

Non-tuberculous mycobacterial lung disease in patients with bronchiectasis: perceived risk, severity and guideline adherence in a European physician survey

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On behalf of the NTM-NET

To cite: Wagner D, van Ingen J, van der Laan R, *et al.* Non-tuberculous mycobacterial lung disease in patients with bronchiectasis: perceived risk, severity and guideline adherence in a European physician survey. *BMJ Open Res* 2020;**7**:e000498. doi:10.1136/bmjresp-2019-000498

► Additional material is published online only. To view please visit the journal online (<http://dx.doi.org/10.1136/bmjresp-2019-000498>).

Received 17 September 2019
Revised 25 February 2020
Accepted 3 April 2020



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ABSTRACT

Background Patients with bronchiectasis are at increased risk of developing non-tuberculous mycobacteria lung disease (NTM-LD), and published guidelines recommend regular testing for NTM infection in this patient population.

Objective This study aimed to survey physicians managing patients with bronchiectasis to understand the perceived risk of NTM to their patients, perceived disease severity and frequency of testing for NTM.

Methods The study comprised an online survey of hospital-based physicians in the UK, Germany, Italy, France and the Netherlands. The target group were hospital-based physicians who had managed at least 10 adult patients with bronchiectasis over the preceding 12 months.

Results In total, 280 physicians completed the survey. Most (87%) thought their patients to be at particular risk of NTM, although it was perceived as a moderate risk versus other respiratory pathogens. Most perceived NTM-LD to impact patient morbidity (84%), and 61% indicated that NTM-LD significantly impacted mortality. 68% of all respondents did not test for NTM prior to initiating macrolide monotherapy, despite guidelines recommending testing. The perceived risk of and screening for NTM varied among countries.

Conclusions The study demonstrates that physicians understand the risk of NTM-LD and associated morbidity in patients with bronchiectasis; however, a minority do not perceive that NTM-LD significantly affects mortality. Greater awareness of the need to test for NTM infection before initiating macrolide monotherapy for bronchiectasis is essential due to potential emergence of drug-resistant NTM.

INTRODUCTION

Non-tuberculous mycobacteria (NTM) are ubiquitous environmental bacteria, capable of causing opportunistic infection in humans.^{1,2} NTM lung disease (NTM-LD) is by far the most common clinical manifestation of NTM diseases.¹ Two forms of the disease are generally recognised: the slowly progressing nodular-bronchiectatic form, most commonly

Key messages

What is the question?

► How do physicians managing patients with bronchiectasis perceive the risk and disease severity of non-tuberculous mycobacteria lung disease (NTM-LD) in their patients, and how often and when do they test for NTM?

What is the bottom line?

► Physicians managing patients with bronchiectasis understand the association between bronchiectasis and the risk of NTM-LD, although current NTM screening practices prior to introducing macrolide monotherapy treatment are not compliant with existing guidelines.

Why read on?

► This study gives an insight into how pulmonologists perceive NTM in relation to their patients with bronchiectasis in terms of disease severity, and highlights a lack of understanding of when patients with bronchiectasis should be tested for NTM infection.

associated with postmenopausal women and the fibrocavitary form, which has a much more rapid progression and is associated with middle-aged (former) smokers with a history of underlying lung disease.³

In particular, patients with bronchiectasis and chronic obstructive pulmonary disease (COPD), especially those treated with corticosteroids, have been found to have a substantially increased risk of NTM-LD. One study reported an adjusted ORs of 187.5 (95% CI 24.8 to 1417.4) among patients with bronchiectasis and 15.7-fold (95% CI 11.4 to 21.5) among patients with COPD.⁴ NTM isolation prevalence in patients with bronchiectasis ranges from 2% to 63%.⁵⁻⁸

European guidelines for the management of bronchiectasis recommend regular testing for NTM isolation, particularly where NTM are suspected as a cause of bronchiectasis. Testing should be carried out prior to initiation of long-term macrolide monotherapy to prevent exacerbations, in order to avoid development of macrolide-resistant NTM.^{9 10} Local guidelines from the UK from 2010 for management of bronchiectasis recommend regular monitoring for NTM if patients prove culture positive for NTM.¹¹ Yet, the physician perception of the risk of NTM-LD in patients with bronchiectasis—and its impact on testing practices—has never been investigated.

In this study, we surveyed hospital-based physicians managing adult patients with bronchiectasis in the UK, Germany, Italy, France and the Netherlands. Our aims were to understand current testing practices in the surveyed countries, and to measure the current perception of risk and severity of NTM-LD in the adult population with bronchiectasis.

METHODS

The physician survey was carried out via a secure online platform. Surveys were conducted in the respondent's native language, and respondents received a financial incentive for participation in the study. The target group were hospital based (spending at least 80% of their time in the clinic) pulmonologists who had managed at least 10 adult patients with bronchiectasis over the preceding 12 months. The survey took place in the UK, Germany, Italy, France and the Netherlands.

Panel members were recruited via phone, referral schemes and via conferences by M3 Global Research (Abingdon, UK). Registered panellists were required to update their profile on a bimonthly basis, and their credentials were verified against bodies that maintain official registers of pulmonologists in each country. To ensure that the panel was representative of the total

population of pulmonologist in each market, the recruitment process was randomised.

M3 Global Research holds European Union (EU) compliance certifications to ensure the protection of panel information (eg, Data Protection Authority (DPA), European Pharmaceutical Market Research Association (EphMRA), British Healthcare Business Intelligence Association (BHBIA), General Data Protection Regulation (GDPR), physician verification). The panel is also ISO 26362 certified.

The following terms were used in the survey: 'NTM' when asking questions about testing for the presence of NTM in respiratory secretions; 'NTM infection' when asking about risk of contracting NTM leading to NTM-LD, that is, NTM sputum culture positivity; and 'NTM-LD' when asking about agreement with statements regarding the clinical impact of NTM-LD.

Spearman's r (correlation coefficient) was calculated to explore correlations between ordinal responses. Group differences were evaluated by Mann-Whitney U test or X^2 test for ordinal or categorical variables, respectively. The physician survey is included in online supplementary appendix 1.

RESULTS

Respondent characteristics

The number of physicians invited, complete and incomplete surveys, and number of respondents screened out are detailed in online supplementary table S1. The survey was closed when the targeted number of surveys were completed: Germany ($n=60$), the UK, ($n=60$), Italy ($n=60$), France ($n=60$) and the Netherlands ($n=40$). Relatively few respondents who treated patients with NTM were excluded during the screening process, although more physicians from Germany who were not hospital based were excluded from the survey compared with physicians from other countries (see online supplementary table S2). The sample of respondents included physicians working in academic and general hospitals, and was spread across the regions in the countries (see online supplementary figure S1).

Respondents reported managing an average of 51 patients with bronchiectasis over the preceding 12 months; this ranged from 31 patients in the Netherlands to 66 in the UK, and 74% of respondents had personally managed at least one patient with NTM-LD during this period. On average, respondents managed 10 patients with NTM-LD over the 12-month period, ranging from 4 in the Netherlands to 17 in Germany. Respondents treating more patients with bronchiectasis also managed more patients with NTM-LD (Spearman's r 0.48, $p<0.05$).

Perceived risk of NTM infection in patients with bronchiectasis

The majority of surveyed physicians (87%; range 77% in Italy to 93% in the Netherlands) considered their patients with bronchiectasis to be at particular risk of

Table 1 Percentage of physicians considering patients with bronchiectasis to be at particular risk of NTM infection (A) and estimated percentage of adult patients with bronchiectasis contracting NTM during the course of their disease (B)

Country (n)*	A: Perceived risk for NTM infection	B: Estimated NTM prevalence*
UK	90% (n=60)	13% (n=47)
Germany	92% (n=60)	21% (n=44)
Italy	77% (n=60)	23% (n=40)
France	87% (n=60)	17% (n=45)
The Netherlands	93% (n=40)	12% (n=26)
Total	87% (n=280)	18% (n=202)

*Respondents who could not estimate the risk of NTM infection in their patients were not included in this analysis.
NTM, non-tuberculous mycobacteria.

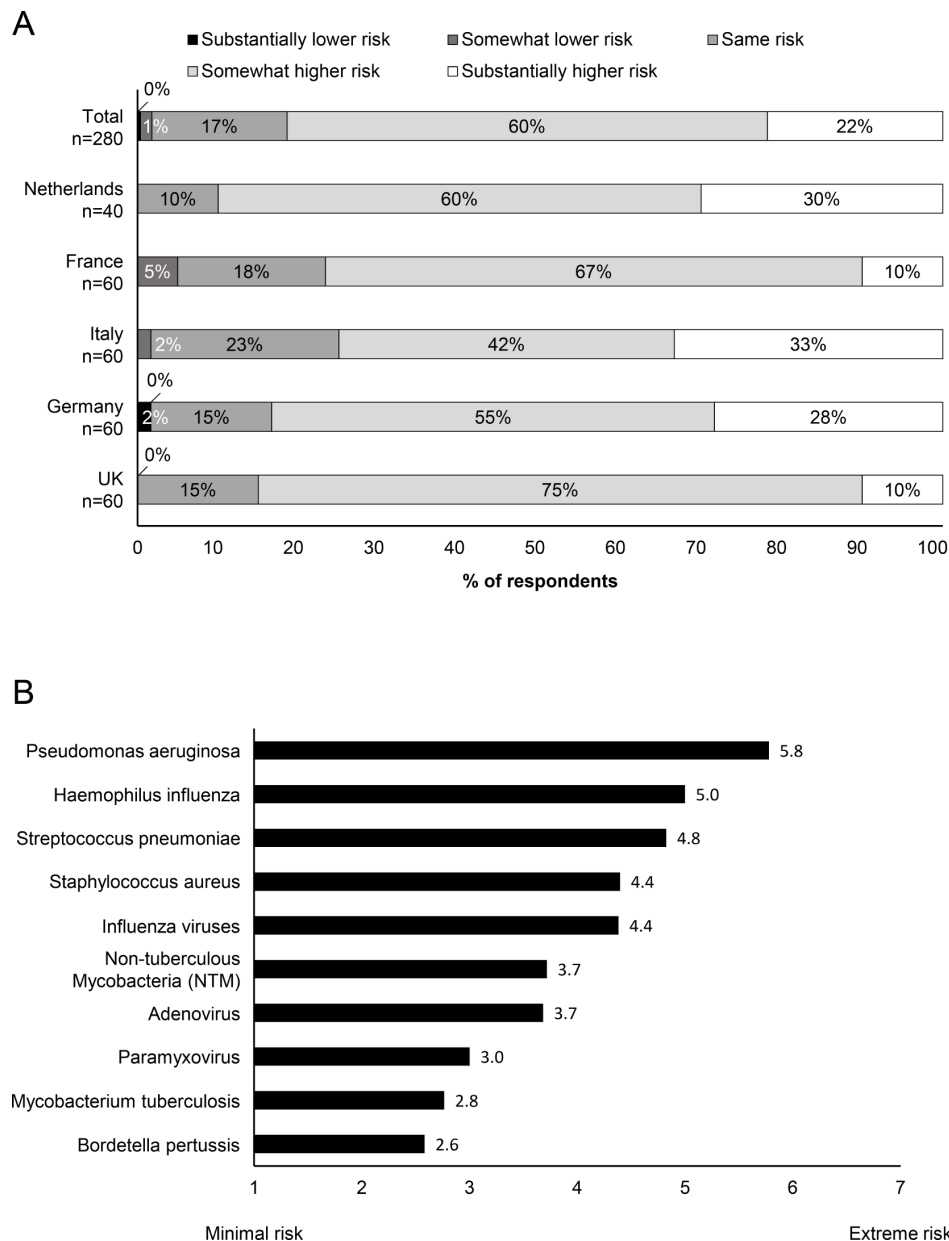


Figure 1 Perceived risk of NTM and respiratory infections in patients with bronchiectasis (A) Perceived risk of NTM infection in patients with bronchiectasis versus patients with moderate-to-severe COPD. (B) Perceived risk of respiratory infections for patients with bronchiectasis. Risk was rated from 1 (minimal risk) to 7 (extreme risk). COPD, chronic obstructive pulmonary disease.

NTM infection (table 1A). Overall 82% of respondents considered patients with bronchiectasis to be at somewhat higher or substantially higher risk of NTM infection than patients with moderate-to-severe COPD (figure 1A).

Survey participants ranked the risk of NTM infection in patients with bronchiectasis (on a scale of 1 (minimal risk) to 7 (extreme risk)) as 'moderate', equivalent to adenovirus (rated at 3.7), with *Pseudomonas aeruginosa* being ranked as the respiratory pathogen with the greatest risk (5.8) and *Bordetella pertussis* with the lowest risk (2.6) (figure 1B).

Overall, 53% of respondents estimated the risk of their patients with bronchiectasis contracting NTM to be $\leq 20\%$. This rating varied widely between the surveyed

countries; for example, in the UK 68% respondents estimated a risk of $\leq 20\%$, whereas in Italy only 36% gave this estimate (figure 2). Respondents estimated the number of patients with bronchiectasis who contracted an NTM infection during the course of their disease as 18% (table 1B), which is similar to the overall estimates of the percentage of patients with bronchiectasis that had been tested were tested positive for NTM (17%) (figure 3A).

Perception of NTM severity

Most physicians across the surveyed countries judged NTM-LD as a significant factor for worsening of respiratory function (89%), increasing morbidity and hospitalisation

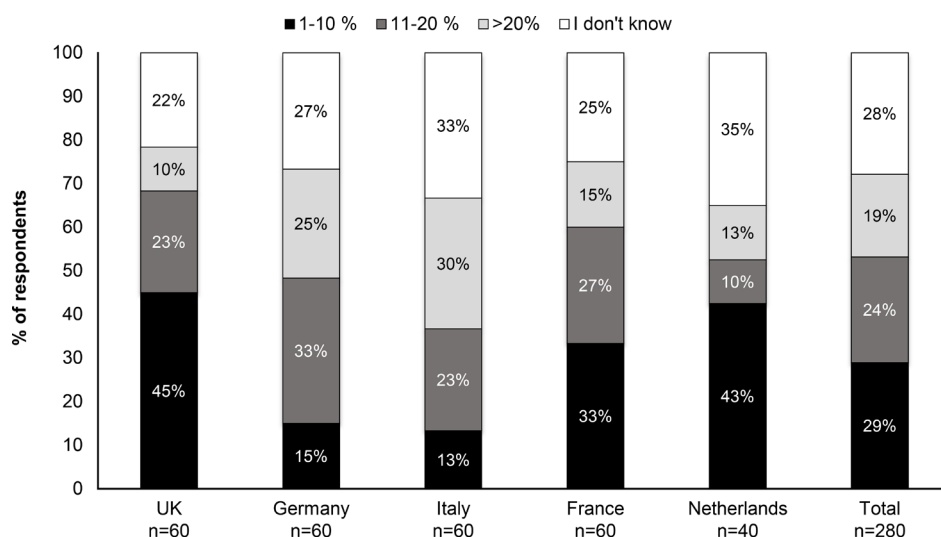


Figure 2 Reported proportion of patients with bronchiectasis contracting NTM. NTM, non-tuberculous mycobacteria.

frequency (84%) and mortality risk (61%). A quarter of respondents were unsure about the impact of NTM-LD on mortality risk (table 2, online supplementary table S3).

Testing for NTM infection in patients with bronchiectasis

The majority of respondents (85%) tested at least some of their patients with bronchiectasis for NTM culture positivity, and this proportion was similar in all countries (see online supplementary figure S2A). Of those not testing their patients for NTM infection, 78% indicated they had not suspected NTM in any patient, 17% preferred to send the patient to an expert for diagnosis and 5% were unaware how to test and diagnose NTM (see online supplementary figure S2B).

Those physicians who did not test for NTM sputum culture positivity perceived NTM as a lower risk (2.8 vs 3.9, $p<0.01$). Additionally, these physicians managed significantly fewer patients with NTM-LD (2.9 vs 11.7, $p<0.01$) and fewer patients with bronchiectasis (30 vs 55, $p<0.01$) than those who did test. Respondents who tested their patients with bronchiectasis for NTM tested 51% (range: 40% (France) to 70% (the Netherlands)) of their patients (figure 3A). Overall, an average of 17% patients who were tested were estimated to be positive for NTM (figure 3A).

Overall, 49% of respondents tested all patients with bronchiectasis for NTM culture positivity at diagnosis or initial presentation. Changes in radiological features of the lung that lead to suspicion of NTM-LD were the main prompt for surveyed physicians to test for NTM. (figure 3B).

In terms of frequency of testing for sputum culture positivity, 64% of respondents test at least once per year (see online supplementary figure S3). There was a trend for managing a greater number of patients with NTM among those respondents testing every 6 months in comparison to those physicians testing less frequently for NTM (14.4

vs 8.6 patients, $p<0.05$). Referral to or management by other physicians was the most important reason for less frequently testing for NTM, reported by 49% of respondents (see online supplementary table S4).

Management of patients with bronchiectasis

Physicians reported that 42% of their patients with bronchiectasis received long-term (≥ 3 months) macrolide monotherapy (range: 35% in France to 60% in the Netherlands, $p=0.06$) (figure 4A). Only 38% of physicians testing for NTM carried out the test prior to initiating macrolide monotherapy to manage patients with bronchiectasis (range: 24% (Germany) to 66% (UK)) (figure 4B). Considering all physicians surveyed, 68% do not test for NTM prior to initiating macrolide monotherapy. In terms of guidelines followed for management of respiratory diseases, 79% respondents' employed European Respiratory Society (ERS) guidelines, 40% American Thoracic Society (ATS) guidelines (which are not specific for patients with bronchiectasis) and 34% local or national guidelines overall across the surveyed countries (data not shown). Testing for NTM before initiating macrolide monotherapy was not related to following/using guidelines for treatment decisions. Namely, 94% of physicians reported to follow or use the guidelines in either case, that is, testing or not testing for NTM before initiating macrolide monotherapy.

DISCUSSION

A low index of suspicion among physicians regarding the risk of NTM-LD and its severity may mean that physicians are less likely to test their patients with chronic lung disease for NTM culture positivity. This may lead to NTM-LD going undetected, development of macrolide resistance and worse longer-term outcomes for patients.^{12 13} Our study aimed to identify how physicians perceive risk of NTM infection in patients with bronchiectasis, how they

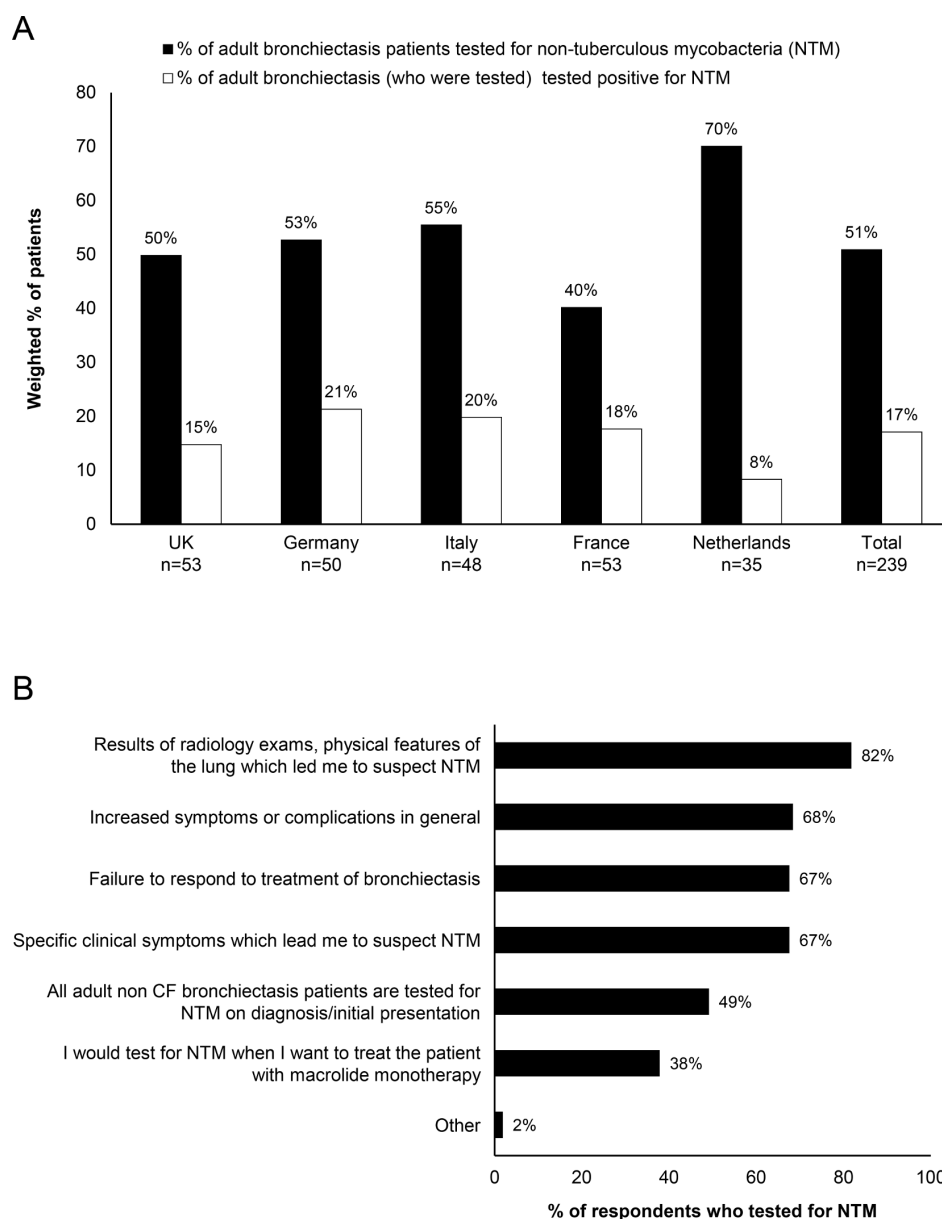


Figure 3 Testing for NTM infection in patients with bronchiectasis. (A) Proportion of patients with bronchiectasis tested for NTM. (B) Triggers for NTM testing in patients with bronchiectasis. NTM, non-tuberculous mycobacteria.

monitor their patients for NTM infection and whether they adhere to published guidelines for management of respiratory diseases.

Bronchiectasis is an even stronger risk factor for the development of NTM-LD in comparison with COPD,⁴ and most surveyed physicians appeared to have an understanding of this. This risk is perceived as moderate by the participating physicians in comparison with the risk of contracting *P. aeruginosa* and *Haemophilus influenzae*, probably since these are regularly identified as causative agents of exacerbations in patients with COPD and bronchiectasis.^{9 14 15}

Despite this, there was a general agreement among the surveyed physicians that NTM-LD significantly increases morbidity, leading to increased hospitalisations, and that it has a large clinical impact, in line with recently

published observations.¹⁶ In contrast, the proportion of respondents who perceived a significant impact of NTM-LD on mortality was somewhat lower overall. Studies exploring the impact of NTM-LD on mortality have recently been published, showing that NTM-LD is associated with an increased risk of death irrespective of other comorbidities.^{16–18} Previous studies showed that patients with specific NTM-LD manifestations like cavitary disease¹⁹ or specific NTM species like *Mycobacterium xenopi*²⁰ have a higher mortality risk. Specific NTM-LD registries may provide further evidence on the respective risk factors in the future.^{21 22}

The perception of risk of NTM among respondents was associated with the number of patients with NTM managed, for example, physicians who manage more patients with NTM-LD have a better awareness of

Table 2 Agreement with statements regarding impact of NTM-LD on morbidity and mortality

Countries	Strongly agree	Agree	Unsure	Disagree	Strongly disagree
'NTM-LD significantly increases morbidity and leads to more frequent hospitalisations'*					
UK	12	73	12	3	0
Germany	25	58	15	2	0
Italy	13	67	10	10	0
France	22	70	8	0	0
The Netherlands	13	65	20	3	0
Mean percentage	17	67	13	4	0
'NTM-LD has no significant impact on mortality risk, as mortality is determined by the underlying condition'					
UK	3	10	23	55	8
Germany	0	7	18	53	22
Italy	0	13	32	43	12
France	2	20	28	32	18
The Netherlands	3	10	25	53	10
Mean percentage	1	12	25	47	14

The percentage of physicians choosing an answer is shown. n=280.

*Agreement with this statement weakly correlated with perceived risk of NTM in patients with bronchiectasis (Spearman's r 0.185, $p < 0.01$) and number of patients with NTM managed (Spearman's r 0.174, $p < 0.01$).

NTM-LD, non-tuberculous mycobacterial lung disease.

NTM-LD. This reinforces the idea that NTM-LD should be managed in collaboration with physicians with expertise in the treatment of these patients as recommended in national guidelines in the UK and USA.^{3 23} Another possible explanation for the perceived lack of impact of NTM on mortality is insufficient data regarding the long-term follow-up of patients with NTM, as registries for patients with NTM-LD have only recently been started in Europe.^{21 22}

We identified that most surveyed physicians tested their patients for NTM infection and approximately half tested all of their patients with bronchiectasis at initial presentation or diagnosis. Testing behaviour was significantly associated with the number of NTM-LD and patients with bronchiectasis managed, with those physicians who did not test their patients for NTM tending to manage fewer patients with NTM or bronchiectasis than those who did test.

These findings differ from a recent Europe-wide longitudinal cohort study forming part of the European bronchiectasis registry (European Multicentre Bronchiectasis Audit and Research Collaboration, EMBARC) which shows approximately 30% of patients were tested for NTM infection, regardless of the number of relevant comorbidities present.²⁴ As the EMBARC registry is a much larger study covering a wide range of European countries and centres, it may be more reflective of trends in the whole of Europe rather than the five countries surveyed in our study. Other triggers for testing included radiology results, structural lung defects and worsening symptoms. This is an encouraging finding as it shows many physicians are aware of the risk of NTM infection in patients with bronchiectasis. Our finding of common triggers of

NTM testing including increased symptoms or complications is in line with results from EMBARC showing that severe exacerbations are a predictor of NTM testing in patients with bronchiectasis.²⁴ In this study, the main predictor for NTM testing by far was a history of NTM infection. It is unclear how this finding applies to the patient population surveyed in our study as information regarding whether respondent's patients had previously suffered from NTM-LD was not available.

Both the ERS bronchiectasis and European/US Cystic Fibrosis (CF) guidelines recommend testing for NTM culture positivity prior to initiation of macrolide monotherapy.^{9 10} Despite most respondents stating that they follow ERS guidelines, all aspects of these recommendations do not appear to be put into practice. This is also reflected by other studies that show that adherence to guideline recommendations is often poor.^{25–27}

Long-term macrolide monotherapy is often used to prevent exacerbations in patients with bronchiectasis,^{9 28} reflected in the high proportion of the patients with bronchiectasis reported in our survey receiving the treatment. However, macrolide monotherapy is not recommended for treatment of NTM-LD, as there is an increased risk of macrolide resistance emergence, which decreases the chance of an NTM-LD cure.^{12 13} Since 68% of survey respondents do not test their patients for NTM prior to starting macrolide treatment, education of physicians, alongside promotion and enforcement of current guidelines⁹ is necessary. While studies still have to show whether the risk of macrolide-resistant NTM disease is increased in patients receiving macrolide maintenance treatment, case reports have recorded this phenomenon.²⁹ Conversely, macrolide monotherapy may be

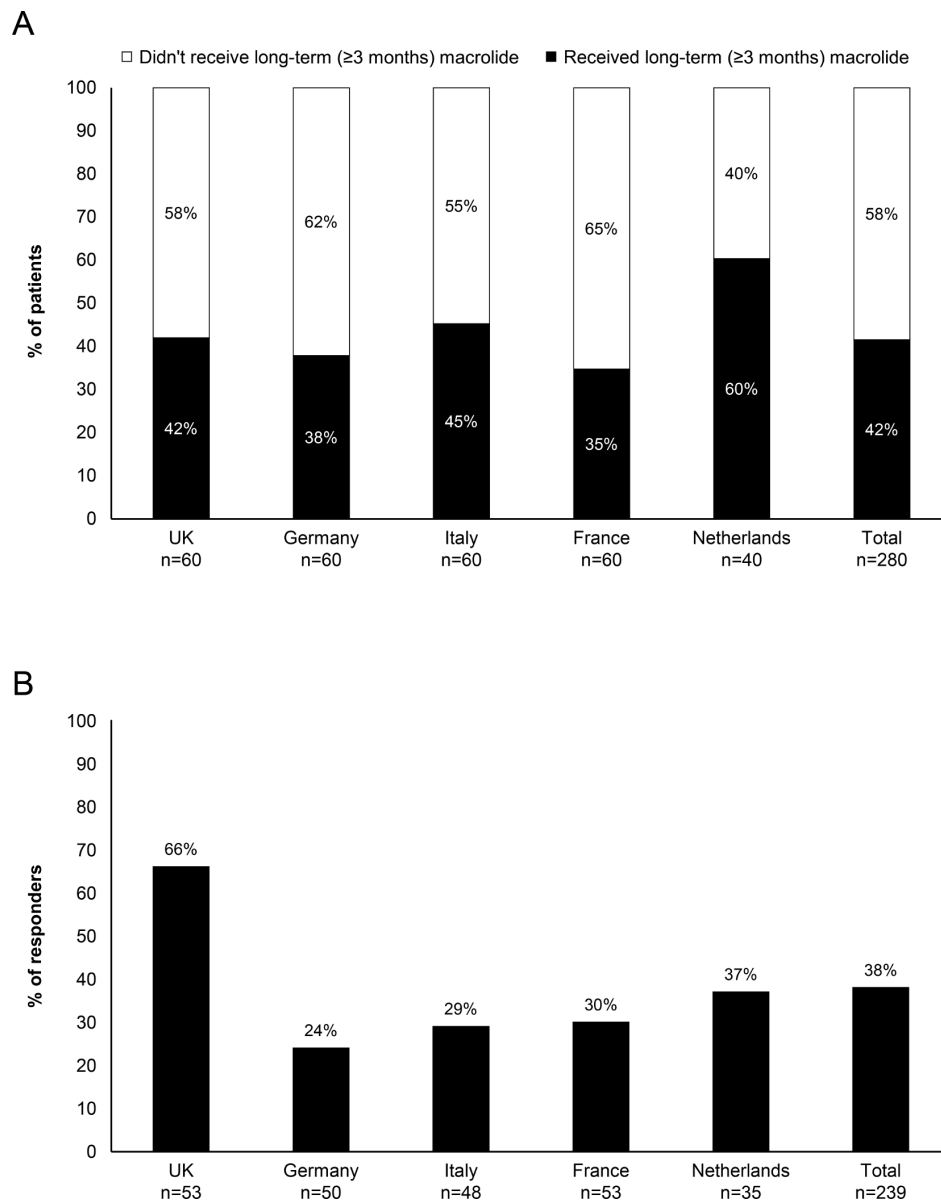


Figure 4 Use of macrolides in patients with bronchiectasis. (A) Prescription of long-term macrolide (eg, clarithromycin, azithromycin) monotherapy (≥ 3 months) to patients with bronchiectasis. (B) Testing for NTM before initiating a macrolide monotherapy for the treatment of bronchiectasis (respondents who did not test for NTM did not answer this question). NTM, non-tuberculous mycobacteria.

beneficial and even reduce the incidence of NTM culture positivity in patients with bronchiectasis who are not yet infected with NTM, as suggested by a study of patients with CF.³⁰

Our survey has several limitations: The sample size of this survey (n=280) is limited relative to the European population; however, there was good regional coverage within countries among the respondents. Moreover, as the information collected on the rate of NTM testing and risk was based on estimates by the responding physicians rather than on data from medical records, this may have resulted in some degree of over and/or under-representation of the real rates of testing and level of risk. Similarly the fact that the physicians received a small incentive for their participation may have resulted

in overreporting of treated patients with bronchiectasis. Our study also did not explore how patients with bronchiectasis or NTM-LD are managed in individual countries, or the severity of bronchiectasis disease in the patients managed by the respondents. This information could help to understand the noted differences between countries, however, further research is needed here.

The results indicate that physicians treating adult patients with bronchiectasis are aware of the association between bronchiectasis and the risk of NTM-LD. The majority of physicians perceive that NTM-LD can lead to severe health consequences, although a minority do not perceive that it can lead to a significant increase in mortality. Testing practices when diagnosing bronchiectasis as well as prior to starting macrolide maintenance

therapy must be improved to be compliant with existing guidelines and improve the care of patients with bronchiectasis.

Acknowledgements IDR Medical (Cheltenham, UK) performed the survey on behalf of the authors. Medical writing support was provided by Christopher Lamb of Physicians World Europe GmbH (Mannheim, Germany).

Contributors All authors contributed to the study design and data analysis, and reviewed and approved the manuscript.

Funding Funding for this study was provided by Insmmed.

Competing interests Jvl: Advisory board member for Insmmed. Supported by a personal grant from the Netherlands organisation for scientific research NOW/ ZonMW (Veni 016.176.024). RvdL: Employee of Insmmed Netherlands BV. MO: Employee of Insmmed Germany GmbH.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as online supplementary information.

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Correction: *Non-tuberculous mycobacterial lung disease in patients with bronchiectasis: perceived risk, severity and guideline adherence in a European physician survey*

Wagner D, van Ingen J, van der Laan R On behalf of the NTM-NET, *et al.* Non-tuberculous mycobacterial lung disease in patients with bronchiectasis: perceived risk, severity and guideline adherence in a European physician survey. *BMJ Open Respiratory Research* 2020;7:e000498. doi: 10.1136/bmjresp-2019-000498.

The name of the co-author of this paper was misspelt. Marko Obradovic is the correct name.

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BMJ Open Resp Res 2020;7:e000498corr1. doi:10.1136/bmjresp-2019-000498corr1

