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Review Article

Nontuberculous mycobacterial lung disease epidemiology in Taiwan: A systematic review

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Nontuberculous mycobacteria (NTM) are critical emerging global infectious pathogens. Though NTM can be mere colonizers when isolated from human specimens, NTM are also responsible for diverse human infections. NTM—lung disease (NTM-LD) is the most common human disease entity. The present review aims to provide general insight into NTM-LD epidemiology in Taiwan.

In reviewing NTM epidemiology in Taiwan, we discovered three distinguishing features. First, NTM disease incidence has increased in Taiwan over the past decade. Second, the distribution of NTM varies geographically in Taiwan. *Mycobacterium avium-intracellulare* complex (*MAC*) is the dominant species in northern Taiwan, whereas *Mycobacterium abscessus* complex and *MAC* may be equally dominant in southern Taiwan. Third, researchers in Taiwan have published valuable research investigating NTM among special patient populations, including patients in intensive care units, with ventilator dependency, with pulmonary tuberculosis, and who are infected with specific NTM species. The largest obstacle to clarifying NTM epidemiology in Taiwan may be the lack of routine NTM species identification in laboratories. Increased awareness of NTM diseases and acknowledgment that NTM species identification is crucial and guides clinical management are essential steps for facilitating the identification of NTM species in laboratories.

Abbreviations: LD, lung disease; *MAC*, *Mycobacterium avium-intracellulare* complex; MALDI-TOF, matrix-assisted laser desorption/ionization mass spectrometry—time of flight; NTM, nontuberculous mycobacteria; TB, tuberculosis.

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Introduction

Overview of nontuberculous mycobacteria

NTM are a group of mycobacteria that cause clinical diseases. NTM, as indicated by their name, are mycobacteria species other than *Mycobacterium tuberculosis* (*M. tb*) complex and *Mycobacterium leprae*.[1,2] NTM are ubiquitous in the environment, including in water and soil.[1,2] More than 170 species of NTM are currently recognized, and the number of subspecies identified is rapidly increasing.[3] *Mycobacterium avium-intracellulare* complex (*MAC*), *Mycobacterium abscessus* complex, and *Mycobacterium kansasii* are the three species predominantly responsible for human diseases and pulmonary infections.[1]

NTM disease

NTM were formerly considered to be of little clinical significance. Over the past 20 years, NTM have acquired recognition as a pathogenic bacterium that can cause various clinical diseases.[1,4,5] In humans, the most common disease they cause is NTM-LD.[1] NTM-LD usually manifests as a chronic and progressive disease with aggravating respiratory or constitutional symptoms. Radiographically, nodular bronchiectasis and cavitation are two common features, but consolidation and infiltrates can also be present.[1]

In the 2007 NTM-LD guidelines of the American Thoracic Society and Infectious Disease Society of America, a list of detailed diagnostic criteria was provided for use when making an NTM-LD diagnosis. The diagnosis of NTM-LD requires clinical and microbiological criteria to be fulfilled.[1] A detailed review of the diagnosis of NTM-LD is provided in this mini-review series in an article entitled "Clinical relevance and diagnosis of nontuberculous mycobacteria pulmonary disease in populations at risk."

Identification of NTM species

In the 2017 British Thoracic Society guidelines, the identification of isolates of NTM is recommended to be performed to at least the species level by using validated molecular or mass spectrometry techniques.[6] Furthermore, this guideline recommends that isolates of *M. abscessus* complex be subspeciated using appropriate molecular techniques.[6] This recommendation is based on the considerable effect of species identification on the diagnosis and epidemiology of NTM-LD. Diagnoses of NTM-LD can be unreliable and difficult to make without information regarding the isolated NTM species. For instance, isolation of *Mycobacterium gordonae* and *Mycobacterium fortuitum* from respiratory specimens is of less clinical significance compared with other pathogenic NTM species, such as *MAC*.[7,8] Over the past decade, numerous novel species and subspecies of NTM have been discovered. The identification of new species, however, relies on the application of molecular techniques. For instance, the identification of *M. abscessus* subspecies *massiliense (Mycobacterium massiliense)* and *M. abscessus* subspecies *abscessus* requires *rpoB* gene sequencing, multilocus gene sequence typing, and erm gene sequencing.[9] Additionally, differentiation between *M. avium* and *Mycobacterium intracellulare* may require internal transcribed spacers between 16S and 23S ribosomal DNA.[10] Elucidating the epidemiology of NTM in Taiwan is therefore dependent on the feasibility of laboratories differentiating NTM species at study sites. The ability of many hospital laboratories to identify and differentiate between NTM species remains limited. Although clinical significance, drugs of choice, and treatment duration vary for different NTM species, inadequate ability to correctly identify NTM species results in a great barrier to high-quality patient management and care.

Several commercial kits are available for identifying NTM species. These commercial kits include the INNO-LiPA Mycobacteria 2 (Fujirebio, Gent, Belgium), GenoType Mycobacterium CM 1.0, and GenoType NTM-DR 1.0 (Hain Lifescience).[11] The DR. TBDR/NTM IVD Kit (DR. Chip Corporation) is a commercial kit manufactured by a Taiwanese company. This kit utilizes nucleic acid amplification and specific probe hybridization methods for species identification. The target species for identification include *M. tb*, rifampin-resistant *M. tb*, and 15 NTM species. This kit specifically employs multiplex polymerase chain reaction targeting the 16S–23S rRNA gene internal transcribed spacer and *RNA polymerase B subunit* gene. In one validation study, this kit was discovered to have favorable accuracy for identifying *Mycobacterium* species (95.5%, 105/110).[12] Another made-in-Taiwan commercial kit was BluePoint MycoID plus kit (Bio Concept Corporation, Taichung, Taiwan). This kit also targeted 16S–23S rRNA gene internal transcribed spacer and the gene encoding the subunit B of DNA gyrase (*gyrB*).[13] In one study with 16S rRNA gene sequencing as reference method, the accuracy rate of this kit for identification of all *Mycobacterium* species was 96.3% (905/940). In identifying specific NTM species, the kit correctly identified 99.8% (476/477) NTM species.[13] Currently, no direct comparison between made-in-Taiwan kits and other commercial kits was available.

Recently, matrix-assisted laser desorption/ionization mass spectrometry–time of flight (MALDI-TOF) has attracted attention for its ability to identify *M. tb* species. MALDI-TOF may offer the advantages of low cost and short turnaround time.[14] Several studies conducted in Taiwan have evaluated its performance in identifying NTM species, including novel subspecies.[15] Although some of these results may be promising, the accuracy of MALDI-TOF remains a concern and limitation.[14] In one meta-analysis, the accuracy of NTM species identification was 0.82 (95% CI: 0.75–0.88), 0.80 (95% CI: 0.69–0.91), 0.55 (95% CI: 0.34–0.76) and 0.81 (95% CI: 0.75–0.88) for *M. abscessus* complex, *M. avium*, *M. intracellulare* and *M. kansasii*.[16]

Furthermore, MALDI-TOF equipment may not be available in all mycobacteriology laboratories.

Geographic variation of NTM species: global level

The epidemiology of NTM and NTM-LD varies considerably worldwide. In America, *MAC* was found to be responsible for 64%–85% of NTM cases, followed in prevalence by *M. abscessus/chelonae* (3%–13%).[17] In Europe, *MAC* may be less common, with *M. kansasii*, *Mycobacterium xenopi*, and

Mycobacterium malmoense accounting for a larger proportion of cases.[17] Many recent studies have been published regarding NTM prevalence of Africa, where NTM were originally considered to be less common. In one recent study conducted in northern Tunisia, 0.6% (60/10,466) of specimens sent for tuberculosis (TB) investigation yielded positive results for NTM. *M. kansasii* (23.3%) was the predominant species.[18] In Asia, *MAC* is the most frequently isolated species (34%), followed by *M. abscessus* complex (16%).[17]

In one systematic review comparing the species distribution of NTM across different regions, *M. abscessus* complex was found to be more frequently isolated in Asia than America or Europe.[19]

Geographic variation of NTM species: Asia

Even in Asia, NTM epidemiology has considerable variation. In South Korea, a single-center study (n = 17,915 isolates) conducted during 1993–2006 revealed that *MAC* was the most prevalent species (n = 11,705, 65%), followed by *M. abscessus* complex (n = 2,076, 11.59%) and *M. fortuitum* (n = 1,279, 7.14%).[20] In Saudi Arabia (n = 73 pulmonary isolates), *M. fortuitum* (n = 25, 34.2%) and *M. abscessus* complex (n = 21, 28.8%) were the two dominant species.[21] In a nationwide surveillance study conducted in Japan on patients with NTM-LD (n = 2652), *MAC* was the most common species (n = 2,355, 88.8%), followed by *M. kansasii* (n = 113, 4.3%).[22] In a study conducted in southern and eastern China (n = 1450 isolates), the most frequently isolated NTM were *M. abscessus* complex (n = 605, 41.7%) and *MAC* (n = 330, 22.8%).[23]

Reviewing NTM-LD epidemiology in Taiwan

This review targets NTM-LD epidemiology in Taiwan. The evidence on the NTM disease burden, NTM species distribution, and unique NTM disease characteristics in Taiwan are summarized. This review hopes to inform physicians and health care providers of the current NTM disease epidemiology in Taiwan, which could help inform routine patient care.

Methods and materials

Search strategy

We searched PubMed and Embase using the keywords "nontuberculous mycobacteria" or "atypical mycobacteria" or "mycobacteria other than tuberculosis" or "NTM" and "Taiwan". We also searched the Guide to Periodicals Published in the ROC database provided by the National Central Library by using the keyword "nontuberculous mycobacteria" or "NTM." This review did not limit the results to a specific article type, language, or year of publication.

Results

History of NTM in Taiwan

Tracing back NTM epidemiology in Taiwan, NTM keratitis was the first reported disease entity, after which occurred a pseudoepidemic of *Mycobacterium chelonae* infection caused by contamination of a fiber-optic bronchoscope suction channel.[24,25] Shih et al. investigated the clinical significance of 201 isolates of NTM recovered from clinical specimens from 143 patients. A total of 86 isolates of NTM were considered clinically significant; they were cultured from 39 patients with soft-tissue infections and/or osteomyelitis (n = 16, 41%) and those with isolated pulmonary infections (n = 10, 25.6%).[26] The most common pathogenic species involved in pulmonary infection were *MAC* (n = 4, 40%) and *M. chelonae-abscessus* (n = 2, 20%).[26] The first observational study to describe and analyze the clinical outcome of NTM pulmonary disease was that conducted by Yeh et al. at Chang Gung Memorial Hospital in 2007, which involved the analysis of 46 patients with *MAC* and revealed an association between an inadequate *MAC* regimen and higher risk of sputum conversion failure.[27]

Disease burden of NTM-LD

Over the past decade, increasing NTM incidence has been reported by several studies conducted in Taiwan. At National Taiwan University Hospital, located in northern Taiwan, the annual incidence of NTM-LD increased from 3.4 per 100,000 patients in 2000 to 13 per 100,000 patients in 2012.[28] In a study involving two university-affiliated hospital systems, the incidence of NTM-LD in 2014 was 21.9 per 100,000 patients in northern Taiwan and 106.4 per 100,000 patients in southern Taiwan.[29]

NTM/TB isolation ratio in Taiwan

In contrast to *M. tb*, NTM have been considered to constitute only a minority of all mycobacterial isolates. This phenomenon, however, has changed. In the past decade, the frequency of NTM has increased. In studies conducted in Chung Shan Medical University Hospital, *M. tb* constituted 6.06% (n = 691) of all mycobacterial cultures (n = 11,414), whereas NTM constituted 1.28% (n = 147) in central Taiwan in 2002. By 2014, NTM constituted 7.46% (n = 647), whereas *M. tb* constituted 5.23% (n = 453).[30,31] In another study, conducted at National Taiwan University Hospital by Chien et al., NTM accounted for 56.9% of cultures among 13,652 patients who tested positive for mycobacteria cultures during 2000–2012.[28]

NTM-LD epidemiology: the entirety of Taiwan

MAC, *M. abscessus complex*, and *M. kansasii* have been consistently identified as the most common species in NTM-LD in Taiwan.[28,29] A multicenter, longitudinal study published by Huang et al. may provide general insight into NTM epidemiology in Taiwan.[29] This multicenter study was primarily conducted in two university-affiliated hospital

systems and discovered that during 2010–2014, the NTM-LD incidence rate was 46.0 episodes per 100,000 hospital-based patient-years. *MAC* was the dominant species in northern Taiwan (n = 337, 42.3%) followed by *M. abscessus* complex (n = 165, 20.7%), whereas in southern Taiwan, *MAC* (n = 240, 27.3%) and *M. abscessus* complex (n = 243, 27.7%) were equally predominant.[29]

Geographic variation in NTM epidemiology

Considerable geographic variation of NTM clearly exists in Taiwan, especially for the predominant pathogenic species. In northern Taiwan (National Taiwan University Hospital, 2010–2014), *MAC* (42.3%) is the predominant species, whereas in southern Taiwan (Kaohsiung Medical University Hospital, 2010–2014), *M. abscessus* complex (27.7%) and *MAC* (27.3%) may be equally predominant.[29] In central Taiwan, a report from Chung Shan Medical University Hospital revealed that *MAC* (n = 478, 34.3%) was the most common in these regions, followed by *M. abscessus* complex (n = 363, 23.1%) and *M. gordonae* (n = 119, 8.5%).[32] Other than the report by Huang et al., a study conducted in Kaohsiung Chang Gung Memorial Hospital from 2004 to 2005 revealed that *M. abscessus* complex (44.8%) was the most commonly isolated species, followed by *M. fortuitum* (23.9%).[33] The epidemiology of NTM species distribution is illustrated in Fig. 1.

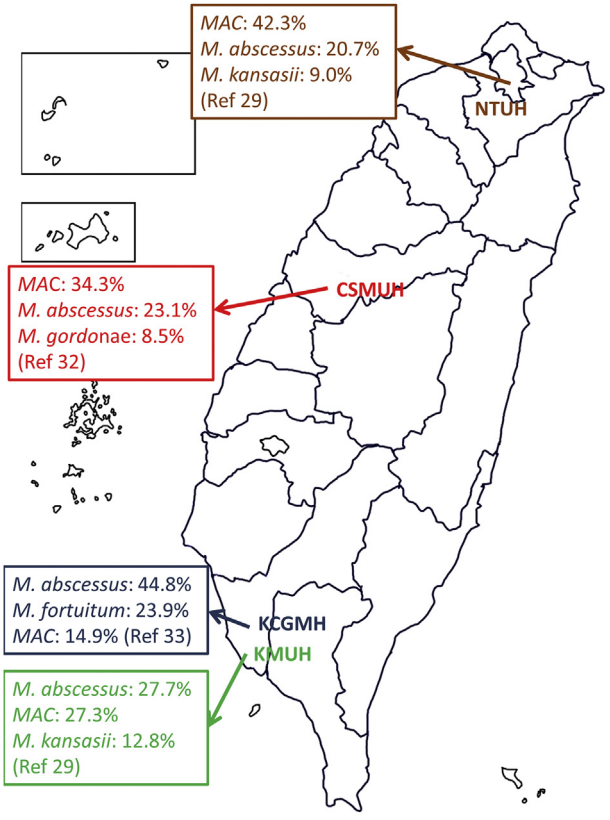

Figure 1 NTM species distribution in Taiwan. NTUH, National Taiwan University Hospital; CSMUH, Chung Shang Medical University Hospital; KCGMH, Kaohsiung Chang Gung Memorial Hospital; KMUH, Kaohsiung Medical University Hospital.

NTM epidemiology in special patient populations

NTM in ventilator-dependent patients

Taiwan's National Health Insurance is a unique health care system with universal and continuous care for critical patients, and respiratory care wards are not uncommon in Taiwan.[34,35] NTM epidemiology among ventilator-dependent patients is also a topic of interest. Two studies, published by Huang et al. and Lee et al., have provided some insights into this group of patients.[34,35] In the long-term respiratory care ward of a hospital in central Taiwan, Huang et al. discovered either an outbreak or high level of endemic infection of *M. abscessus* complex among ventilator-dependent patients. Among 43 of these patients, 15 were diagnosed with pulmonary *M. abscessus* complex infection.[34] Lee et al. further found that acquisition of *M. abscessus* complex in respiratory care wards was not uncommon. By enrolling and following ventilator-dependent patients in five respiratory care wards in northern Taiwan, Lee et al. discovered that the proportion of patients with isolation of *M. abscessus* complex increased from 15.3% (11/72) at study initiation to 30.6% (22/72) in the 3rd month and 38.9% (28/72) in the 6th month.[35] In this study, the chest X-rays of enrolled patients were not available and the clinical significance of *M. abscessus* complex isolation, therefore, remained undetermined.[35] Although the clinical significance of isolation of *M. abscessus* complex in ventilator-dependent patients remains undetermined, infection control measures could be considered and implemented to halt transmission of *M. abscessus* complex in Taiwan's respiratory care wards.

NTM in critical care patients

NTM are generally considered chronic diseases, and the isolation of NTM in acute critical care patients is also of interest. Shu et al. discovered that mycobacterial cultures from respiratory samples were obtained from 2866 (53.3%) of 5378 patients admitted into intensive care units. NTM were isolated from 5.8% of patients (n = 169).[35] Of them, 47 cases (27.8%) were considered to be NTM-LD. *MAC* (n = 20, 42.6%) and *M. abscessus* complex (n = 8, 17%) were the most common pathogens. Additionally, NTM infection was found to be associated with poorer survival in patients in an intensive care unit (ICU).[36]

Single sputum positivity for NTM

Although at least two positive sputum isolates are required for NTM-LD diagnosis in most cases, single sputum isolate positivity is also of clinical significance. In one single-center study conducted in northern Taiwan, 202 patients with single sputum isolate positivity were reviewed. Among them, 71 were positive for *M. fortuitum* (35.1%). *MAC* (n = 70, 34.7%) was also among the dominant NTM species isolated, followed by *M. chelonae-abscessus complex* (n = 40, 19.8%) and *M. kansasii* (n = 21, 10.4%); 21.8% of patients (n = 44) had subsequent positive cultures of the same NTM species following a median of 26 months, whereas 4.0% of patients (n = 8) had bronchiectasis and developed NTM-LD.[37]

Another study which focused on single *M. kansasii* isolation from ≥3 sputum samples found that among 83

patients with single *M. kansasii* isolation, 16 (19%) cases progressed to lung disease. Among patients who developed *M. kansasii* lung disease, all experienced radiographic progression, and 44% died within 1 year. High acid-fast smear grade (≥3), elementary occupation workers, and initial radiographic score >6 were risk factors.[38]

NTM *in patients with pulmonary TB*

Coexistence of NTM and TB in one patient may not be uncommon. Huang et al. discovered that among 2133 patients with pulmonary TB, 48 (2.3%) had multiple NTM isolates whereas 106 (5.0%) had one isolate of NTM. In the 48 patients with multiple NTM isolates, *M. abscessus* complex was the most common species (n = 15, 31%), followed by *MAC* (n = 14, 29%). Among the 106 patients with a single NTM isolate, *M. fortuitum* was the most common (n = 30, 28%), followed by *MAC* (n = 23, 21%).[39] Although the isolation of NTM from patients with pulmonary TB may not infer different treatment outcomes compared with patients with pulmonary TB but without NTM isolation, NTM being more frequently isolated from patients with pulmonary TB and radiographically visualized cavities may indicate more severe underlying structural damage to the lungs.[39] The authors, however, did not specify the proportion of NTM-LD among positive NTM cultures in TB patients in this article.[39]

NTM pleurisy

The description of NTM in pleural effusion in Taiwan can be traced back to 1997 in the study by Shih et al.[26] In the study by Ding et al., they found that among 412 patients with NTM-associated diseases, 245 patients (59.5%) had pulmonary disease or pleurisy.[40] In another study conducted by Yuan et al., pleural effusion was present in 3 (15%) of 20 NTM-LD patients.[41]

In a single-center study, Shu et al. investigated 35 patients with NTM pleurisy. *MAC* (n = 16, 45.7%) was discovered to be the most common species.[37] Notably, the 1-year mortality in the NTM pleurisy group was found to be 37%, and anti-NTM treatment was associated with better survival.[42]

NTM in patients with a history of TB

Bronchiectasis was previously considered the most critical disease underlying further NTM colonization and infection.[1,6] However, in Taiwan, a country in which TB was once endemic, TB plays a more crucial role. TB has been reported to be strongly associated with bronchiectasis, residual cavitation, and chronic obstructive pulmonary disease.[43,44] In one study, 45% of patients with NTM-LD had a history of TB.[45]

NTM in elderly patients

Lai et al. investigated the clinical significance of NTM in elderly (age > 65 years) Taiwanese patients. In the 1633 elderly patients with NTM isolates, *MAC* (n = 592, 36.3%) was the most prevalent species; 80% (n = 1339) of the patients were considered to have NTM colonization, whereas 20% (n = 326) were considered to have NTM diseases. Pulmonary NTM infections were the most common disease entity among elderly patients (n = 294, 90.2%).[46] For elderly patients with NTM infection, the most common species is *MAC* (n = 124, 38%), followed by *M. abscessus* complex (n = 84, 25.8%).

The aforementioned articles, which investigated the role of NTM in special patient populations, are summarized in Table 1.

NTM-LD for specific NTM species

MAC-LD

In a multicenter study, Pan et al. investigated the clinical significance of persistent *MAC* growth. *MAC* exhibited persistent growth in 60% (n = 75) of 126 patients with *MAC*-LD. Patients with microbiologic persistence of *MAC* had a high risk of radiographic progression (54%). Factors predicting *MAC* persistence were low body mass index, nodular-bronchiectatic pattern, and high acid-fast bacilli smear grade.[47]

M. abscessus complex-LD

Tung et al. investigated 106 patients with *M. abscessus* complex—LD in southern Taiwan during 2006—2012. They discovered that for patients with *M. abscessus* complex—LD who were receiving antibiotics, previous mycobacterium pulmonary disease and cavitary lesion were risk factors for persistence of *M. abscessus complex*.[48]

M. kansasii-LD

Liu et al. investigated the clinical course of *M. kansasii*—LD and found that radiographic progression occurred in 70 (64%) patients, with a 1-year mortality rate of 43%. Fibrocavitary pattern, leukocyte count >9000/μL, old age, pure *M. kansasii* in sputum without other NTM, and absence of diabetes were independent risk factors for radiographic progression.[49]

Another crucial finding with practical clinical relevance in Taiwan was made by Huang et al., who discovered increases in *M. kansasii* isolation and LD in southern Taiwan.[29] This phenomenon has been hypothesized to result from environmental factors such as local industrial activity and air pollution.[29] More studies may be required to monitor this trend and prevent the development of a public health hazard in southern Taiwan.

Discussion

Our study obtained several valuable findings. First, we discovered that NTM-LD is an emerging disease in Taiwan. During the past decade, NTM-LD incidence has increased gradually along with the increasing proportion of NTM among mycobacterial isolates. Second, we found that even within Taiwan, considerable variation in NTM species exists. *MAC* may predominate in northern and central Taiwan, whereas *M. abscessus* complex may be the dominant species in southern Taiwan. Ample research has been conducted in Taiwan regarding NTM among special populations, including patients with ventilator-dependence, single sputum-positivity, critical illness, pleurisy, prior TB, old age and specific NTM species. These studies provided valuable information regarding patient outcome and prognostic factors.

Table 1 Epidemiologic studies among special patient populations in Taiwan.

	Patient population	Number of cases	NTM species distribution	Key findings
NTM in ventilator-dependent patients				
Huang et al.[34]	Ventilator-dependent patients	38 patients, 28 NTM+	100% *M. abscessus* complex	Either an outbreak or high level of endemic infection in a respiratory care ward
Lee et al.[35]	Ventilator-dependent patients	72 patients, 28 NTM+	100% *M. abscessus* complex	Acquisition of *M. abscessus* complex was common among ventilator-dependent patients
NTM in critical care patients				
Shu et al.[36]	ICU patients	47 patients who were NTM+	42.6% *MAC*, 17% *M. abscessus* complex	NTM infection may be associated with poor outcome in patients in intensive care units
Single sputum positivity for NTM				
Lee et al.[37]	Patients with single NTM + isolate	202 patients	35.1% *M. fortuitum*, 34.7% *MAC*	4% of patients with single NTM isolate progress to clinical disease
Huang et al.[38]	Patients with single *M. kansasii* isolation	83 patients	100% *M. kansasii*	16 (19%) progressed to lung disease within one year and 7 (44%) died
NTM in patients with pulmonary TB				
Huang et al.[39]	Pulmonary TB	154 patients who were TB+ and NTM+	24% *MAC*, 22.7% *M. fortiuitum*	NTM may infer different clinical presentations of TB
NTM pleurisy				
Ding et al.[40]	NTM disease patients	412 cases of NTM disease	39.1% *MAC*	245 (59.5%) of 412 NTM disease had NTM-LD and pleurisy
Yuan et al.[41]	NTM-LD patients	20 cases of NTM-LD patients	NA	3 (15%) of 20 NTM-LD had pleural effusion on CT
Shu et al.[42]	NTM pleurisy patients	35 cases of NTM pleurisy	45.7% *MAC*	NTM with pleurisy has a high 1-year mortality rate (37%)
Elderly patients				
Lai et al.[45]	Elderly patients (age > 65 years)	326 cases of NTM disease	38% *MAC*, 25.8% *M. abscessus* complex	*MAC* and *M. abscessus* complex are critical pathogenic NTM species in elderly patients

Note: CT, computed tomography; *MAC*, *Mycobacterium avium-intracellulare* complex; NA, not available; NTM, nontuberculous mycobacteria; TB, tuberculosis; NTM+, positive NTM culture; TB+, positive TB culture.

Taiwan has an intermediate TB burden and an annual incidence rate of 38.9 per 100,000 persons, with 9179 new cases in 2018.[50] As the result of the high TB treatment success rate in Taiwan, the number of patients with a history of TB is undoubtedly increasing. Older patients are at increased risk of developing superimposed infection such as chronic pulmonary aspergillosis, but NTM-LD is also a disease entity that should not be overlooked.[44]

Our study revealed that *M. abscessus* complex is prevalent in southern Taiwan whereas *MAC* is dominant in northern Taiwan.[29,33] Furthermore, the incidence of NTM-LD appears to be higher in southern Taiwan than in northern Taiwan. Interestingly, in mainland China, rapidly growing mycobacteria were more prevalent in southern China than in northern China. Slow-growing mycobacteria reportedly constitute 63.7% and 53.0% of all NTM isolates in northern and southern China, respectively. Furthermore, the NTM prevalence was found to be higher in southern China than in northern China.[51] The humidity and temperature differences between northern and southern Taiwan may be a crucial factor that can explain this phenomenon. In South Korea and Japan, *MAC* constitutes the majority of NTM isolates, also indicating that latitude may affect the distribution of NTM species.[20,22]

Our review found that in vulnerable patient populations such as elderly and critical illness patients, NTM should not be overlooked. NTM can be present in respiratory samples in those patients. It was worth mentioning that NTM may be

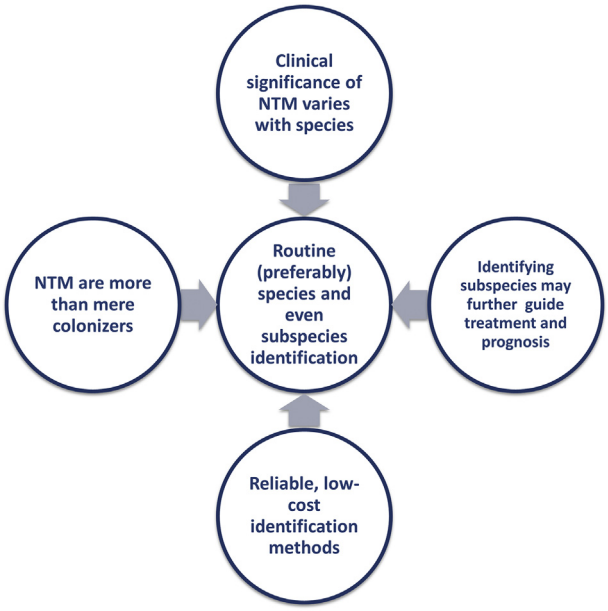

Figure 2 Proposed rationale for improving NTM species identification.

neglected as a weak pathogen.[1,2] Careful assessing if patients fulfill the criteria of NTM-LD and judicious follow-up may be mandatory. Also, prognostic factors explored by epidemiologic studies may also guide physicians throughout clinical course. High disease burden, high acid-fast stain grade and cavitary lesions are important risk factors for disease persistence or progression.[38,47–49] Physicians should also pay special attention to patients with these risk factors.

Our review also identified several crucial needs for clarifying NTM epidemiology. Notably, NTM epidemiology data on eastern Taiwan are lacking. Published articles from certain hospitals regarding NTM epidemiology are also limited. The inability of laboratories to perform detailed species identification, the cost of performing detailed species identification, and physicians' negligence regarding the clinical significance of NTM have also contributed to NTM species identification remaining infeasible in numerous hospitals. Increasing awareness of NTM disease may be the first step. Furthermore, detailed subspecies identification may provide prognostic information and could guide therapy. Differentiation between *M. abscessus* subsp. *abscessus* and *M. abscessus* subsp. *massiliense* has proven the clinical utility of differentiating NTM subspecies.[52] We therefore propose an algorithm for facilitating NTM species identification (Fig. 2).

There remains a lack of definitive evidence regarding the nationwide epidemiology of NTM diseases. Nationwide, population-based data on NTM disease prevalence and burden are lacking. In the future, studies using the Taiwan National Health Insurance (NHI) claims database may help to address this data gap.[53–56] International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10) codes, which was used by NHI claims database since 2016, may provide more detailed information on NTM diseases and has been used in previous epidemiologic study for NTM-LD.[57]

This review also has limitations. First, we did not perform meta-analysis of NTM-LD incidence and species distribution. The reason of not performing meta-analysis is in part due to the different study periods and paucity in study number. Second, we did not describe much regarding global epidemiology and this article may not be of particular interest to readers outside Taiwan. This study, however, was intended to serve as a local epidemiologic reference for physicians in Taiwan.

Conclusion

NTM-LD is an emerging clinical disease in Taiwan over the past decade. *MAC* was the most important pathogenic NTM species in northern Taiwan while *M. abscessus* complex and *MAC* may be equally prevalent in southern Taiwan. The isolation of NTM from respiratory samples was not uncommon among different vulnerable patient groups and merits clinical attention.

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Author contributions

M.R. Lee, L.Y. Chang, J.C. Ko, H.C. Wang and Y.W. Huang have made substantial contributions to conception and design; M.R. Lee and Y.W. Huang drafted this manuscript. All authors have proved the final version of manuscript.

Declaration of Competing Interest

The authors have no conflicts of interest relevant to this article.

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