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RESEARCH ARTICLE

Changing incidence and characteristics of non-tuberculous mycobacterial infections in Scotland and comparison with *Mycobacterium tuberculosis* complex incidence (2011 to 2019)

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Background: An increase in infections with non-tuberculous mycobacteria (NTM) has been noted globally and their incidence has overtaken that of *Mycobacterium tuberculosis* complex (MTBc) in many countries. Using data from a national reference laboratory, we aimed to determine if this trend was observed in Scotland.

Methods: We undertook a retrospective review of all NTM isolates received by the Scottish Mycobacteria Reference Laboratory (SMRL) over 9 years from 2011 to 2019 inclusive. Clinical episodes were defined as per 2017 BTS and 2020 ATS/ERS/ESCMID/IDSA NTM guidelines. These rates were compared with Scottish tuberculosis rates over the same period.

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Results: Of 8552 NTM isolates from 4586 patients in 2011 to 2019, 7739 (90.5%) were considered clinically relevant. These represented 2409 episodes of NTM infection, with *M. avium, M. intracellulare* and *M. abscessus* complex being most common. 1953 (81.1%) were pulmonary NTM infection episodes from 1470 patients and 456 extra-pulmonary episodes from 370 patients. We estimated a rise in incidence from 3.4 to 6.5 per 100,000 person-years (2011-2019 inclusive) with an increase in NTM incidence over MTBc incidence in Scotland by 2017.

Conclusion: The incidence of NTM infection in Scotland has overtaken MTBc incidence. NTM infection leads to a costly healthcare burden, possibly as much as UK £1.47 million (US$ and Euro 1.73 million) annually. We recommend standardisation of isolate referral with clinical surveillance and implementation of agreed standards of care delivered through multi-disciplinary teams. This would improve diagnosis and patient management as well as assessment of diagnostics and novel treatments through clinical trials.

Key Words: Non-tuberculous mycobacteria; Scotland; standardised surveillance; multi-disciplinary management of infections; incidence

INTRODUCTION

The incidence of non-tuberculous mycobacteria (NTM) infections has increased to similar levels or higher than the incidence of *Mycobacterium tuberculosis* complex infections (MTBc) in England, the USA and several European countries in the last decade [1-3]. NTM infections are associated with significant morbidity and mortality, and their management is costly to healthcare systems [4–6]. The increase in NTM infections seems to be driven by an ageing population and advances in modern medicine such as increased use of long-term central venous access devices and new cancer and immunomodulatory treatments [3,7]. Previous work by colleagues at the Scottish Mycobacteria Reference Laboratory (SMRL) showed an increase of 45% in the incidence of *M. avium* complex during an 11- year period from 2000 to 2010, during which time *M. avium* complex was the leading cause of NTM infection in Scotland [8]. However, the incidence of NTM infections (2.4 per 100,000 person-years) had not overtaken the incidence of MTBc (9.6 per 100,000 person-years) in Scotland by 2010 [8–10].

The apparent increase in NTM incidence makes consistent diagnostic approaches and surveillance truly relevant. Clinicians will be familiar with *M. avium*, which rose in prominence during the HIV pandemic [11]. Further, patients with Cystic Fibrosis (CF) are known to be susceptible to NTM infections including *M. abscessus* complex which can lead to a delay in receiving a lung transplant [12]. The 2017 British Thoracic Society (BTS) and 2020 American Thoracic Society/European Respiratory Society/European Society of Clinical Microbiology and Infectious Diseases/Infectious Diseases Society of America (ATS/ERS/ESMID/IDSA) guidelines for the management of non-tuberculous mycobacterial pulmonary disease (NTM-PD)

are improving consistency both in diagnostic and laboratory approaches, but variations in practice remain [13,14]. Extrapulmonary NTM infections including blood stream and cutaneous infections are commonly misdiagnosed often leading to treatment delay [15].

NTM infections frequently require prolonged treatment with combinations of nebulised, oral and intravenous antimicrobials. Toxicity is common and efficacy variable, which can lead to failure in treatment adherence [4]. Without knowing the incidence, appropriate resources to diagnose and manage patients with NTM infections cannot be planned and deployed. This can compromise treatment outcomes and laboratory capacity as well as increase costs for healthcare systems. Research into new diagnostic tools and drug development is difficult as shown by a lack of randomised clinical trials [13,16].

We undertook an analysis of all NTM isolates received at SMRL from 2011 to 2019 to determine the trends in NTM infection in the Scottish population and compare this with the incidence of MTBc.

METHODS

Data collection

We retrospectively reviewed records of consecutive isolates of NTM received at SMRL from Scottish hospital microbiology laboratories over 9 years from January 2011 to December 2019 inclusive. This data is routinely stored for public health surveillance, laboratory governance and clinical purposes. All consecutive NTM isolates received by SMRL were included as identified by searching the SMRL database. Isolates from patient samples collected after this period were not included due to the potential influence of the COVID-19 pandemic on NTM diagnostics.

In 2019, Scotland had a population of 5,463,300 persons. The Scottish healthcare system is divided into 14 areas, called Regional Health Boards. The most populous Boards are Greater Glasgow and Clyde (2019: 1,183,120 persons) and Lothian (2019: 907,580 persons).

Eight of 14 Scottish Health Boards, covering 47.9% of the Scottish population, submit samples from patients with a suspicion of MTBc or NTM infection directly to the NHS Lothian microbiology laboratory, co-located with SMRL, which increases consistency of diagnostic testing. Other Boards refer clinically relevant first isolates to SMRL directly and variably thereafter. Molecular diagnostics used at SMRL remained unchanged from 2011 to 2019 with identification using GenoType Mycobacteria line probe assays (Brucker Hain Lifesciences, Nehren, Germany). *M. abscessus* complex isolates (comprising M. *abscessus ssp. abscessus, M. abscessus ssp. bolletti* and *M. abscessus ssp. massiliense)* were reported as *M. abscessus*. Sample meta-data stored by SMRL includes age, sex, known cystic fibrosis diagnosis, anatomic site and NTM species identified.

Data analysis

All data was collected and analysed in Excel 2007 (Microsoft). Statistical calculations were performed by χ^2 test in Prism, online calculator 2022 version (GraphPad Software). Graphs were drawn in Excel 2007 for Windows (Microsoft) and Prism 9 for macOS, Version 9.3.1 (GraphPad Software). The analyses reported are part of the remit of SMRL.

Annual population estimates for calculating population rates were obtained from the General Register Office in Scotland.

Only routinely collected laboratory data from SMRL was included, therefore a distinction was made between isolates received, clinically relevant isolates (excluding contaminants) and infection episodes with the following definition:

M. gordonae isolates were excluded as these represent likely contamination/colonisation with low clinical relevance consistent with previous publications on NTM incidence [17–19].

The remaining isolates were considered clinically relevant but had to meet standard microbiological criteria to count towards infection episodes in keeping with a previous study by SMRL analysing isolates from 2000 to 2010 [8, 13,14]. Therefore, if a patient had ≥2 sputum cultures containing the same NTM on separate days or a single culture-positive bronchoalveolar lavage (BAL) this constituted an episode of infection. Single sputum cultures were excluded. If there were multiple culture-positive pulmonary samples containing the same species within 12 months this was counted as one episode and subsequent isolates received within 12 months were excluded.

Single positive NTM isolates from sterile sites or biopsies were considered significant (multiple samples positive for the same species within 3 months were counted as one episode).

RESULTS

Overall findings

Between 1st January 2011 and 31st December 2019, a total of 8552 NTM isolates from 4586 patients were received by SMRL (Figure 1). There were 7739 clinically relevant isolates from 1840 patients with 2409 episodes of infection. A total of 813 isolates were excluded as these represented contamination with *M. gordonae.* These comprised 770 pulmonary isolates (including 66 from bronchoalveolar lavages), 29 extra-pulmonary isolates [mainly from urine] and 14 without clinical information.

A male: female ratio of 1.03 was observed for all NTM infections (Table 1). Male:female differences were not statistically significant for most *Mycobacterium* species, apart from *M.*

kansasii and *M. marinum* which were more likely to be isolated from men ($p<0.05$). However, numbers of infection episodes involving these organisms were small.

There were 1953 episodes of pulmonary infection in 1470 patients. Single pulmonary isolates or multiple isolates within one 12-month episode of pulmonary infection comprised 5148 NTM isolates which were excluded from analysis.

Extrapulmonary infection was less common. There were 67 episodes of blood stream infection, with *M. chelonae* complex and *M. mucogenicum* most frequently isolated. Cutaneous infections comprised 59 episodes, mostly caused by *M. chelonae* complex or *M. marinum*. Thirty-one episodes of adenitis were recorded, with *M. avium* most frequently isolated.

Episodes by Age

Overall, 76.3% of infections were found in patients over 50 years old. In children, the most frequently isolated species were *M. abscessus* complex; most other Mycobacterium species were increasingly isolated with an increase in age (Figure 2). We compared *M. abscessus and M. avium* by age and found a statistically significant difference by χ^2 test ($p=0.001$) for a cut-off of 40 years of age (*M. abscessus* complex in patients ≤40 years old and *M. avium* in patients >40 years old).

Trends across time

An overall increase in the incidence of NTM episodes in Scotland was observed with an incidence of 3.4 (2011) rising to 6.5 (2019) per 100,000 person-years (Figure 3). To enable comparison of *M. avium* complex incidence with previous publications, *M. avium* and *M. intracellulare* episodes were merged into *M. avium* complex (MAC) in Figure 3. The overall increase in NTM was driven by MAC infection episodes, which increased from 1.9 to 4.4 per 100,000 person-years. Episodes of infection with *M. abscessus* complex were the second most frequent in Scotland with an increase from 0.4 (2011) to 0.8 (2019) episodes per 100,000 person-years followed by *M. chelonae* complex and *M. malmoense.*

Comparison with incidence of mtbc in Scotland

MTBc data from the "Enhanced Surveillance of Mycobacterial Infections in Scotland" (ESMI) report was compared with the estimated incidence of NTM infections during the period 2011-2019 [9,10]. NTM incidence increased to 6.5/100,000 person-years, while the MTBc incidence decreased from 8.5 to 4.4/100,000 person-years. The estimated NTM incidence rose above MTBc incidence by 2017 (Figure 4). In 2018, the highest MTBc incidence was found in males aged 25 to 44 years and a treatment completion rate of 85.8% was reported which is the highest reporting rate since reporting began in 2001. The constant decrease in MTBc incidence and the improvement in the management of cases was supported by multi-disciplinary team (MDT) management and demonstrated by effective surveillance.

Site of Infection

Blood stream infections due to NTM were most frequently found in patients aged 46 to 65 years, whilst pulmonary and cutaneous infections due to NTM were most frequently found in elderly patients. Adenitis was most frequent in children under the age of 10 years (Supplementary Figure 1).

The main burden of NTM disease was pulmonary, representing 81.1% of NTM episodes (n=1953). Our results show predominance of isolation for *M. avium* (52.1%, n=950), *M. intracellulare* (22.5%, n= 412) followed by *M. abscessus* (13.5% n=247) (Table 2). Of these pulmonary infections, 79.4% were in patients over 50 years old. The pathogenic potential of some NTM species has been identified as listed in Figure 5 [18,19]. These species of NTM account for an estimated total of 1823 episodes (75.7%) of all NTM infection episodes from 2011 to 2019 in Scotland and constitute a significant challenge to healthcare systems in terms of diagnosis, cost, and antimicrobial management.

We found 1362 pulmonary infection episodes of *M. avium* and *M. intracellulare* (MAC) in 9 years but did not have clinical data available to determine the rate of refractory disease. In 2018, Goring *et al.* determined the cost of managing refractory pulmonary infections with *M. avium* complex to amount to £9727 (range £99-£33,269) per person-year in the UK [6]. This computes (£9,727 x 1362 all MAC pulmonary episodes) to overall costs of up to £13,248,174 (US$ and EUR 15.59 million) averaging £1,472,019 (US$ and EUR 1.73 million) annually for Scotland. The actual annual cost of non-refractory and/or refractory NTM-PD in Scotland is unknown.

Cystic fibrosis

There were 186 infection episodes in 116 CF patients during this nine-year period (Supplementary Table 1); the point prevalence of CF at the end of 2019 was 17.0 per 100,000 Scottish population (n=931 of registered CF patients in Scotland in 2019) [20]. The median age was 21 years (mean: 24y, range: 2-56y), 55% were male and 54.3% episodes (n=101 episodes) were caused by *M. abscessus* complex. This proportion was significant by χ^2 test in comparison with other species (Figure in Appendix, $p<0.0001$). Next most common NTM were *M. avium* (28.0% of episodes, n= 52), *M. intracellulare* (9.1% of episodes, n=17), and *M. chelonae* complex (3.2% of episodes, n=6).

DISCUSSION

NTM infection incidence in Scotland 2011 to 2019

The estimated incidence of NTM infection episodes in Scotland has increased in recent years to 6.5 per 100,000 person-years in 2019. This was consistent with findings by colleagues in the rest of the UK, who had reported an increase in NTM incidence to 7.6/100.000 person-years by 2007

for NTM [1]. Episodes of NTM-PD comprised 81% of infection episodes in Scotland during the period 2011 to 2019 and the number of episodes has risen in the last 20 years [8]. From 2011 to 2019, NTM were most likely to be found in pulmonary samples from elderly patients with a predominance of *M. avium* and *M. intracellulare*, which was consistent with studies in the UK where *M. avium/intracellulare* complex was the most frequent isolate [1,19].

Our data showed the most common mycobacterial species found in each Health Board were consistent with the overall Scottish findings. Despite variation in less common mycobacterial species by geographic area, annual variations prevented definitive conclusions.

Variations in NTM epidemiology by geographic area have been noted globally. *M. malmoense* was isolated at high rates in Scotland, Scandinavian countries and Ireland, but not in the USA or Canada as might have been expected given their similar latitudes [7,17].

Formal surveillance of NTM infections could improve estimates of the annual incidence, inform the appropriateness of testing and reference laboratory isolate submission, and increase certainty around duration, incidence and prevalence of NTM infections. It could detect geographic differences and support investigations into the cause of these including acting as an "early-warning" system if a sudden rise in a specific NTM species or site of infection is noted, for example an increase in *M. chimaera* isolates, which may be relevant due to its association with endocarditis [21].

This could become even more relevant if the impact of climate change leads to a further increase in NTM infections with rising temperatures in Europe, as has been suggested for the Australian continent by Thomson *et al.* [22].

Comparison of the period 2011-2019 with previous published data for the period 2000-2010 in Scotland

During the period 2011 to 2019, a rise was noted in NTM isolates received at SMRL, with over twice as many NTM isolates (8552 isolates) received compared to 2000 to 2010 (4193 isolates). The rise could be due to a rise in infections, an increase in awareness of the need to test for NTMs in at-risk patient groups, reflect the improved diagnostic methods (such as liquid culture) used by regional microbiological laboratories and/or a change in referral patterns since eight Health Boards in Scotland have sent all relevant samples directly to Lothian without local culture since 2014. Variations in referral of isolates are the most likely explanation of a marked difference in NTM rates between Greater Glasgow and Clyde and Lothian.

The incidence of NTM infections in Scotland has increased over the last 20 years, but the distribution of infections in different anatomical sites by age group and the distribution of organisms by age group have remained consistent with the exception of adenitis. There were fewer clinically relevant episodes due to adenitis caused by NTM (2011-2019: n=31) compared with the previous 11 years (2000-2010: n=92). The cause of this drop is difficult to determine

from routinely stored information and clinical case surveillance could help identify causes of variations in NTM incidence over time.

In CF patients annual NTM screening is recommended at a minimum [12]. We identified 186 episodes in 116 CF patients which is a 44.2% increase from the 129 reported episodes in the previous decade. This is likely due to increased awareness of the role of *M. abscessus* lung disease in CF patients and increased sampling. Survival of individuals with CF is improving which may also lead to an increase in prevalence of NTM infections.

NTM incidence compared with mtbc infections

In 2019, the incidence of MTB complex was 4.4/100,000 Scottish population, while we estimated an incidence of NTM infection episodes of 6.5/100,000 Scottish population. The estimated NTM infection incidence in Scotland has therefore overtaken the incidence of MTBc.

A recent study by Mourad *et al.* (2021) demonstrated a significant reduction in the expected survival following the diagnosis of NTM-PD, independently of the presence of other comorbidities [23]. As MTBc cases are generally managed with formal MDT support, it would seem appropriate that NTM infections are similarly managed as care is less standardised than that of MTBc and often at least as complex.

Potential cost implications of NTM infections

Goring and colleagues calculated that in the UK average person costs for refractory MAC pulmonary disease per annum were £9727 (range £99-£33,269 in 2015) [6]. Although we do not know the actual number of refractory MAC patients, the annual healthcare costs in Scotland may be as much as £1,472,019 (US$ and EUR 1.73 million). Research based on improved NTM surveillance could determine more precise estimates of cost.

Evidence also suggests the treatment cost of patients with *M abscessus* and *M. xenopi* may exceed that of patients with MAC [24,25]. Given the marked increase in incidence of NTM infections, costs and complexity of management formal multi-disciplinary team meetings (MDT) for the management of NTM infections both locally and nationally should be considered.

Strengths and limitations

Our report's main strength is that all clinically relevant Scottish mycobacterial isolates for identification are referred to SMRL. It is also a repository for the national collection of Mycobacteria.

Since 2014, eight Scottish Health Boards comprising 48% of the Scottish population have sent their primary samples to Lothian for mycobacterial investigation including culture. This improved consistency of laboratory testing and limited referral pattern differences. Analysis of this consistent data indicated a rise in the incidence of infection episodes in these eight Health

Boards, suggesting this is a genuine increase. Therefore, the rise in other Health Boards' incidence is likely genuine.

A limitation is that differences in implementation of guidelines might explain remaining variations in the referral of isolates to SMRL. This could be addressed by standardised isolate referral and clinical infection surveillance in conjunction with MDTs. Recently we received a delayed second isolate, which was initially considered by the referring laboratory to be the same as the first. The first was *M. avium* but the second *M. tuberculosis*, leading to delayed diagnosis, treatment and public health actions. This shows there is a clear risk in only referring one of several isolates.

Uncertainty remains around the duration of NTM infections. By excluding single sputum isolates as well as repeat sputum samples with the same species isolated within 12 months of the primary sample, we might have missed relevant additional episodes within that time frame. The recent introduction of whole genome sequencing (WGS) for all mycobacteria allows improved genetic discrimination between species such as *M. intracellulare* and *M. chimaera* and may inform estimates of the duration of clinical episodes versus re-infections. WGS also opens up the possibility of NTM intraspecies strain discrimination, informing possible ongoing infection, transmission or contamination events.

The definition of one pulmonary infection episode duration as 12 months maximum might have led to over-counting of episodes if some infection episodes had a longer duration. Since this methodology was consistent with the previous SMRL study, which covered isolates received in 2000 to 2010, the increase in NTM incidence in Scotland remains valid [8]. By comparison, the incidence reported by us in that period was similar to that determined for the rest of the UK [1].

To address many of the limitations of this report and to improve patient care we call for a standardised approach to collecting linked national NTM microbiological and clinical data, allowing better estimates of disease burden, allocation of resources and for multi-disciplinary standards of care as discussed by Lipman *et al.* [26].

CONCLUSION

The incidence in NTM infections in Scotland has increased from 3.4 (2011) to 6.5 (2019) per 100,000 person-years and overtook that of MTBc in 2017 which was 5.3/100,000 person-years. The increase in NTM infections in the elderly population is in keeping with findings in other European countries and globally. Annual costs for NTM-PD may be as high as £1,472,019 (US$ and EUR 1.73 million) in Scotland, UK. Given the rising burden of disease and complexity of treatment we call for surveillance of NTM infection episodes by linking microbiological with clinical data and agreed standards of management, including isolate referral, delivered through NTM MDTs. This would lead to increased consistency in NTM diagnosis and management as

well as provide a platform for the assessment of costs and their mitigation, and for clinical trials assessing novel diagnostics and novel treatments which are currently used in a haphazard manner.

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***Potential Conflicts of Interest*:** We declare no competing interests.

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Patient Consent Statement: The Public Health Scotland Order 2019 in Article 9(2)(i) places an obligation on Public Health Scotland to engage in the control of spread of infectious diseases in accordance with section 43 of the National Health Service (Scotland) Act 1978. In accordance with Sections 15, 16 (5), and 21 (2) of the Public Health etc. (Scotland) Act 2008, PHS is obliged to process data in relation to notifiable diseases, health risk states of patients' notifiable organisms, and carrying out public health investigations, and as such, this work does not include factors necessitating patient consent.

Author contributions: All authors have contributed significantly to the work, and have seen and approved the final manuscript.

Key findings: We described and analysed 8552 NTM isolates and associated referral information as received by the Scottish Mycobacteria Reference Laboratory from 2011 to 2019 and identified 2409 NTM infection episodes. Incidence of NTM infections in Scotland overtook *Mycobacterium tuberculosis* complex incidence.

REFERENCES

1. Shah NM, Davidson JA, Anderson LF, et al. Pulmonary Mycobacterium avium-intracellulare is the main driver of the rise in non-tuberculous mycobacteria incidence in England, Wales and Northern Ireland, 2007-2012. BMC Infect Dis, **2016**; 16:195.
2. Schildkraut JA, Zweijpfenning SMH, Nap M, et al. The epidemiology of nontuberculous mycobacterial pulmonary disease in the Netherlands. ERJ Open Res, **2021**; 7:00207–02021.
3. Winthrop KL, McNelley E, Kendall B, et al. Pulmonary nontuberculous mycobacterial disease prevalence and clinical features: an emerging public health disease. Am J Respir Crit Care Med, **2010**; 182:977–982.

4. Veziris N, Andréjak C, Bouée S, Emery C, Obradovic M, Chiron R. Non-tuberculous mycobacterial pulmonary diseases in France: an 8 years nationwide study. BMC Infect Dis, **2021**; 21:1165.
5. Prevots DR, Loddenkemper R, Sotgiu G, Migliori GB. Nontuberculous mycobacterial pulmonary disease: an increasing burden with substantial costs. Eur Respir J, **2017**; 49:1700374.
6. Goring SM, Wilson JB, Risebrough NR, et al. The cost of Mycobacterium avium complex lung disease in Canada, France, Germany, and the United Kingdom: a nationally representative observational study. BMC Health Serv Res, **2018**; 18:700.
7. Hoefsloot W, Ingen J van, Andrejak C, et al. The geographic diversity of nontuberculous mycobacteria isolated from pulmonary samples: an NTM-NET collaborative study. Eur Respir J, **2013**; 42:1604–1613.
8. Russell CD, Claxton P, Doig C, Seagar A-L, Rayner A, Laurenson IF. Non-tuberculous mycobacteria: a retrospective review of Scottish isolates from 2000 to 2010. Thorax, **2014**; 69:593–595.
9. Public Health Scotland. Enhanced Surveillance of Mycobacterial Infections (ESMI) in Scotland: 2018 tuberculosis annual report for Scotland. **2018**. Available at https://hps.scot.nhs.uk/web-resources-container/enhanced-surveillance-of-mycobacterial-infections-esmi-in-scotland-2018-tuberculosis-annual-report-for-scotland/. Accessed 27 April 2022.
10. Public Health Scotland. Enhanced Surveillance of Mycobacterial Infections, 2019 - Enhanced Surveillance of Mycobacterial Infections - Publications - Public Health Scotland. Available at: https://publichealthscotland.scot/publications/enhanced-surveillance-of-mycobacterial-infections/enhanced-surveillance-of-mycobacterial-infections-2019/. Accessed 27 April 2022.
11. Kirk O, Gatell JM, Mocroft A, et al. Infections with Mycobacterium tuberculosis and Mycobacterium avium among HIV-infected patients after the introduction of highly active antiretroviral therapy. EuroSIDA Study Group JD. Am J Respir Crit Care Med, **2000**; 162:865–872.
12. Floto RA, Olivier KN, Saiman L, et al. US Cystic Fibrosis Foundation and European Cystic Fibrosis Society consensus recommendations for the management of non-tuberculous mycobacteria in individuals with cystic fibrosis. Thorax, **2016**; 71 Suppl 1:i1-22.
13. Haworth CS, Banks J, Capstick T, et al. British Thoracic Society Guideline for the management of non-tuberculous mycobacterial pulmonary disease (NTM-PD). BMJ Open Respir Res, **2017**; 4:e000242.
14. Daley CL, Iaccarino JM, Lange C et al. Treatment of Nontuberculous Mycobacterial Pulmonary Disease: An Official ATS/ERS/ESCMID/IDSA Clinical Practice Guideline . CID **2020;** 17(4): e1-e36.
15. Ahmed I, Tiberi S, Farooqi J, et al. Non-tuberculous mycobacterial infections-A neglected and emerging problem. Int J Infect Dis, **2020**; 92S:S46–S50.
16. Falkinham JO. Challenges of NTM Drug Development. Front Microbiol, **2018**; 9:1613.
17. Spaulding AB, Lai YL, Zelazny AM, et al. Geographic Distribution of Nontuberculous Mycobacterial Species Identified among Clinical Isolates in the United States, 2009-2013. Ann Am Thorac Soc, **2017**; 14:1655–1661.
18. Vande Weygaerde Y, Cardinaels N, Bomans P, et al. Clinical relevance of pulmonary non-tuberculous mycobacterial isolates in three reference centres in Belgium: a multicentre retrospective analysis. BMC Infect Dis, **2019**; 19:1061.

19. Schiff HF, Jones S, Achaiah A, Pereira A, Stait G, Green B. Clinical relevance of non-tuberculous mycobacteria isolated from respiratory specimens: seven year experience in a UK hospital. Sci Rep, **2019**; 9:1730.
20. Charman S, Lee A, McClenaghan E, Ainsley C, Gunn E, Clarke S. UK Cystic Fibrosis Registry Annual Data Report 2019 - Scotland. Available at https://www.cysticfibrosis.org.uk/sites/default/files/2021-03/CC33-A-5-Scottish%20Report%202019.pdf. Accessed 28 April 2022.
21. Van Ingen J, Kohl TA, Kranzer K, et al. Global outbreak of severe Mycobacterium chimaera disease after cardiac surgery: a molecular epidemiological study. Lancet Infect Dis 2017; 17:1033–1041.
22. Thomson RM, Faruya-Kanamori L, Coffey C, et.al. Influence of climate variables on the rising incidence of nontuberculous mycobacterial (NTM) infections in Queensland. Australia 201-2016. Sci Total Environ 2020; 740: 139796.
23. Mourad A, Baker AW, Stout JE. Reduction in Expected Survival Associated With Nontuberculous Mycobacterial Pulmonary Disease. Clin Infect Dis, 2021; 72:e552–e557.
24. Ballarino GJ, Olivier KN, Claypool RJ, Holland SM, Prevots DR. Pulmonary nontuberculous mycobacterial infections: Antibiotic treatment and associated costs. Respir Med, 2009; 103:1448–1455.
25. Leber A, Marras TK. The cost of medical management of pulmonary nontuberculous mycobacterial disease in Ontario, Canada. Eur Respir J, 2011; 37:1158–1165.
26. Lipman M, Cleverley J, Fardon T, et al. Current and future management of non-tuberculous mycobacterial pulmonary disease (NTM-PD) in the UK. BMJ Open Respir Res 2020; 7:e000591.

Table 1: Episodes of NTM infection by *Mycobacterium* species and gender in Scotland 2011 to 2019. Statistical analysis was performed as appropriate by Fisher's exact test or χ^2 test as appropriate on all Mycobacteria species, statistically significant results ($p<0.05$) were indicated with *.

Species	Frequency episodes (n)		Rate M:F
All		(2409)	1.03
M. avium	**45.2%**	(1088)	1.02
M. intracellulare	**19.4%**	(467)	0.97
M. abscessus complex	**11.7%**	(282)	0.83
M. chelonae complex	**5.0%**	(121)	1.12
M. malmoense	**4.1%**	(98)	1.28
M. fortuitum group	**3.1%**	(75)	1.27
M. species only	**1.9%**	(46)	1.30
M. mucogenicum	**1.7%**	(40)	1.35
M. xenopi	**1.6%**	(38)	1.24
M. kansasii	**1.5%**	(36)	2.27*
M. lentiflavum	**0.7%**	(17)	0.55
M. marinum	**0.7%**	(17)	3.25*

M. simiae	**0.6%**	(15)	0.50
M. interjectum	**0.5%**	(13)	2.25
M. peregrinum	**0.4%**	(10)	0.67
M. szulgai	**0.4%**	(10)	4.00
Other Mycobacteria	**1.5%**	(36)	-

Table 2: Episodes of NTM infection (n=2409) by *Mycobacterium* species and anatomic site in Scotland 2011 to 2019. Statistical analysis was performed as appropriate by Fisher's exact test or χ^2 test on all Mycobacteria species (except for Other Mycobacteria species). * : statistically significant results (p<0.05).

Species	**Pulmonary**		**Blood**		**Cutaneous**		**Adenitis**		**Other Sites**	
	% of episodes	(n)	% of episodes	(n)	% of episodes	(n)	% of episodes	(n)	% of episodes	(n)
All	81.1	(1953)	2.8	(67)	2.4	(59)	1.3	(31)	12.4	(299)
M. avium	87.3	(950)*	0.7	(8)	0.1	(1)	1.7	(19)	9.9	(110)
M. intracellulare	88.2	(412)*	0		0		0.2	(1)	11.6	(54)
M. abscessus complex	87.6	(247)*	2.5	(7)	0.7	(2)	0		9.2	(26)
M. chelonae complex	31.4	(38)	21.5	(26)*	26.4	(32)*	0		20.7	(25)
M. malmoense	85.7	(84)	0.0		0		3.1	(3)	11.2	(11)
M. fortuitum group	61.3	(46)	4.0	(3)	1.3	(1)	2.7	(2)	30.7	(23)
M. species only	50.0	(23)	4.3	(2)	2.2	(1)	4.3	(2)	39.1	(18)
M. mucogenicum	25.0	(10)	50.0	(20)*	5.0	(2)	5.0	(2)	15.0	(6)
M. xenopi	86.8	(33)	0		0		0		13.2	(5)
M. kansasii	75.0	(27)	0		2.8	(1)	0		22.2	(8)
M. lentiflavum	94.1	(16)	0		0		5.9	(1)	0	
M. marinum	5.9	(1)	0		82.4	(14)*	0		11.8	(2)
M. simiae	100.0	(15)	0		0		0		0	
M. interjectum	92.3	(12)	0		0		7.7	(1)	0	
M. peregrinum	50.0	(5)	0		10.0	(1)	0		40.0	(4)
M. szulgai	90.0	(9)	0		0		0		10.0	(1)
Other Mycobacteria	69.4	(25)	2.8	(1)	11.1	(4)	0		16.7	(6)

FIGURES

Figure 1: Flow chart of analysis of NTM isolates received at the Scottish Mycobacterial Reference Laboratory, clinically relevant isolates and episodes of NTM infection; 2011-2019.

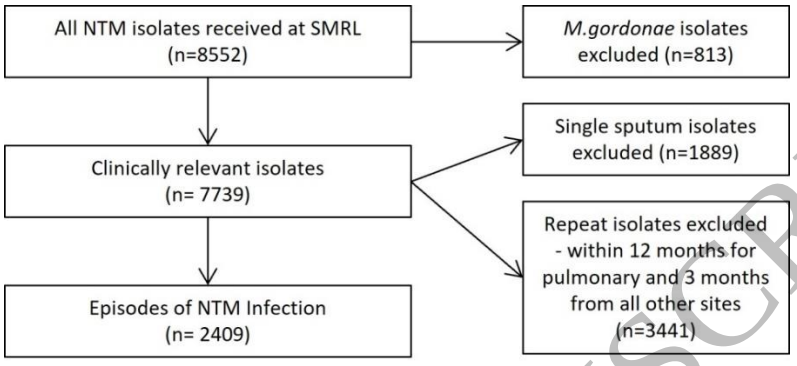


Figure 2: Infection episodes stratified by Mycobacterium species and age group. The Heatmap is showing normalised counts for infection episodes per species.

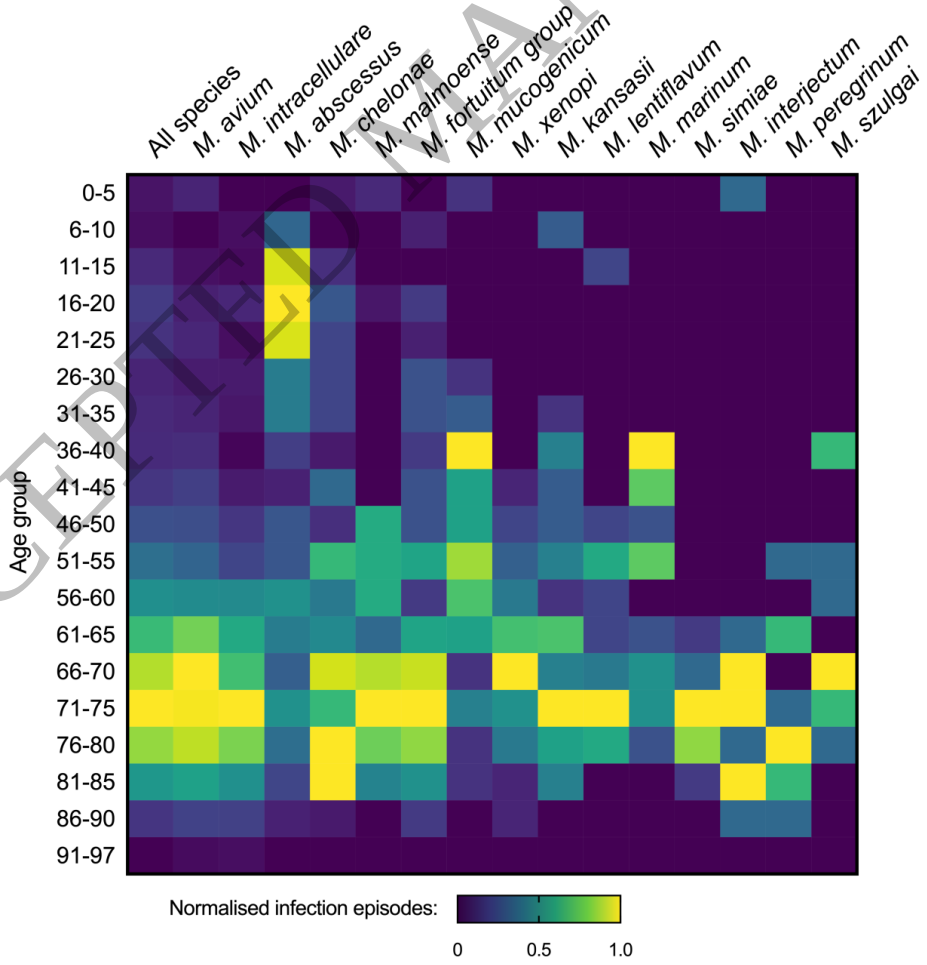
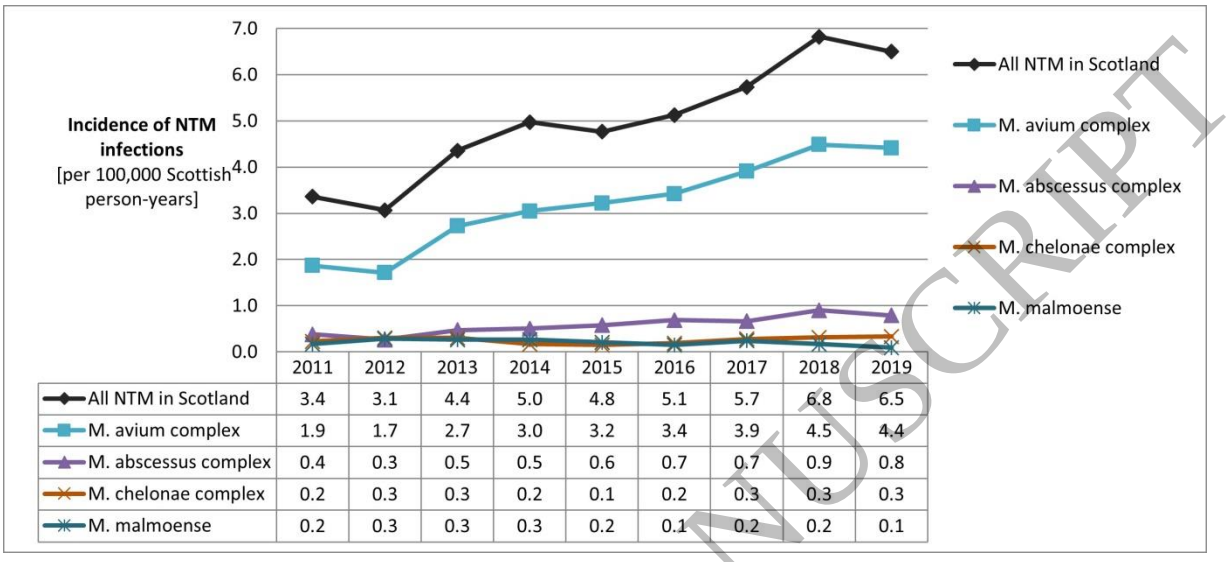
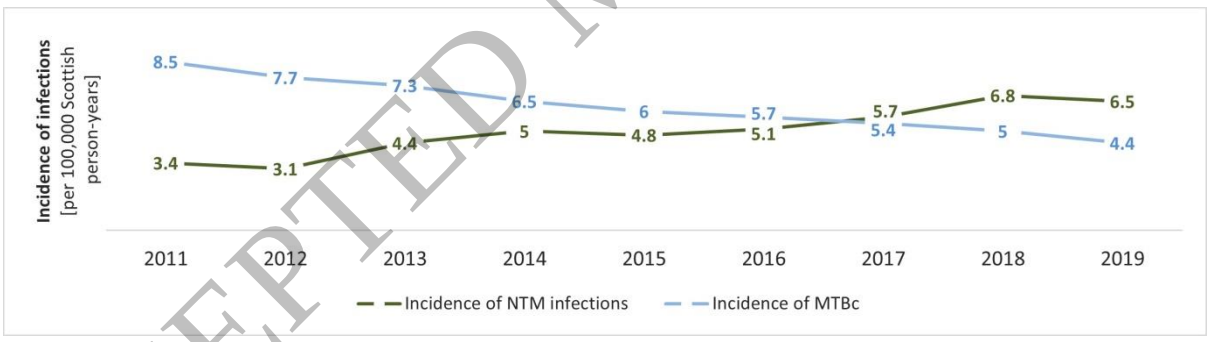


Figure 3: NTM infection episodes in Scotland (2011-2019) detailing the most common mycobacteria causing infection: *M. avium* complex, *M. abscessus* complex, *M. chelonae* complex and *M. malmoense*.



	2011	2012	2013	2014	2015	2016	2017	2018	2019
All NTM in Scotland	3.4	3.1	4.4	5.0	4.8	5.1	5.7	6.8	6.5
M. avium complex	1.9	1.7	2.7	3.0	3.2	3.4	3.9	4.5	4.4
M. abscessus complex	0.4	0.3	0.5	0.5	0.6	0.7	0.7	0.9	0.8
M. chelonae complex	0.2	0.3	0.3	0.2	0.1	0.2	0.3	0.3	0.3
M. malmoense	0.2	0.3	0.3	0.3	0.2	0.1	0.2	0.2	0.1

Figure 4: Incidence of NTM and MTBc infections per 100,000 person-years in Scotland 2011 to 2019.



MTBc data collated from "Enhanced Surveillance of Mycobacterial Infections in Scotland" reports 2018 and 2019 [9,10].

Figure 5: Distribution of pathogenic NTM pulmonary species and infection episodes in Scotland, 2011-2019.