Trends of non-tuberculous mycobacterial pulmonary disease in a low-tuberculosis prevalence setting

Master thesis

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This thesis is submitted in partial fulfilment of the requirements for the degree of Master of Philosophy in Global Health at the Centre for International Health, University of Bergen.

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FOREWORDS

As I embarked on my master's degree journey in August 2020, the world was undergoing a profound transformation due to the COVID-19 pandemic. The pandemic cast a shadow of uncertainty and restriction, challenging us in unprecedented ways. As a student, I too faced numerous obstacles during this period of upheaval. However, we were fortunate to swiftly adapt to digital learning methods, enabling us to persevere in our academic pursuits.

Today, the overwhelming grip of COVID-19 has lessened, and it feels as though we have emerged victorious from a long and arduous battle. Although the pandemic brought forth hardships, it has also taught us valuable lessons about preparedness, adaptability to new challenges, and the importance of caring for our planet. Moreover, it underscored the critical significance of global public health and its role in safeguarding humanity.

Throughout my journey toward completing this master's thesis, I have had the privilege of encountering exceptional individuals who have supported me at every step. Their guidance and encouragement have been instrumental in shaping this scientific paper, which I like to think of as a beacon of knowledge and understanding. I am immensely grateful to my supervisor, Prof. Tehmina Mustafa, from the Department of Global Public Health and Primary Care at the University of Bergen. Her meticulous guidance, unwavering support, and inspirational mentorship have been invaluable.

This thesis, which is presented as "a scientific paper with a mantel," commences from page 26 and has been submitted to the esteemed BMJ Open Respiratory Research. I hope that the insights and findings contained within these pages contribute positively to the existing body of knowledge in this field.

Thank you to all who have played a part in shaping my path, and I eagerly anticipate the new horizons that lie ahead.

Biplob kumar mohanty

Abbreviations

AIDS : Acquired immunodeficiency syndrome

CF : Cystic Fibrosis

COPD : Chronic obstructive pulmonary disease

HIV : Human Immunodeficiency Virus

MAC: Mycobecterium avium complex

MDR-TB : Multidrug Resistant Tuberculosis

NTM : Non-tuberculous mycobacteria

TB : Tuberculosis

Introduction

Although the presence of atypical mycobacteria was known for most of the twentieth century, its role as a human pathogen had taken a backseat, as most of the focus went to two other bacteria from the *Mycobacteriaceae* family (*Mycobacterium tuberculosis* and *Mycobacterium leprae*). The incidence rate of NTM infections has increased during the last decade globally and has resulted in significant mortality and morbidity [1, 2]. Studies show a higher incidence rate of NTM in the elderly population, and it is expected that NTM incidence will continue to rise due to the increasing elderly population until 2050 [3]. NTM infections are not notifiable in many countries, including Norway. Since the detection of infections is based on clinical, radiological, and microbiological criteria, it is therefore difficult to obtain a good overview of prevalence. However, studies from other countries have shown that an increase in the incidence of NTM cannot just be attributed to better diagnostics but can be attributed to factors such as the increasing prevalence of chronic structural lung diseases, immune deficiency conditions, and the use of immune-suppressing therapies [4, 5]. NTM infection is not limited to only the lungs. Some of the other clinical manifestations of NTM diseases also include disseminated infections, skin and soft tissue infections, lymphadenitis, empyema, ocular infections, central nervous system infections, and genitourinary infections. It has also been noted that NTM infection has gained attention in countries with high incidences of TB due to the risk of being misdiagnosed as MDR-TB [6]. It was earlier believed that human-to-human transmission of NTM does not happen. However, studies have shown genetic evidence of human-to-human transmission [7]. Management of NTM pulmonary disease is usually done with antibiotics and poor response to therapy is dealt with surgery that has a high rate of complication [8]. With over 150 species of NTM having been discovered, the management of different species requires different modalities [9].

Global epidemiology and trend

Addressing the epidemiology of NTM poses significant challenges owing to several factors. Firstly, the limited availability of data based on studies restricts a comprehensive understanding of the disease's prevalence and impact. Secondly, the non-reporting of cases in certain regions of the world hinders the formation of a complete global picture. Thirdly, the lack of adequate laboratory facilities often leads to misdiagnosis, further complicating accurate assessments. Lastly, the ubiquitous nature of NTM organisms makes it challenging to discern and interpret positive cultures in individual patients, adding another layer of complexity to the epidemiological analysis.

Studies across Europe have been conducted using different methodologies, such as single-center [10], nationally representative [11], sentinel-site [12], and population-based studies [13], involving diverse study populations. Most of these studies have focused on respiratory specimens [14, 15], while only a few have explored extrapulmonary samples [16]. Consequently, there is a discrepancy in the reported incidence of NTM across Europe, with varying rates in different countries. For instance, the NTM incidence rate in the UK, France, and Germany is approximately 1.7 per 100,000 population, 0.74 per 100,000 population, and 2.6 per 100,000 population, respectively [17, 18, 19]. Furthermore, there is also geographic diversity in the distribution of NTM species across Europe (Fig 1) [20].

Across Asia, studies on NTM are scarce, primarily concentrated in Eastern Asian countries like Japan, China, South Korea, India, Thailand, and Taiwan [21]. In Japan, the prevalence of NTM was reported to be the highest in the world, ranging from 33 to 65 per 100,000 population in 2005 [22]. These Asian countries bear a high burden of TB, and some studies have revealed NTM strains in cases of multidrug-resistant TB (MDR-TB), raising concerns about a possible incorrect diagnosis of NTM as *Mycobacterium tuberculosis*.

In Australia, NTM is a notifiable disease, facilitating studies on the significance of NTM isolates. Research in the northern territory of Australia demonstrated a gradual increase in the incidence of NTM, rising from 3.7 per 100,000 population in 1989 to 5.7 in 1997 [24, 25].

In Africa, data lags behind that of high-income countries, but recent studies in some regions have attempted to identify NTM in patients with pulmonary TB [26, 27]. These studies underscore the clinical and diagnostic challenges arising from limited tools for accurate identification of mycobacterial species. Moreover, a high proportion of NTM, approximately 18% each, has been found in treatment failure TB cases and co-infections in chronic TB cases, exacerbating the burden of both diseases [28, 29].

Data from South America primarily consist of laboratory-based information, lacking reliable clinical data, making it challenging to ascertain the true incidence and prevalence of NTM-Pulmonary disease [30]. Most studies in Central and South America fail to meet the ATS guidelines' definition of NTM-pulmonary disease.

In North America, studies from the USA and Canada indicate a high prevalence of NTM. In Canada, NTM prevalence increased from 14.1 to 22.2 per 100,000 population over a 10-year period [31]. Similarly, in the USA, a disease prevalence of approximately 47 per 100,000 population was observed among adults aged ≥65 years, with regional variations in NTM pulmonary disease prevalence across the country [32].

Overall, data from North America, Europe, and Australia have suggested a significant increase in the prevalence of pulmonary NTM isolates and NTM disease in these continents over the course of a few years. Studies from some countries in Eastern Asia have also echoed these findings. However, since NTM disease is not a notifiable disease in most countries, accurate epidemiological data are limited, particularly in countries with low development indices.

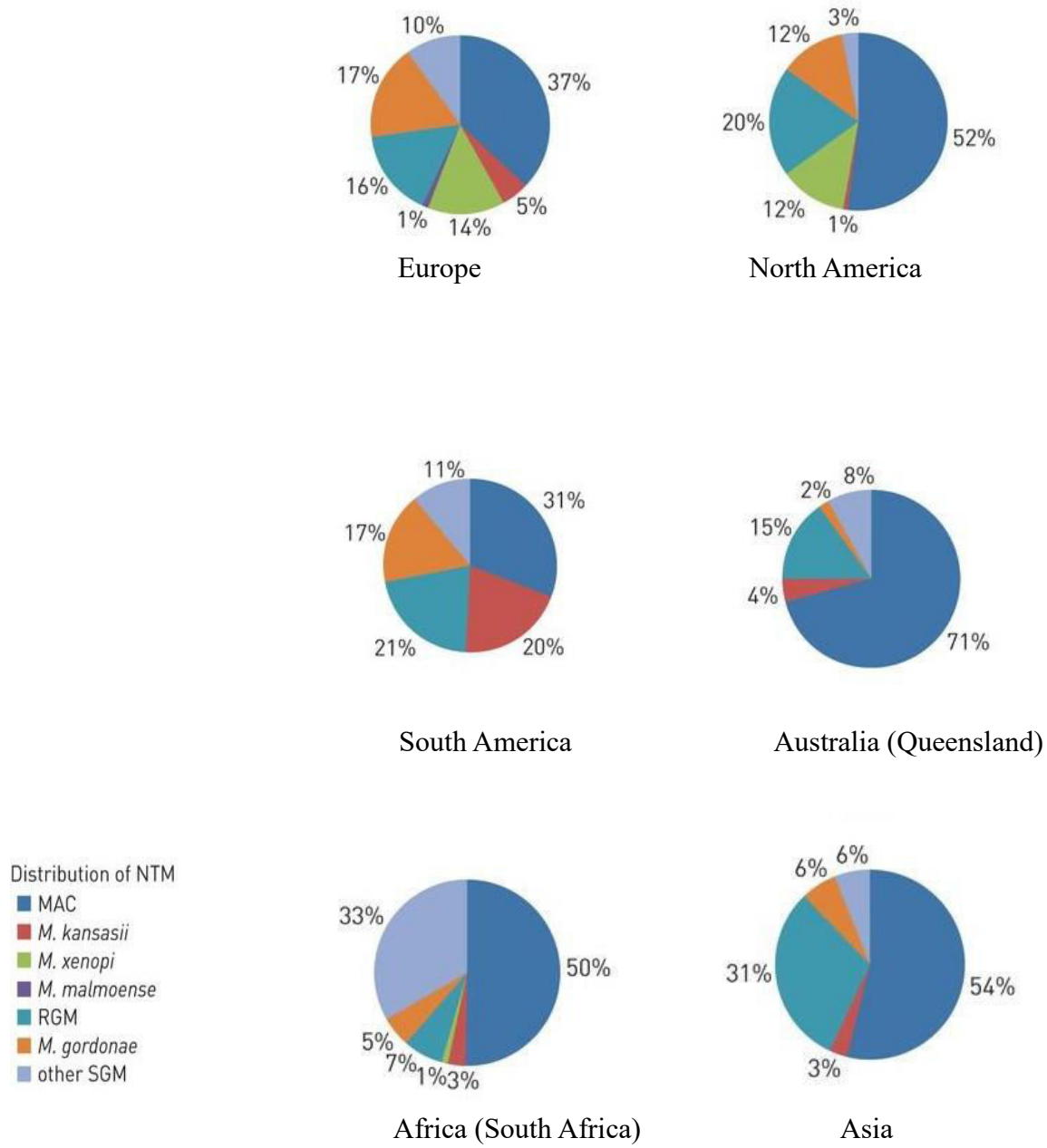

Figure 1: Distribution of respiratory nontuberculous mycobacteria (NTM) isolates [20].

The findings from these studies raise global concerns in several aspects. Firstly, there is evidence of the global spread of antibiotic-resistant *Mycobacterium abscessus* through human-to-human transmission, particularly affecting patients with cystic fibrosis (CF), leading to accelerated inflammatory lung damage and increased morbidity and mortality [7].

Secondly, NTM infection has been linked to an elevated risk of breast and lung cancer, Sjogren syndrome, and Sweet syndrome [33, 34, 35]. Thirdly, while NTM infections often go unnoticed, a systematic review study has highlighted the severity of MAC pulmonary disease, with a five-year all-cause mortality rate exceeding 25%, indicating a poor prognosis and underscoring the urgency for more effective management and data collection [36]. Lastly, the increasing number of hospitalizations due to NTM infections has resulted in a heightened economic burden [19]. These findings collectively emphasize the importance of addressing NTM infections on a global scale, focusing on prevention, improved treatment strategies, and comprehensive data collection.

Pulmonary NTM infection and disease

The current guideline to classify patients as having NTM pulmonary disease includes clinical, radiographic, and microbiologic criteria as mentioned in the Official ATS/ERS/ESCMID/IDSA Clinical Practice Guideline [41]. Any patient just meeting the microbiologic criteria is classified as having NTM pulmonary infection.

Radiologic criteria in Pulmonary NTM disease encompasses three distinct pathologies: fibro-cavitary disease, nodular bronchiectasis disease, and hypersensitivity pneumonitis. The incubation period of NTM varies from months to years, posing challenges in diagnosis and identifying the source of infection. Figure 2a and 2b show the trend of NTM pulmonary infection and disease worldwide. Research has demonstrated that individuals with structural lung diseases like cystic fibrosis, chronic obstructive pulmonary disease (COPD), non-cystic fibrotic bronchiectasis, alpha-1 antitrypsin deficiency, previous pulmonary TB, and lung cancer are at a higher risk of NTM infections. Moreover, immune deficiency conditions, such as AIDS and hematological malignancies, along with acquired states of immune deficiency,

like hematopoietic stem cell transplantation and solid organ transplantation, also render patients more vulnerable to NTM infection [3, 43, 44, 45, 46].

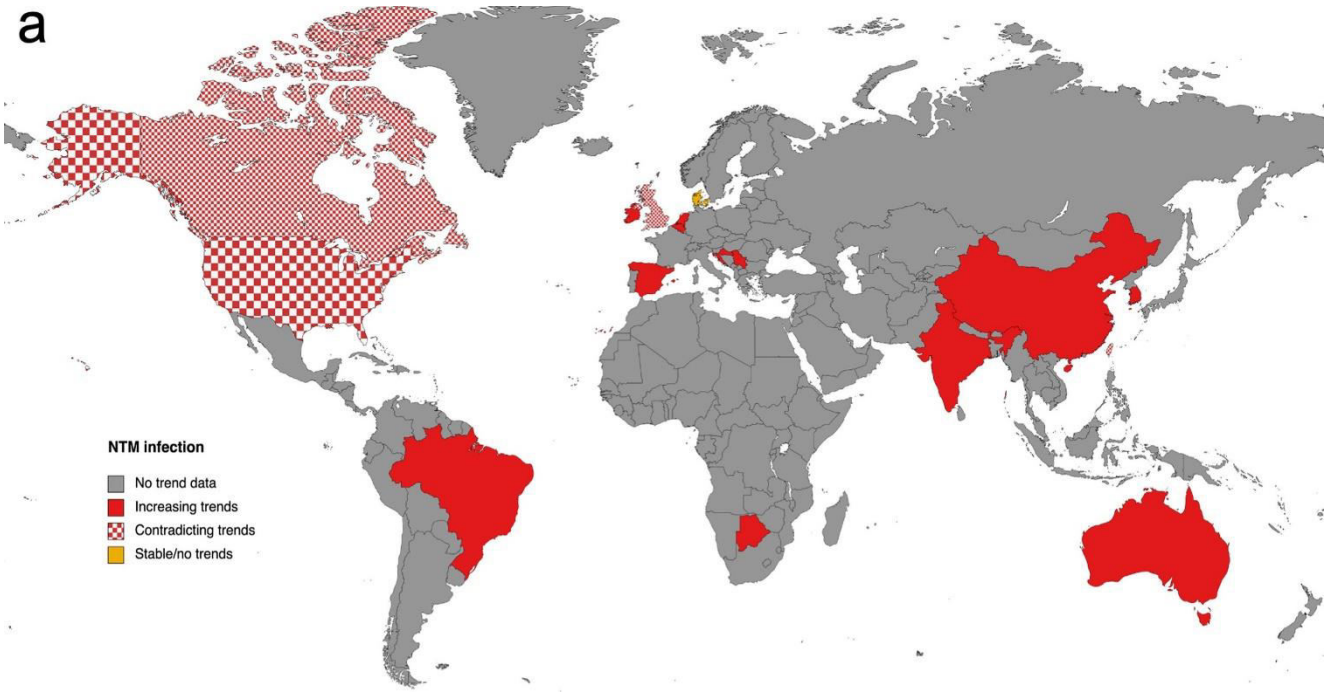

Figure 2a: A world map of culture-based nontuberculous mycobacteria trend data for NTM pulmonary infection [49].

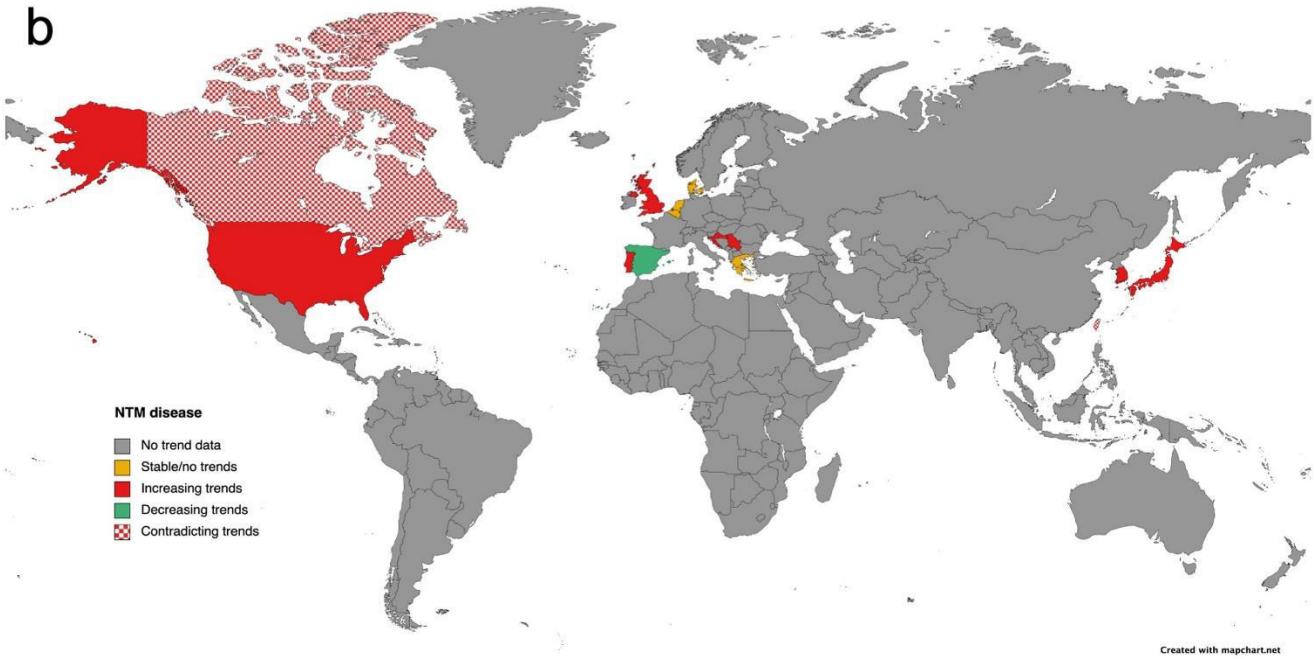

Figure 2b: A world map of culture-based nontuberculous mycobacteria trend data for NTM pulmonary disease [49].

Diagnosis and challenges

Diagnosis of NTM pulmonary disease relies on clinical features, radiographic findings, and microbiological studies. Figure 3 shows the criteria to diagnose NTM pulmonary disease.

Clinical	Pulmonary or Systemic Symptoms	
Radiologic	Nodular or cavitary opacities on chest radiograph, or a high-resolution computed tomography scan that shows bronchiectasis with multiple small nodules	Both Required
and	Appropriate exclusion of other diagnoses	
Microbiologic[b]	1. Positive culture results from at least two separate expectorated sputum samples. If the results are nondiagnostic, consider repeat sputum AFB smears and cultures **or** 2. Positive culture results from at least one bronchial wash or lavage **or** 3. Transbronchial or other lung biopsy with mycobacterial histologic features (granulomatous inflammation or AFB) and positive culture for NTM or biopsy showing mycobacterial histologic features (granulomatous inflammation or AFB) and one or more sputum or bronchial washings that are culture positive for NTM	

Figure 3: Clinical and Microbiologic Criteria for Diagnosis of Nontuberculous Mycobacterial Pulmonary Disease

Diagnosing NTM disease poses considerable challenges. One of the primary difficulties lies in the non-specific symptoms exhibited in NTM pulmonary disease, leading to delayed diagnosis, especially in patients with pre-existing lung conditions [37, 38]. Moreover, the symptoms of NTM closely resemble those of pulmonary TB, further complicating the diagnostic process [39]. Another obstacle is the ubiquity of NTM organisms, making it challenging to distinguish between contamination and actual pathological disease in samples. The diagnosis of pulmonary NTM disease necessitates clinical judgment based on various radiological and microbiological tools, including CT scans, MRI scans, culture, line probe assay, gene sequencing, and invasive procedures like bronchoscopy and may be biopsy, as well as culture and histopathologic examination [40]. Regrettably, these diagnostic tools are not always accessible in resource-poor settings and can be financially burdensome.

Treatment and challenges

The treatment of NTM pulmonary disease is guided by American and British guidelines [41, 42]. The decision to initiate antimicrobial therapy for NTM pulmonary disease should be personalized, considering a combination of clinical factors, the infecting species, and individual patient priorities. For instance, individuals diagnosed with MAC pulmonary disease are recommended to undergo susceptibility-based treatment for macrolides and amikacin instead of empiric therapy [41]. These guidelines aim to enhance patient care and optimize treatment outcomes for NTM pulmonary disease cases.

Upon diagnosis of NTM pulmonary disease, immediate treatment initiation is not always necessary, and the decision to treat depends on several critical factors. Patient-related considerations hold considerable significance, including the severity and progression of radiological changes, the presence of underlying lung disease, associated comorbidities, the potential need for additional treatments like immunosuppressive agents, and the consideration of surgical interventions. Furthermore, mycobacterial factors must be taken into account, such as the pathogenicity of the specific NTM species and the bacterial load present.

Each NTM species responsible for inducing pulmonary disease requires a distinct antibiotic regimen, which can be complex and may result in adverse reactions and drug interactions. Therefore, a comprehensive assessment before treatment initiation becomes imperative. Additionally, the high cost of NTM treatment and the increased utilization of secondary care significantly amplify the economic burden of managing NTM cases [47, 48]. Hence, an informed and individualized approach to treatment decisions is essential to optimize outcomes and mitigate the economic impact of NTM pulmonary disease.

Surgery becomes a viable consideration under specific circumstances, such as when there is a poor response to drug therapy, the development of resistance to the antimicrobial regimen, or the presence of significant disease-related complications like hemoptysis. The treatment

endpoint is determined based on symptomatic, radiographic, and microbiologic improvement. However, underlying pulmonary disease can complicate the attainment of symptomatic and radiographic improvement. One major challenge in this context is the limited availability of clinical trials, which hampers the ability to establish optimal treatment regimens effectively.

Rationale of Study

There has been a gradual increase in the incidence of NTM worldwide. Initially affecting immunocompromised patients, the pathogen has now emerged to cause pulmonary infections in both immune-competent children and adults. Despite this growing prevalence, the diagnosis and treatment of NTM remain challenging. International guidelines are primarily based on clinical experience, case studies, and existing literature. However, there is a scarcity of literature supporting the incidence, prevalence, diagnosis, or treatment of this condition. Notably, the Norwegian Institute of Public Health lacks specific guidelines addressing NTM.

Therefore, we have undertaken this research to gain insights into NTM disease in Bergen, Norway, which has a low TB prevalence. Our focus is to identify and understand the challenges associated with NTM diagnosis and treatment, as well as to explore factors influencing treatment outcomes in this setting. The anticipated findings from this study hold the potential to enhance local clinical practices and improve the quality of patient care. Furthermore, the results are expected to be generalizable to similar clinical settings, contributing much-needed evidence to the management of NTM disease on a global scale.

This study serves a vital purpose in filling the gap in global data concerning NTM in Norway and emphasizes the importance of recognizing NTM as a global challenge. It highlights the urgency to develop effective strategies to tackle these challenges and improve patient outcomes worldwide.

Study Objectives

Main Objective

To review the NTM pulmonary disease among Norwegian patients at a tertiary care hospital in western Norway during 2000- 2021.

Specific Objectives

1) To study the demographic characteristics, clinical, radiological, and microbiological characteristics.

2) To study the factors associated with the initiation of treatment and favourable treatment outcomes.

3) To study the prevalence of mycobacterial species, and their trend over the period of study.

Methodology

The methodology of the study is presented in the attached manuscript.

Results

The findings of the study are presented in the attached manuscript.

Discussion

A discussion of the study is presented in the attached manuscript.

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Trends of non-tuberculous mycobacterial pulmonary disease in a low-tuberculosis prevalence setting.

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Abstract

Background: Limited data are available regarding factors associated with initiation of treatment and treatment outcomes after diagnosis of non-tuberculous mycobacteria (NTM) pulmonary infection and disease.

Objective: To investigate trends of NTM pulmonary infections, patient characteristics and factors associated with initiation of treatment and treatment outcomes in patients with NTM pulmonary infection and disease.

Methods: We evaluated 154 patients with NTM pulmonary infection, identified by having at least one record coded with ICD-10 A31.0 at Haukeland University Hospital in Bergen, Norway, from 2000 to 2021. A univariate and multivariate binary logistic regression was carried out to find the odds of factors associated with the initiation of treatment and treatment outcomes.

Results: 70% of the patients were older than 65 years. 49 % of patients had pulmonary comorbidity and the three most common symptoms were cough, dyspnoea, and weight loss. The most frequently observed mycobacterial species was *M. avium complex* (MAC), followed by *M. malmoense*, and *M. abscessus*. There was a decreasing trend in NTM pulmonary infection and NTM pulmonary disease from the year 2000 to 2014, while an increase was observedfrom 2015 to 2019. A total of 72 (47%) patients received antibiotic treatment. Patients with high symptom scores, those below the age of 65, and those with MAC infection had more than three times the odds of receiving antibiotic treatment (P = 0.006, P = 0.006, and P = .005 respectively). Of 72 patients who received treatment, 53 (74%) had a favourable response and culture conversion. 17 (32%) of them had a relapse. Out of 82 patients who did not receive treatment, 45 (55%) had spontaneous culture conversion. 8 (18%) of them had a relapse. No factor was identified to be significantly associated with a

favourable treatment response including the time taken to start treatment or presence of pulmonary cavities.

Conclusion: Favourable response to treatment was seen in 74% patients whereas spontaneous culture conversion was seen in 55% of non-treated patients. Factors associated with favourable treatment response were not found.

Keywords: NTM pulmonary infection, MAC, treatment

Introduction

Non-tuberculous mycobacterial (NTM) infections are a public health problem worldwide. Despite being overshadowed by infections from other members of the *Mycobacteriaceae* family, such as *Mycobacterium tuberculosis* and *Mycobacterium leprae*, NTM infections are associated with considerable mortality and morbidity [1, 2]. The incidence of NTM infections is particularly high in the elderly population, and it is projected to continue to rise in the coming years due to the increasing number of elderly individuals [3].

NTM infections can cause a range of diseases, including non-tuberculous mycobacterial pulmonary disease (NTM-PD). Some of the more common NTM species known to cause NTM-PD are *Mycobacterium avium complex* (MAC), *Mycobacterium kansasii, Mycobacterium xenopi, Mycobacterium abscessus,* and *Mycobacterium malmoense* [4]. These infections typically occur as comorbidities in patients with underlying respiratory diseases such as chronic obstructive pulmonary disease (COPD), bronchiectasis, and cystic fibrosis (CF) [5]. However, diagnosis of NTM infections can be challenging, and patients often face a lengthy time to diagnosis or misdiagnosis, leading to a poor long-term outcome. Information on the prevalence of NTM infections is usually lacking as NTM infections do not require official notification. However, there is a need to investigate the trends and characteristics of NTM infections in specific geographic areas to provide information for the timely diagnosis and treatment of these infections.

This study aimed to investigate the trends and characteristics of NTM pulmonary infections and NTM-PD over the past two decades at a tertiary care hospital in western Norway. We aimed to identify factors associated with initiating treatment for NTM infection and treatment outcome.

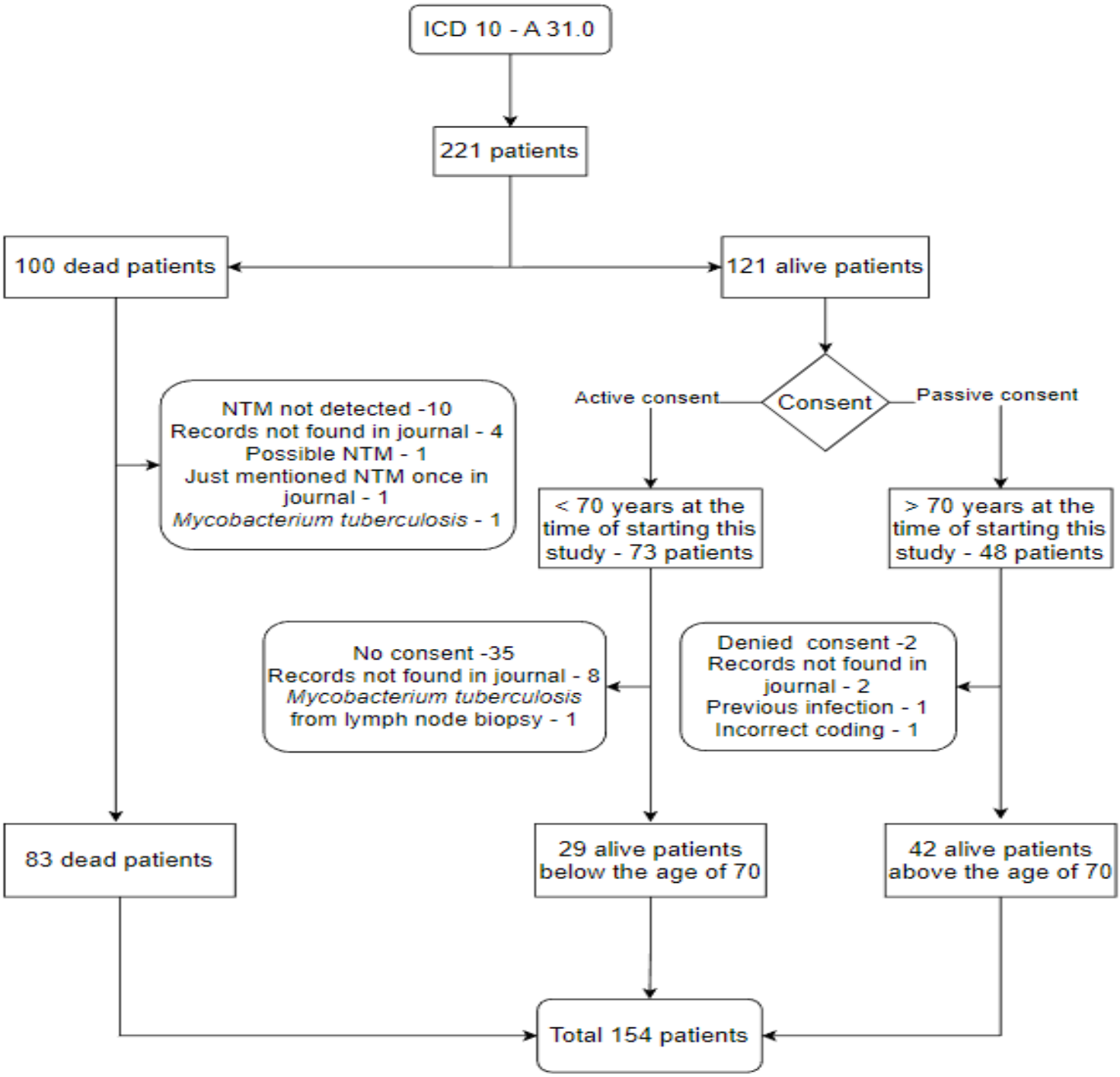
Methodology

Study setting and design

The study is a retrospective cohort investigation carried out at Haukeland University Hospital, Bergen, Norway. To identify eligible cases, all inpatient and outpatient records were searched for the International Classification of Diseases, 10th Revision (ICD-10) code A31.0 (pulmonary mycobacterial infection) between the years 2000 and 2021. Patients diagnosed with NTM pulmonary infection and NTM-PD that met the current American Thoracic Society (ATS) criteria were included in the study.

Figure 1 presents the selection process for the study sample. Two hundred and twenty-one potential patients with NTM pulmonary infection were identified by having at least one record coded with A31.0. NTM pulmonary infection was defined as a positive culture for NTM from two separate expectorate sputum samples or positive culture from one bronchoalveolar lavage. NTM-PD was defined as NTM pulmonary infection with pulmonary or systemic infection, symptoms, and nodular or cavitary opacities on chest X-ray or chest computer tomography (CT) scan. Among the 100 deceased patients records with NTM pulmonary infection from 83 patients with confirmed NTM pulmonary infection were available. Thirty-five patients who were alive and under 70 years old did not provide consent and excluded. For alive patients above the age of 70, 42 records were available. The final study sample included 154 patients.

Figure 1. Flow chart showing inclusion and exclusion of patients in the study



Relevant data were collected from the electronic medical records of the Department of Thoracic Medicine, Haukeland University Hospital. The variables collected included sex, age, presence of pulmonary comorbidities, symptoms, microbiological findings, radiological

findings (both chest X-ray and chest CT scan), treatment history, and treatment outcome. Six symptoms of particular interest were recorded: fever, cough, haemoptysis, night sweats, dyspnoea, and weight loss. A symptom score was calculated, which was defined as a sum of the total number of symptoms where a score of 1 is given for each symptom. A score of 3 or more was considered a high symptom score. A favourable response to treatment or culture conversion was defined as at least two consecutive negative mycobacterial cultures from respiratory samples.

Data management and analysis

The collected data were analysed using IBM SPSS statistics software version 27. Binary logistic regression was used for univariate and multivariate analyses to identify factors associated with starting of treatment and factors associated with treatment outcome. The unadjusted odds ratio (OR) and 95% confidence interval (CI) for each variable were first calculated using univariate regression. Multivariate regression was then performed. All variables were included in the final model. The adjusted OR (aOR) and 95% CI was calculated for each included variable. A p-value ≤ 0.05 was considered statistically significant.

Ethical clearance

Ethical clearance was obtained from the Regional Committee for Medical Ethics Western Norway. Active consent was obtained from patients below the age of 70, while passive consent was taken from patients above the age of 70. In the case of deceased patients, consent was not required. All data were de-identified to protect patients' privacy (i.e., social security numbers, names, or other directly identifiable characteristics were removed), in accordance with local regulations.

Results

The demographic and clinical characteristics of patients with NTM pulmonary infection and NTM-PD is presented in Table 1. 70% of the study sample were patients older than 65 years. The most commonly reported symptoms were cough (82%), dyspnoea (43%), and weight loss (33%). Pulmonary cavities were observed in 25% of the patients. Among the patients with NTM pulmonary infection and NTM-PD, 30% were found to have COPD and 19% had bronchiectasis. A total of six main groups/species causing NTM infections were identified, including *M. avium complex* (MAC), *M. malmoense*, *M. abscessus*, *M. gordonae*, *M. fortuitum*, and *M.* xenopi.

The proportion of different NTM species in NTM pulmonary infections and NTM-PD over the past 22 years is presented in Figures 2.1 and 2.2 respectively. Figure 2.3 shows that the number of NTM infection cases declined every 5 years, with 48 (31%), 36 (23%), and 19 (12%) cases reported for the time periods 2000-2004, 2005-2009, and 2010-2014, respectively. There was an increase in the number of cases in the period 2015-2019, with 38 (25%) cases reported. The trend for NTM pulmonary disease followed a similar pattern. All species follows similar trend across the years.

Table 2 shows the clinical characteristics of patients with NTM pulmonary disease caused by different species. All species were associated with low symptom scores and predominantly non-cavitary disease. Apart from *M. gordonae*, infections with all species received treatment. All species showed a positive response to treatment in more than 60% of the cases except for *M. malmoense*, where a positive response to treatment was shown in only 25% of cases. In *M. malmoense* infections, relapse was seen in 100% of cases.

A total of 71% of patients with *M. abscessus* infection, 57% of patients with MAC infection, 40% of patients with *M. xenopi* infection, and 33% of patients with *M. malmoense* and *M.*

fortuitum received treatment. Table 3 shows the factors associated with initiation of antibiotic treatment. Of the 154 patients with NTM pulmonary infection, 79 patients fulfilled criteria for NTM-PD. Treatment was started for both patients with infection and disease. In all, 72 (47%) patients received antibiotic treatment. Of these, 49 patients had NTM-PD and 23 patients had NTM pulmonary infection. Patients with high symptom scores, those below the age of 65, and those with MAC infection had more than three times the odds of receiving treatment (P = 0.006, P = 0.006, and P = .005 respectively). Thirty-one (56%) patients were started on treatment more than 6 months after diagnosis. The first guidelines on the treatment of NTM lung disease in 2007 did not impact the decision to start treatment.

Figure 3 shows the comparison of culture conversion between treatment and non-treatment groups. Out of 72 patients who received treatment, 53 (74%) had a favourable response and had culture conversion. 17 (32%) of them had a relapse. Out of 82 patients who did not receive treatment, 45 (55%) had spontaneous culture conversion. 8 (18%) of them had a relapse.

Table 4 shows the factors associated with favourable response to treatment. No factor was identified to be significantly associated with a favourable treatment response including the time taken to start treatment or presence of pulmonary cavities.

Table 1. Demographic and clinical characteristics of patients with NTM pulmonary infection and NTM-PD.

Characteristics	**N =154**
Sex	
Male	71 (46 %)
The age range at the time of diagnosis in years	
17-49	10 (6 %)
50 - 65	38 (25 %)
66 - 80	89 (58 %)
81 - 94	17 (11 %)

Characteristics	N =154
Symptoms	
Cough	126 (82 %)
Dyspnoea	66 (43 %)
Weight loss	51 (33 %)
Haemoptysis	21 (14 %)
Fever	16 (10 %)
Night sweats	15 (10 %)
Radiological feature	
Cavitary	39 (25 %)
Pulmonary comorbidities	
COPD	46 (30 %)
Bronchiectasis	30 (19 %)
COPD + Bronchiectasis	20 (13 %)
Mycobacterial species	
M. avium complex (MAC)	99 (64 %)
M. malmoense	12 (8 %)
M. abscessus	7 (5 %)
M. gordonae	7 (5 %)
M. fortuitum	6 (4 %)
M. xenopi	5 (3 %)
Mixed infection	4 (2 %)
Others*	10 (6 %)
Unknown**	4 (2 %)
Isolation of other respiratory pathogenic bacteria	
Haemophilus influenzae	14 (9 %)
Staphylococcus	13 (8 %)
Streptococcus	10 (6 %)
Pseudomonas	7 (5 %)
Mycobacterium tuberculosis	5 (3 %)
Haemophilus parainfluenzae	3 (2 %)

*2 cases each of M. *chelonae* and M. *simiae*. 1 case each of M. *celatum*, M. *gadium*, M. *neoaurum*, M. *nonchromogenicum*, M. *peregrinum,* and M. *triplex*

**NTM species not mentioned in the patient's journal

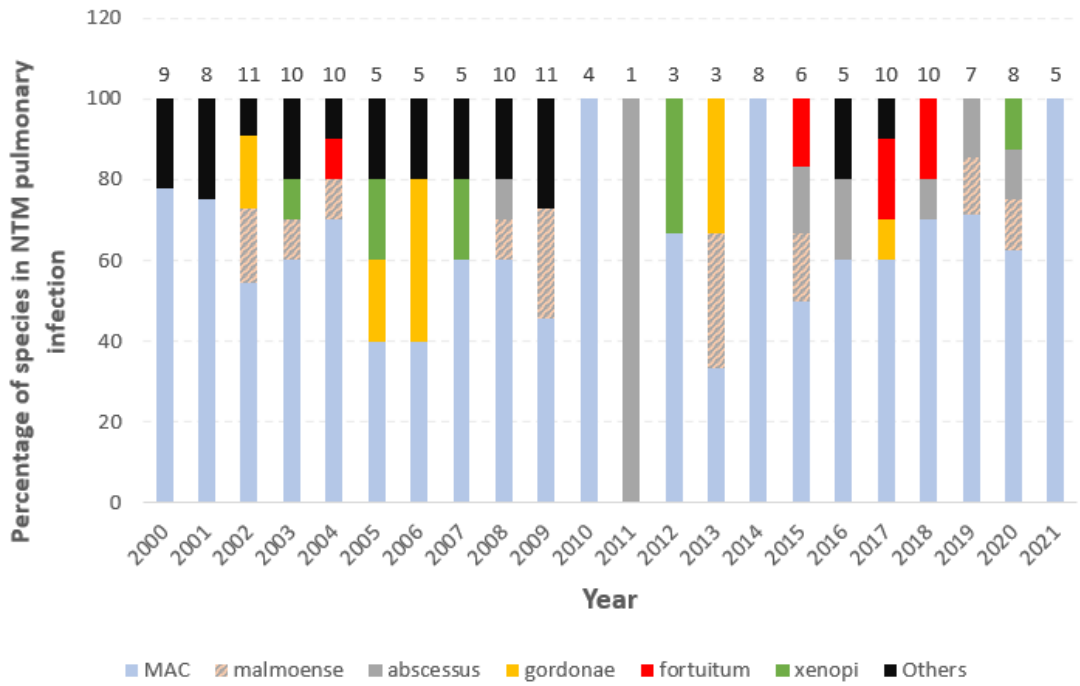
Data reported as absolute numbers (%).

Table 2: Clinical characteristics of patients with NTM pulmonary infection caused by different species

Category	MAC (N = 99)	M. malmoense (N = 12)	M. abscessus (N = 7)	M. gordonae (N = 7)	M. fortuitum (N = 6)	M. xenopi (N = 5)
Age below 65	31 (31)	5 (42)	4 (57)	1 (14)	2 (33)	2 (40)
Male	43 (43)	7 (58)	1 (14)	4 (57)	3 (50)	2 (40)
Cavities	24 (24)	5 (42)	1 (14)	1 (14)	2 (33)	2 (40)
High symptom score	37 (37)	4 (33)	2 (29)	0 (0)	1 (17)	2 (40)
Treatment given	56 (57)	4 (33)	5 (71)	0 (0)	2 (33)	2 (40)
Positive response to treatment*	42 (75)	1 (25)	3 (60)	NA	2 (100)	2 (100)
Relapse**	15 (36)	1 (100)	0 (0)	NA	0 (0)	1 (50)

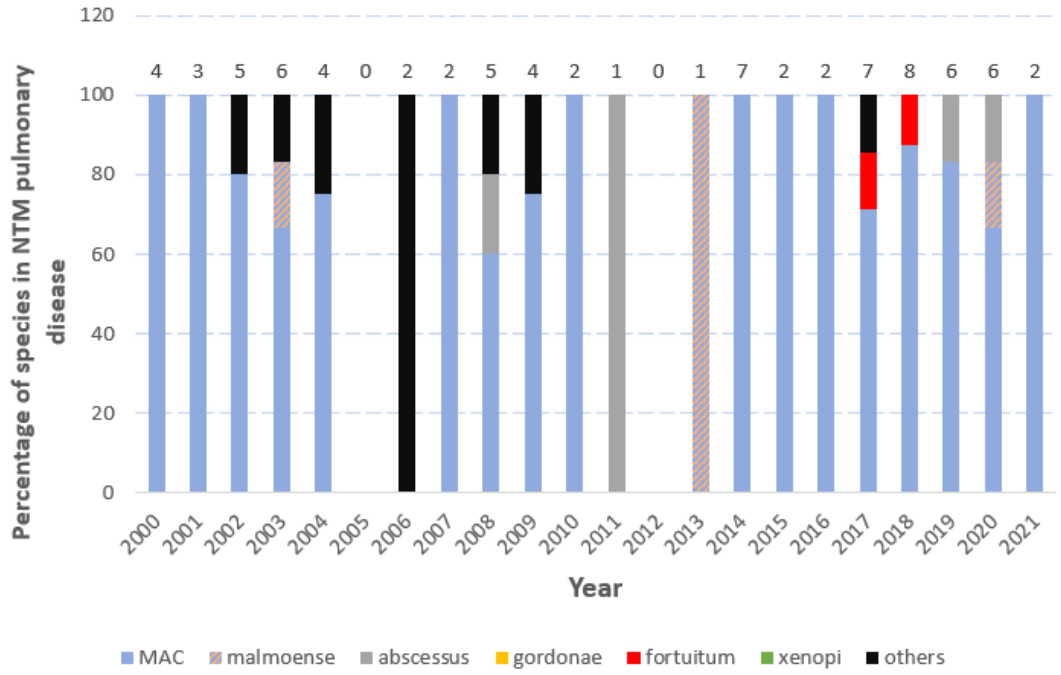
Data reported as n (%)
Percentage calculated by the formula n x100/N
*N is equal to n of treatment given
**N is equal to n of positive response to treatment

Figure 2.1: Proportion of different species in NTM pulmonary infection from the year 2000 to 2021



Total number of NTM pulmonary infection for each year at the top of the bars

Figure 2.2: Proportion of different species in NTM pulmonary disease from the year 2000 to 2021



Total number of NTM-PD for each year at the top of the bars

Figure 2.3: Trend of different species in NTM pulmonary infection in 5 years period from the year 2000 to 2019

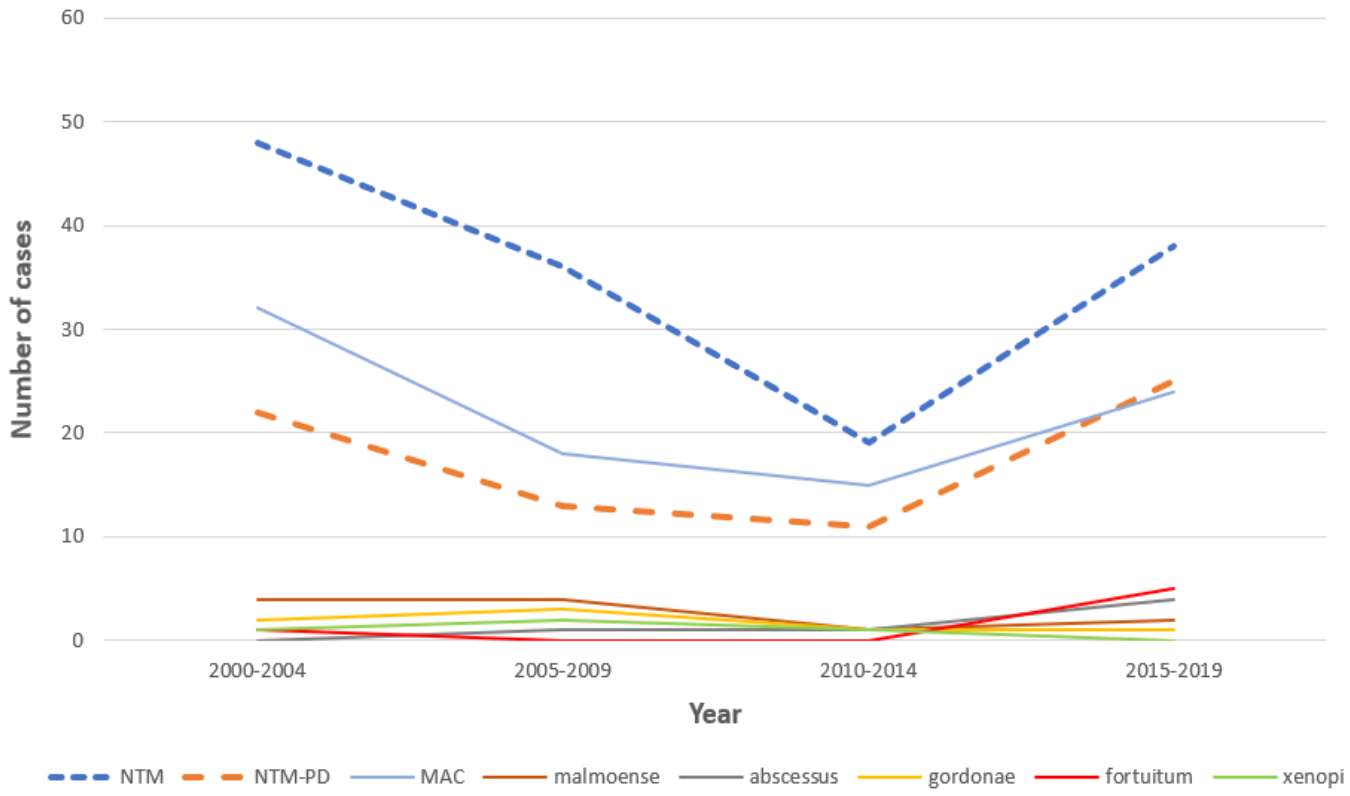


Table 3: Factors associated with initiation of antibiotic treatment for eradication of non-tuberculous mycobacteria (NTM) among patients with NTM pulmonary infection

		Treatment, n(%)	No treatment, n (%)	Unadjusted odds ratio (95% CI)	p-value	Adjusted odds ratio (95% CI)	p-value
Total Patients (N=154)		72	82				
Sex	**Male**	30 (42)	41 (50)	0.71 (0.38 - 1.35)	0.3	0.82 (0.39 - 1.72)	0.6
	Female	42 (58)	41 (50)	1		1	
Age	**Below 65**	30 (42)	15 (18)	3.19 (1.54 - 6.62)	0.002	3.18 (1.4 - 7.21)	0.006
	Above 65	42 (58)	67 (82)	1		1	
Symptom score	**SS 3-6**	33 (46)	20 (24)	2.62 (1.32 - 5.2)	0.006	3.08 (1.37 - 6.89)	0.006
	SS 0-2	39 (54)	62 (76)	1		1	
Radiological feature	**Cavitary**	15 (21)	24 (29)	0.64 (0.30 - 1.34)	0.23	0.58 (0.24 - 1.39)	0.22
	Non-cavitary	57 (79)	58 (71)	1		1	
Pulmonary comorbidity	**Yes**	42 (58)	54 (66)	0.72 (0.38 - 1.4)	0.17	0.87 (0.4 - 1.9)	0.72
	No	30 (42)	28 (34)	1		1	
Microbiological species*	**MAC**	56 (79)	43 (54)	3.13 (1.52 - 6.4)	0.002	3.04 (1.39 - 6.63)	0.005
	Others	15/71 (21)	36/79 (46)	1		1	
Isolation of respiratory bacteria	**Yes**	24 (33)	20 (24)	1.55 (0.77 – 2.13)	0.11	1.51 (0.67 - 3.39)	0.32
	No	48 (67)	62 (76)	1		1	

Year of treatment	**Before 2007**	27 (38)	31 (38)	0.99 (0.51 - 1.9)	0.97	1.63 (0.73 - 3.64)	0.23
	In/after 2007	45 (62)	51 (62)	1		1	

*NTM species is not known in 1 case where treatment has been given and in 3 cases where treatment has not been provided. Therefore N = 71 and N = 79 respectively for treatment and no treatment
Data reported as n(%)

Figure 3: Comparison of culture conversion between patients with NTM pulmonary infection who received or did not receive treatment

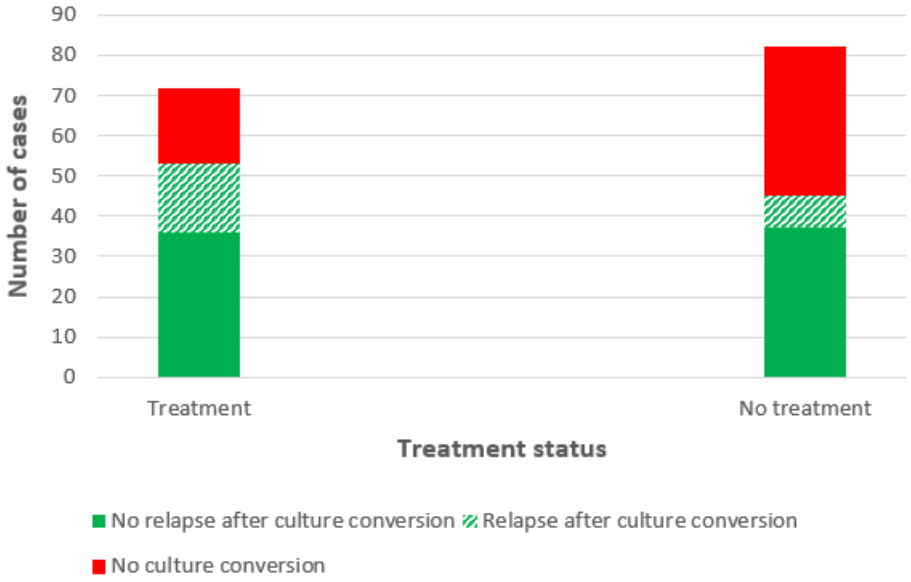


Table 4: Factors associated with favourable response to treatment among patients with NTM pulmonary infection

		Favourable response to treatment, n(%)	**No response to treatment, n (%)**	**Unadjusted odds ratio (95% CI)**	**p-value**	**Adjusted odds ratio (95% CI)**	**p-value**
Total patients (N)		53 (74)	19 (26)				
Sex	***Male***	21 (40)	9 (47)	0.73 (0.25 - 2.1)	0.56	0.85 (0.27 - 2.64)	0.78

		Favourable response to treatment, n(%)	No response to treatment, n (%)	Unadjusted odds ratio (95% CI)	p-value	Adjusted odds ratio (95% CI)	p-value
Age	***Female***	32 (60)	10 (53)	1		1	
	Below 65	20 (38)	10 (53)	0.55 (0.19 - 1.57)	0.26	0.55 (0.17 - 1.72)	0.3
	Above 65	33 (62)	9 (47)	1		1	
Symptom score	***SS 3 – 6***	25 (47)	08 (42)	1.22 (0.43 - 3.54)	0.7	1.16 (0.36 - 3.72)	0.8
	SS 0 - 2	28 (53)	11 (58)	1		1	
Radiological feature	***Cavitary***	10 (19)	5 (26)	0.65 (0.19 - 2.23)	0.5	0.63 (0.16 - 2.39)	0.49
	Non-cavitary	43 (81)	14 (74)	1		1	
Time taken for initiation of treatment*	***Less than 6 months***	23 (55)	8 (62)	0.69 (0.34 - 1.41)	0.31	0.73 (0.34 - 1.56)	0.42
	More than 6 months	19 (45)	5 (38)	1		1	
Pulmonary comorbidity	***Yes***	28 (60)	8 (53)	2.08 (0.71 - 6.1)	0.18	1.95 (0.58 - 6.50)	0.28
	No	25 (40)	10 (47)	1		1	
Hypertonic saline inhalation	***Yes***	19 (36)	7 (37)	0.96 (0.32 - 2.84)	0.94	0.77 (0.23 - 2.54)	0.67

		Favourable response to treatment, n(%)	No response to treatment, n (%)	Unadjusted odds ratio (95% CI)	p-value	Adjusted odds ratio (95% CI)	p-value
Microbiological species**	***No***	34 (64)	12 (63)	1		1	
	MAC	42 (81)	14 (74)	1.63 (0.5 - 5.29)	0.42	1.69 (0.46 - 6.13)	0.43
	Others	10 (19)	5 (26)	1		1	

*Since information is not available on time to initiation of treatment in 17 patients, the value of N changes to N = 42 for favorable response to treatment and N = 13 for response to treatment.
**In one patient with favorable outcome to treatment, species is not mentioned in journal of the patient. So, N = 52 for favorable response to treatment in this case.
Data reported as n(%)

Discussion

To our knowledge this is the first study to investigate the trends of NTM pulmonary infections, and factors associated with initiation of treatment and outcomes from a high-income and low TB-endemic setting of Western Norway over a period of 20 years. The major species observed were MAC, *M. malmoense*, and *M. abscessus*. The NTM infections showed a declining trend till 2014 following an increase in later years. This increasing trend could be attributed to better diagnostic modalities and increased focus on the detection of mycobacteria from the respiratory samples. Furthermore, increase in life expectancy with pulmonary comorbidities could also be a contributing factor, as indicated by an increased risk of getting NTM infection with increased age and presence of pulmonary comorbidity in the current study. Several studies have shown that age is a significant factor associated with the rise in incidence rates of NTM pulmonary disease among older populations, with higher increase in the annual prevalence in individuals aged ≥ 60 years than in those aged < 60 years [6,7,8]. Al-Houqani et al. [9] found that age is a significant contributor to the increase in

incidence rates of NTM-PD, however accounting for less than a quarter of the total increase. This suggests that other factors may also play a role in the rise of NTM pulmonary disease incidence rates. One such factor is chronic lung diseases, including COPD, bronchiectasis, and cystic fibrosis, which are known predisposing factors for NTM pulmonary disease development [10]. In the present study, COPD was the most associated chronic lung disease (30%), followed by bronchiectasis (19%). Both diseases have increased in prevalence over the last 30 years, and are themselves associated with higher age. COPD and bronchiectasis both disrupt the normal architecture of the airways, resulting in chronic bronchitis, with disruption of the epithelial membranes and increases in mucus production [11]. This unfortunately is an ideal environment for bacterial colonization and overgrowth. In addition, several patents with COPD may have reduced general immunity due to age or poor nutrition. Patients with COPD are prone to develop cachexia [12]. Finally, many COPD patients use inhaled corticosteroids (ICS) to prevent COPD exacerbations, which are often of viral initiation. In some COPD patients, ICS treatment may also increase their risk of bacterial infections, including NTM pulmonary disease [13]. In cystic fibrosis, due to impaired mucociliary clearance there are viscous airway secretions which predisposes the patient to bacterial colonization and infection [14]. A systematic review and meta-analysis review of 95 studies have reported prevalence of NTM infection in cystic fibrosis to be 7.9% and increasing over time [15].

In our data, 47% patients received antibiotic treatment for eradication of NTM. Patients with high symptom scores had greater odds of receiving treatment, and the odds of receiving treatment were much higher when the patient was below the age of 65. Interestingly, the presence of a cavity did not have a major impact on the initiation of treatment. In a study, it was found that patients had increased odds of receiving treatment in case of cavitation on CT imaging, presence of night sweats, and weight loss [16]. One study from South Korea

demonstrated that long-term treatment success rate decreased with age, particularly in patients aged ≥80 years. Whereas the rate of adverse drug reactions requiring discontinuation of treatment increased with age, and the number was twice as high in patients aged ≥80 years than in those aged <50 years [17]. These findings support the decision to treat relatively younger patients where better treatment outcomes are expected with lesser side effects. However, our study did not find that younger age is associated with favourable treatment response.

In the present study the odds of receiving treatment increased if the patient had MAC infection. As per study, the principal causative species for NTM-PD are members of MAC. Several groups in multiple countries have documented the increasing incidence of MAC related pulmonary disease [18]. Not all patients will require treatment initially but most of the patients will require treatment during the course of the disease. Interestingly, the first guidelines on the treatment of NTM lung disease in 2007 did not impact the decision to start treatment.

In the present study the patients who were initiated with treatment within 6 months or later did not differ in their time to culture conversion. One previous study [19] has noted that the waiting period between diagnosis and treatment of NTM-PD patients did not impact culture conversion in patients. There are reports of patients with infection by *M. abscessus*, MAC, and elderly patients having associations with treatment failure [20]. However, in the current study patients with MAC infection had higher odds of culture conversion. This could be due to predominance of MAC species.

An interesting finding in this study was the spontaneous culture conversion in 55% of patients who did not receive antibiotics with a relative lower relapse rate, as compared to culture conversion among 74% patients who received antibiotics with a relatively higher

relapse rate. This highlights the importance of bronchial hygiene measures for improved clearance of mucus from the lungs [21]. These measures should be tried hopig for a spontaneous remission before initiation of antibiotics.

The current study has some limitations. It has a retrospective cohort design, and some missing clinical data, especially the susceptibility to drugs. The study has a limited sample size, which may skew the results and factors toward MAC, as it constitutes the majority of NTM infections. Additionally, a small sample size may not provide an accurate representation of the trends. Another limitation is the accuracy of data input, as we obtained our data from by reviewing patients' journals. However, since a digital patient file system was first used in the early 2000s, data entry during the initial years may not have been accurate, which could impact our findings. Therefore, we suggest that the results of this study need verification by large, multi-centre, prospective cohort studies.

Conclusion

Our study found that the major species causing NTM pulmonary disease in Western Norway from 2000 to 2021 were MAC, *M. malmoense*, and *M. abscessus*. Increased age and presence of pulmonary comorbidity increased the risk of getting NTM pulmonary infection. Patients with high symptom scores, below the age of 65 and, MAC infection have higher odds of receiving treatment. Favourable treatment response was seen in 74% of patients given antibiotic treatment. Spontaneous remisison was found in 55% of cases who did not receive treatment. Factors associated with favourable treatment response were not found. Further research is required to determine the extent to which these comorbidities may have influenced the presentation and diagnosis of NTM pulmonary infection and disease.

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