mycobacteria other than tuberculosis.

NTM infection is commonly acquired from environmental sources including water and soil, from which they have been isolated. Mycobacterium avium intracellulare complex (MAC), the NTM most studied, has been identified in animals, but animal to human transmission is deemed unimportant as suggested by serological and plasmid analysis (2–4). These organisms are not always pathogenic when isolated from human samples, and the identification of which isolates are disease causing and which are contaminants or colonisers is based on internationally recognised criteria (9,10). Most immunocompetent individuals can effectively resist infection by these organisms without tissue invasion occurring.

Common NTM pulmonary infections are noncavitatory, often complicating chronic lung fibrosis of varying aetiology, chronic obstructive airways disease, and bronchiectasis. The common NTM extrapulmonary infections are benign cervical adenopathy in children (5), skin lesions, and disseminated disease in the immunocompromised person. In developed countries, NTM infection can also cause diverse infections including tenosynovitis (4,6), skeletal infection, arthritis, bursitis, tendon sheath infection, otomastoiditis (7), and prostatic tissue infection (8). Disseminated MAC is a common bacterial infection in patients with acquired immune deficiency syndrome (AIDS), occurring in 20–40% of all patients in several reported series prior to the advent of highly active antiretroviral therapy (HAART) (9).

The NTM organisms that can cause human disease include MAC, Mtycobacterium kansasi, M. marinum, M. malmoensae, M. abscessus, M. ulcerans, M. xenopi, M. fortuitum-cheloni, M. szulgai, M. simiae, and M. scrofulaceum.

We initiated a study to assess the extent of disease caused by NTM over a 14-year period from 1987 to 2000.
in the Southwest region of Ireland, to compare the variation of incidence of NTM with *M. tuberculosis* and *M. bovis*, to identify the type of infections caused, to identify the NTM isolates involved, and to assess the patients demographic characteristics of patients infected by this disease.

**MATERIALS AND METHODS**

The catchment area, the Southwest Ireland (Southern Health Board Region comprising Counties Cork and Kerry), is both urban and rural with a predominantly indigenous Caucasian population with a minority of other ethnic races (less than 1% combined African, Eastern European, and Asian). The population in 1986 was 536,900 and increased to 563,000 by the end of 2000 (average approximately 550,000). The population over 65 increased from less than 60,000 in 1987 to 66,900 at the end of 2000. The temperate climate of the area has an average annual temperature of 9°C. The annual number of days with more than 1 mm of rain is approximately 200 in the Southwest part of the country.

NTM isolates in Southwest Ireland between 1987 and 2000 were identified. Only human isolates were included. The sources of the samples included all the hospitals in the above area, as well as sputum samples sent in directly from General Practitioners. Clinical samples were analysed at the Regional Medical Microbiology Laboratory in Cork University Hospital. The Medical Microbiology Laboratory in Cork University Hospital is the main microbiology laboratory for a number of hospitals in Cork City, but also acts as a referral laboratory for specimen analysis for all other hospitals in the Health Board region.

All data were gathered from the Cork University Hospital Medical Microbiology Database, which included patient identification, anatomical source of sample, and information on the decision to treat. Repeated positive isolates from the same site in a single individual were counted as one in data analysis.

The decision to treat in our population was based on consultation between the responsible clinician and the microbiology team.

NTM isolates were considered disease causing if they fulfilled the criteria established in 1990 by the American Thoracic Society for NTM disease (9). The criteria for pulmonary disease are briefly as follows:

1. Greater than or equal to two sputum specimens (or one sputum and one bronchial washing specimen) that are smear-positive for acid fast bacilli (AFB) or that yield moderate to heavy growth culture.
2. Exclusion of other reasonable causes of the disease processes.

Alternatively, the following may be diagnostic:

1. A tissue biopsy specimen that yields NTM in culture and has consistent histopathological features.
2. Tissue biopsy specimens that are culture-negative but contain granulomas or AFB, when two previously obtained sputum/bronchial-washing specimens have been culture-positive.

Skin/soft tissue disease was identified if a culture of a swab or biopsy specimen of a lesion involving skin, subcutaneous tissue, muscle, or synovium yielded NTM.

Disseminated disease was identified if the causative species was isolated from blood or bone marrow.

Lymphadenitis was identified if culture of a biopsy specimen or swab of a clinically pathological lymph node yielded NTM.

The criteria for diagnosis of disease caused by NTM has been revised in the 1997 American Thoracic Guidelines with stricter bacteriological, radiographic, and clinical criteria (10).

All cases of NTM deemed contaminants or colonisers were cultured from urine, sputum, or bronchial washings where repeat samples were not clinically indicated or were negative, and treatment was not considered by the responsible clinician in consultation with the microbiology laboratory. All *M. tuberculosis* and *M. bovis* cases were deemed disease causing.

Until January 1998, all samples of Mycobacteria were cultured on Lowenstein Jensen Medium, supplemented with pyruvic acid. Since 1998, Middlebrooks Liquid Culture using a Camlic (Continuous Automated Monitored Liquid Culture) system has been used. Thiosemi-carbazone, TCH (thiopen2carboxylic acid hydrazine), and p-nitrobenzoic acid media are used to identify organisms.

All statistical analyses were carried out using unpaired t-test. A significant value of less than 0.05 was used.

**RESULTS**

In total, there were 960 mycobacterial (*M. tuberculosis*, *M. bovis* and NTM) isolates over the 14-year period. Eight hundred and seventeen of the total 960 isolates were disease causing, the remaining 143 were considered contaminant or colonising NTM. This is highlighted in Table I.

Figure 1 plots the incidence of *M. tuberculosis* and *M. bovis* in the study population.

Of the 817 total culture positive isolates, 749 (91.6%) were due to *M. tuberculosis*. The mean incidence of *M. tuberculosis* was 53.5 (± 8.7 SD), 9.72/100,000 population per year. This incidence has significantly dropped since 1993 (P = 0.004). The incidence in 2000 was 7.94/100,000. Of the *M. tuberculosis* isolates 37.5% were female patients (mean age 55 years) and 62.5% were male (mean age 46 years).

The total number of *M. bovis* cases was 36. The incidence of *M. bovis* remained stable until 1999 with an
average of 2.57 cases per year (± 1.65sd), 0.47/100 000. Fifty per cent of M. bovis cases were male (mean age 53 years) and 50% were female (mean age 63 years). Fifty-three per cent of M. bovis cases were pulmonary and 47% were extrapulmonary.

One hundred and seventy-five isolates of NTM were grown, of which 143 were considered contaminants or colonisers and 32 disease causing. Table 2 highlights the breakdown of NTM into disease-causing isolates and contaminants or colonisers.

The mean incidence of disease-causing NTM was 0.4/100,000/year; Fig. 2 plots the trend of incidence of disease-causing NTM over the 14-year period. Our disease-causing NTM-to-M. tuberculosis ratio was 4.3% for the 14-year period. The ratio of disease-causing isolates to contaminant/colonising NTM over the 14-year period was 18%

Fifty per cent of disease-causing NTM cases were male. The average male age was 32, female age was 48, and the average total age of disease-causing NTM cases was 40.

Fifty-three per cent of disease-causing NTM cases were pulmonary. Forty-seven per cent were extrapulmonary including 10 cases (31%) involving skin, three cases (9%) of lymph node involvement, one case of parotid gland infiltration (3%), and one culture from bone marrow (3%) (see Table 3). The difference between actual initial skin involvement and breakdown from deeper lymph node involvement was difficult to elucidate from documentation and it is probable that some of the MAC isolates from skin were lymph node abscess breakdown.

Of the 32 cases of NTM considered disease causing, there were 23 MAC cases (2.8% of the total 831 disease-causing mycobacterial isolates), five M. malmoense cases (0.6%), two M. abscessus cases (0.22%), one M. marinum case (0.1%), and one M. kansasii case (0.1%).

There was a statistically significant increase in disease-causing NTM infection since and excluding 1994, P value = 0.01, with 20 cases occurring in the 6 years since 1995 inclusive and 12 cases occurring in the 8 years prior to and including 1994, the increase being principally in pulmonary disease. Of these 20 NTM cases since 1994, 16 were MAC, 11 pulmonary, and five extrapulmonary. There were three pulmonary MAC cases prior to 1994. Two pulmonary M. malmoense cases occurred since 1995 and one prior to this.

| Table 1. Total number of mycobacteria isolates in Southwest Ireland, 1987–2000 |
|------------------|-----------------|-----------------|------------------|
| Mycobacterium     | Disease causing | Contaminant or coloniser | Total            |
| MTB               | 749 (78%)       | 0                | 749 (78%)        |
| M. bovis          | 36 (4%)         | 0                | 36 (4%)          |
| NTM               | 32 (3%)         | 143 (15%)        | 175 (18%)        |
| Total             | 817 (85%)       | 143 (15%)        | 960 (100%)       |

MTB = M. tuberculosis; M BOVIS = M. bovis; NTM = Nontuberculous mycobacteria.
Seventy-two per cent of disease-causing NTM isolated in Southwest Ireland was MAC. Of the total of 36 MAC isolates, 23 (64%) were disease causing. The contaminant/colonising MAC cases were all from single sputum specimens. Sixty-one per cent of the disease-causing MAC isolates were from pulmonary specimens. The mean incidence of disease-causing MAC was 1.6 (± 1.35d), 0.3/100,000 population per year. Three cases of MAC were AIDS associated, one prior to 1995, one in 1999, and one in 2000. One of these was isolated from a bone marrow sample signifying disseminated disease and two were pulmonary isolates.

Since the introduction of the newer culture method in 1998, there was a statistically insignificant increase in disease-causing NTM disease identified (P = 0.16). There was a statistically insignificant increase in total NTM isolates since 1995 (P = 0.15) and 1998 (P = 0.13).

There were two peaks in M. chelonae culture, both of which arose from bronchoscope colonisation in separate hospitals. One of these peaks occurred in 1992 and the other in 2000. Five M. xenopi isolates have been isolated since 1999 from various geographical locations. Both B.C.G. (Bacille Calmette-Guerin) isolates were in urine samples during transitional cell bladder tumour treatment with B.C.G.

**DISCUSSION**

NTM disease is not reported in many countries making reliable estimates of its incidence difficult. Despite this, in a number of population studies in many different countries, there has been a rise in the incidence of NTM-related disease over the last 15 years. Worldwide incidence is also hampered by a lack of uniformity of defining NTM disease.

The incidence in our study population, at 0.4/100,000 from 1987 to 2000 and from 1995 to 2000 at 0.62/100,000, is comparable to the Zurich study from 1983 to

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**Table 2.** Nontuberculous mycobacteria in Southwest Ireland, 1987–2000

<table>
<thead>
<tr>
<th>Mycobacterium</th>
<th>Number</th>
<th>% of total mycobacteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease-causing NTM</td>
<td>32</td>
<td>3</td>
</tr>
<tr>
<td>MAC</td>
<td>23</td>
<td>2</td>
</tr>
<tr>
<td>M. malmoense</td>
<td>5</td>
<td>0.5</td>
</tr>
<tr>
<td>M. abscessus</td>
<td>2</td>
<td>0.2</td>
</tr>
<tr>
<td>M. marinum</td>
<td>1</td>
<td>0.2</td>
</tr>
<tr>
<td>M. kansasii</td>
<td>1</td>
<td>0.1</td>
</tr>
<tr>
<td>Contaminant/colonising NTM</td>
<td>143</td>
<td>15</td>
</tr>
<tr>
<td>M. fortuitum</td>
<td>27</td>
<td>3</td>
</tr>
<tr>
<td>M. gordonae</td>
<td>27</td>
<td>3</td>
</tr>
<tr>
<td>M. terrae</td>
<td>26</td>
<td>3</td>
</tr>
<tr>
<td>M. chelonae</td>
<td>20</td>
<td>2</td>
</tr>
<tr>
<td>Envir. Scotochromogens</td>
<td>19</td>
<td>2</td>
</tr>
<tr>
<td>MAC</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>M. xenopi</td>
<td>5</td>
<td>0.5</td>
</tr>
<tr>
<td>M. flavescens</td>
<td>2</td>
<td>0.2</td>
</tr>
<tr>
<td>B.C.G.</td>
<td>2</td>
<td>0.2</td>
</tr>
<tr>
<td>M. malmoense</td>
<td>1</td>
<td>0.1</td>
</tr>
<tr>
<td>Unclassified</td>
<td>1</td>
<td>0.1</td>
</tr>
</tbody>
</table>

NTM = nontuberculous mycobacteria; MAC = M. avium intracellulare; Envir. Scotochromogens = Environmental Scotochromogens; B.C.G. = Bacille Calmette-Guerin.
1988 (0.4–0.9/100 000) (11), but less than the incidences found in North Australia from 1989 to 1997 (3.9 cases/100 000 in the general population, 2.1 cases/100 000 in human immunodeficiency virus negative patients, this study was used the 1990 American Thoracic Society criteria) (12) and in the U.S.A. from 1981 to 1983 1.8/100 000 (13).

There appears to be a considerable amount of variation throughout the world in relation to the strain of NTM found. MAC (predominantly pulmonary) was more predominant in North Australia (12), U.S.A. (13), South-East of England (14), Liverpool (15), and M. kansasii was more common in South Africa (16), a Netherlands coal mining population (17), M. ulcerans in West Africa (18), and M. fortuitum was more common in Taiwan (19). A Scottish review from 1990 to 1993 found a surprisingly high incidence of M. Malmoense pulmonary disease (20).

The variation in percentage of disease-causing isolates to total isolates, 18% in the Southwest of Ireland (1987–2000), 6.6% in the Zurich study (1983–1988), and 42% in the Taiwan study (1992–1996), is related to a number of factors including reporting, definition of disease, and laboratory technique.

In contrast to a lower incidence of NTM in the Southwest of Ireland, there is still a relatively high incidence of M. tuberculosis in comparison to Europe and the United States. A study in Sweden indicated that B.C.G. vaccination might play a role in protection against disease caused by NTM (21) having relevance in Ireland, where B.C.G. vaccination in childhood is mandatory. Previous laboratory data have also suggested that cross-immunity between species may exist, and a reduction in incidence of M. tuberculosis may lead to a mycobacteria-susceptible population (22).

Fibrotic lung disease is a risk factor for the development of pathogenic NTM disease, although there is increasing evidence of pulmonary disease in immunocompetent patients without prior lung disease (23). Although industrial lung disease is uncommon in Southwest Ireland, fibrotic lung disease secondary to pulmonary tuberculosis is prevalent BCG vaccination is mandatory in many districts.

The increasing incidence of NTM from different geographical locations is due in part to increased sensitivity of methods of detection, although the incidence in the Southwest of Ireland began to increase prior to the introduction of the newer culture system. We can therefore assume that this did not significantly affect the data observed. Future development of DNA analysis and skin testing will help improve the sensitivity of mycobacterial detection. One such method has been previously reviewed in the same population (24). Increasing incidence may also reflect an increased awareness by hospital medical staff and general practitioners of NTM infection.

The ageing population in the Southwest of Ireland may also be a factor in the increasing incidence of NTM. The population over 65 increased from less than 60 000 in 1987 to 66 900 at the end of 2000 in the Southwest of Ireland. The lower average population age in the Southwest of Ireland (40 years) than in the Australia (age 57 in pulmonary non-HIV cases) and Liverpool (61.5) studies, and suggested by the Southeast of England Geriatric group, may reflect a bias by physicians not to diagnose and treat older patients. Inclusion of skin and lymphadenopathy cases in our analysis of age also reduces the age average in comparison with the above two groups.

Sex distribution was equal in our population, 64% male in the Liverpool study and 71% male in the Australia study; the predominance of non-HIV-related pulmonary NTM was thought to be associated with higher rates of chronic lung disease also reduces the age average in comparison with two of the above groups.

The increasing incidence in our population does not appear to be AIDS related. Three cases in total of significant NTM were found to be AIDS related, two since 1995 and one prior to 1995. The incidence of AIDS is decreasing in the Republic of Ireland (6.8 per million population in 1999 compared to 11.9 in Britain, 77.1 in Spain for the same year) (25). The incidence of AIDS defining illness, including MAC, has decreased dramatically from 30.7/100 patient-years during 1994 to 2.5/100 patient-years in 1998 in Europe (26) with similar findings in the U.S.A. (27). The advent of HAART therapy is the most important

### Table 3. Site of NTM disease in Southwest Ireland, 1987–2000

<table>
<thead>
<tr>
<th>NTM</th>
<th>Pulmonary</th>
<th>Extrapulmonary</th>
<th>Lymph node</th>
<th>Skin</th>
<th>Other</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAC</td>
<td>14</td>
<td>9</td>
<td>2</td>
<td>5</td>
<td>2</td>
<td>23</td>
</tr>
<tr>
<td>M. malmoense</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>M. marinum</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>M. kansasii</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>M. abscessus</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>17 (53%)</td>
<td>15 (47%)</td>
<td>3 (9%)</td>
<td>10 (31%)</td>
<td>2 (7%)</td>
<td>32 (100%)</td>
</tr>
</tbody>
</table>

aOne parotid gland infection, one bone marrow infection indicating disseminated disease in an immunocompromised patient.

NTM = nontuberculous mycobacteria; MAC = M. avium intracellulare.
contributor. The lower average population age may also reflect a higher incidence of AIDS-associated NTM infection not identified in the data analysed.

Other factors responsible for the increasing incidence of significant NTM may be external factors causing either changes in the distribution or virulence of mycobacteria in the environment; NTM has shown to be isolated from areas where water temperatures are high (28).

The isolation and eradication of one of the M. cheloneae bronchoscopysis outbreaks has been described previously (29). The five M. xenopi isolates grown since 1999 were from various geographical locations. A previous report highlighted hospital water system contamination as a cause of increased M. xenopi isolation (30).

The incidence of M. bovis remained stable until 1999, similar to a previous study of M. bovis from the same population (31).

In conclusion, the increasing incidence of NTM in the Southwest of Ireland, principally in pulmonary MAC disease, over the past 14 years, reflects trends from other population analyses from other countries hampered by a lack of uniformity of defining disease-causing NTM isolates and lack of adequate surveillance data. It may reflect an ageing population that is more susceptible to infection, although the average age of diagnosis is less than in other cited studies and increasing reflection of fibrotic lung disease in the area secondary to M. tuberculosis, with reducing incidence of new M. tuberculosis disease leading to less cross-immunity. It may also reflect environmental mycobacterial factors, with the cooler climate possibly explaining a slower rise in NTM disease in the Southwest of Ireland that in other analysis mentioned. Both detection methods and AIDS incidence appear not to have influenced our data. Further study of the epidemiology, source, and disease caused by NTM will help in its prevention and help identify patients in whom early aggressive therapy will improve outcome.

REFERENCES

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