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The epidemiology of nontuberculous mycobacterial pulmonary disease in the Netherlands

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Abstract

Background
Nontuberculous mycobacteria (NTM) are emerging opportunistic pathogens of humans. Because NTM-PD is not a notifiable disease in Europe, the epidemiology of NTM-PD is not well known. However, the prevalence of NTM-PD is thought to be increasing, particularly in countries where tuberculosis rates have decreased. Here we aim to determine the prevalence of NTM-PD in the Netherlands.

Annual prevalence estimates of NTM-PD in the Netherlands (2012- 2019) were derived from four separate databases, including two drug dispensing databases, an ICD-10 code database and a hospitalization database. Databases covered a fraction of the Dutch population and were extrapolated. In addition, annual NTM-PD prevalence was also estimated by means of a pulmonologist survey.

The estimated annual prevalence of NTM-PD using databases is between 2.3 and 5.9 patients / 100,000 inhabitants. Prevalence estimates derived from the drug dispensing databases, the hospitalization database and the claims database were 2.3, 5.9, 3.5 and 4.5 / 100,000 inhabitants, respectively. The annual prevalence estimated in the pulmonologist survey was between 6.2 and 9.9 / 100,000 inhabitants. The annual prevalence remained stable over the included period.

The estimated annual prevalence of NTM-PD using databases was between 2.3 and 5.9 patients / 100,000 inhabitants. Due to the possible presence of tuberculosis patients and low coverage in one dispensing database, we believe an annual prevalence of between 2.3 and 4.5 patients / 100,000 inhabitants is more probable which still renders NTM-PD a serious health threat. This estimate is lower than the estimate from the pulmonologist survey, indicating physicians likely overestimate prevalence.

Introduction

Nontuberculous mycobacteria (NTM) are opportunistic pathogens of humans. The most frequent manifestation of NTM disease is a chronic pulmonary infection. Depending on host factors, this NTM pulmonary disease (NTM-PD) can be a severe fibro-cavitary disease that resembles pulmonary tuberculosis or can be a milder nodular-bronchiectatic disease. NTM-PD is notorious for its highly complex, toxic and poorly efficacious treatments, where 1.5-2-year courses of three to four antibiotics yield cure rates of 50-60% at best[(1)].
Since NTM-PD is not a notifiable disease anywhere in Europe, the epidemiology of NTM-PD in the region is not well known. Studies in Denmark (period 2000-2010), Scotland (1997-2008), Germany (2014) and The United Kingdom (2006-2016) have produced estimated annual prevalence rates of 2.43, 2.44, 3.3 and 6.4 cases per 100,000 per year respectively[(2-5)]. Another study aimed at determining prevalence in five European countries estimated the prevalence to be 6.2 / 100,000 inhabitants in 2016[(6)]. Like in many countries where rates of tuberculosis infection have decreased, the prevalence of NTM-PD in the Netherlands is thought to be increasing[(7)]. However, the exact prevalence of NTM-PD in the Netherlands is unknown and clinical awareness remains low and therefore patients with suspected NTM-PD may not be subsequently diagnosed and recognised.

By using existing data sources on drug prescriptions and disease registration codes, we wanted to make an estimate of the prevalence of NTM-PD in the Netherlands, in order to determine the scale of the problem and raise clinical awareness, thereby contributing to improved recognition and diagnosis.

Methods

To come to a reliable estimation of the prevalence of NTM-PD in the Netherlands over the time period 2012-2019, we have collated data from pharmacy drug dispensing databases, primary care diagnostic code databases, hospitalization databases and from a survey among pulmonologists.

Drug prescription databases
We accessed two independent drug prescription databases. The first was IQVIA's Real-World Data Longitudinal Prescription database (LRx, Amsterdam, The Netherlands)[(8)]. The LRx-database contains anonymized prescription records from hospital and community pharmacies. Data is included regarding patient characteristics, all dispensed medication (including dose), dispensing pharmacy, date and length of prescription. Overall, approximately 57% of outpatient prescriptions for NTM infections (based specifically on the five NTM-drugs in focus, see table 1), within the Netherlands are included in the LRx database, although coverage was difficult to determine as it differed per included antibiotic in this study. Secondly, The Out-patient Pharmacy Database of the PHARMO Database Network (PHARMO) with a coverage of approximately 28% for outpatient dispensings per year[(9)].

These drug prescription databases we used to define both "probable NTM-PD patients" (three-drug regimen) and "possible NTM-PD patients" (two-drug regimen) based on drug combinations used for NTM-PD treatment, shown in Table 1. Both databases were searched for prescriptions of the drug combinations presented in Table 1, in the 2015-2019 (IQVIA) or 2013-2017 (PHARMO) period, only patients receiving treatment for >30 days were included, as treatment for <30 days was deemed too short for NTM-PD. The IQVIA database was additionally queried for prescriptions of regimens for the most prevalent causative agents of NTM-PD (*M. avium* complex, *M. malmoense* and *M. kansasii*)[(10)].

These regimens included at least two of the following molecules: rifampicin, rifabutin, ethambutol, clarithromycin and azithromycin. Unfortunately, these combinations do not cover the rapidly growing NTM. Prescriptions of clindamycin were used to enable exclusion of patients treated for prosthetic joint infections[11]. All patients with regimens that at one point contained pyrazinamide for >30 days were excluded assuming these were tuberculosis patients. All data is anonymized according to Dutch and European privacy legislation through a trusted third party.

To estimate the overall annual prevalence of NTM-PD infections in the Netherlands, the total number of probable and possible NTM-PD patients was determined using the mean of the Dutch population census (https://opendata.cbs.nl/statline/#/CBS/nl/dataset/37556/table?ts=1581944556208) in 2013-2017 (PHARMO, 17,004,781) or 2015 - 2019 (IQVIA, 17,084,920) as denominator. Prevalence estimates were then corrected for the coverage of the databases, the proportion of NTM-PD patients that remain untreated, estimated from two previous studies (48%), and inability of these drugs to identify the proportion of NTM-PD caused by *M. abscessus* and other rapidly growing NTM (20%)[12-14], an overview of all extrapolations are shown in supplementary Table 1.

Diagnostic codes database

In the Netherlands, health insurance claims are submitted by the treating physician and claimed from the insurance companies by the hospital based on the official diagnosis code (ICD-10), description can be found online (https://www.whofic.nl/familie-van-internationale-classificaties/referentie-classificaties/icd-10). IQVIA's claims database is comprised of the claims submitted to a sub-set of these health insurance companies, representing about a quarter of the Dutch population. The Healthcare insurance claims data contained an anonymous patient ID, claim indication, specialist involved, official diagnosis code (ICD-10) and diagnosis description. In our study we selected all patients with ICD-10 code A31.0 (NTM pulmonary disease code) in the 2012-2016 period, they are referred to as "confirmed NTM-PD patients". These data were used to estimate and annual prevalence of confirmed NTM-PD, using the mean population census from 2012-2016 was used as denominator[12]. Prevalence estimates were then corrected for the limited sensitivity (50%) of ICD-10 codes for NTM-PD seen in previous studies[15].

Hospitalization database

In addition to the previous methods, we calculated the annual prevalence of patients with a hospital admission for NTM-PD (ICD-10 code A31.0) in the period from 2014 to 2017 using the Hospitalization Database of the PHARMO Database Network, extended with data from the Radboudumc Center of Expertise for mycobacterial disease, only patients with a hospital admission requiring hospital stay were included. The overlap between the catchment area of the Hospitalization Database and the catchment area of the NTM Centre of Expertise could not be determined. Therefore, we calculated a conservative and liberal estimate of annual NTM-PD prevalence of patients with a hospital admission for NTM-PD by using either the number of people in the catchment area of hospitals in the PHARMO Database Network (liberal) or total population in the Netherlands (conservative) as denominator for the calculations. Findings were then extrapolated to total NTM-PD prevalence using estimates of NTM-PD hospitalization rate from Germany, approximately 14.7%, based on an annual average of 0.91 hospitalisations per 100,000 population between 2005-2011 and an overall prevalence of NTM-PD of 6.2 / 100,000 inhabitants in 2016[6, 16].

Pulmonologist survey

To assess the clinical perception of the prevalence of NTM-PD, we have performed a survey among pulmonologists in the Netherlands in 2018. The survey was completed via a secure online platform and 154 participants were approached; no reminder was sent. The survey addressed a broader topic

of diagnostic testing for NTM in patients with bronchiectasis and was aimed at hospital-based pulmonologists who had consulted NTM-PD patients and at least 10 patients with bronchiectasis in the previous 12 months[17]. The respondents were asked to estimate the number of patients with NTM-PD they consulted in the previous 12 months. Based on the total number of registered pulmonologists, we estimated the prevalence of patients with NTM-PD. To estimate the NTM-PD prevalence based on expert opinion, we used the 2018 Dutch national population census and the number of registered pulmonologists, as recorded by the Netherlands Society for Pulmonary Diseases and Tuberculosis Physicians (https://www.nvalt.nl). A conservative estimation was calculated by excluding pulmonologist who had treated less than 10 bronchiectasis patients in the previous year assuming they also had not treated NTM-PD patients, and a liberal estimation was calculated by assuming all pulmonologist treated the same number of NTM patients as was indicated by the pulmonologists who were included in the questionnaire study.

Data analysis

Statistical analysis was performed using R version 3.3.3. The prevalence was determined as the total number of individuals in each database per year, divided by the Dutch population in each year (per 100,000) using the Dutch national population census. A 95% CI interval was calculated for each prevalence both before and after extrapolation.

Results

Drug databases

Using the "probable" case definition for NTM-PD treatment, we identified a total of 174 patients with a combination of rifamycin, ethambutol and a macrolide from PHARMO in the study period (2013-2017). From the IQVIA LRx data (2015-2019), we identified 356 patients with a prescription for the triple drug regimen. Using the criteria for "possible NTM-PD" (at least two of the three drugs in the triple drug regimen), the PHARMO and IQVIA database yielded 373 and 430 patients possibly treated for NTM-PD, respectively. The annual prevalence of NTM-PD that required antibiotic treatment using the "probable NTM-PD" and "possible NTM-PD" case definitions of treatment was 0.20 / 100,000 (95%CI 0.14 - 0.26) and 0.64 / 100,000 (95% CI: 0.48-0.80), respectively in the PHARMO database. Using data from the IQVIA LRx database the criteria for "probable NTM-PD" yielded an annual prevalence of 0.42 / 100,000 (95% CI 0.32 - 0.51) while the criteria for "probable NTM-PD" and "possible NTM-PD" yielded an annual prevalence of 0.50 /100,000 (95% CI 0.39 – 0.62). After correction for database coverage, untreated patients and proportion of NTM-PD caused by *M. abscessus*, projected NTM-PD prevalence estimates for a combination of "possible NTM" and "probable NTM" patients were 5.9 / 100,000 (95%CI: 4.9 – 7.0) and 2.3 / 100,000 (95%CI: 1.9 – 2.7) in the PHARMO and IQVIA database, respectively, shown in figure 1.

Diagnostic codes database

In 2015 and 2016, there were 470 patients with the ICD-10 code A31.0 for NTM pulmonary disease in IQVIA's Claims database. Based on the Dutch population in 2015, this corresponds with an annual prevalence of 0.56 / 100,000 (95%CI: 0.42 - 0.70). After correction for database coverage and limited sensitivity of ICD-10 codes this yields an annual projected NTM-PD prevalence of 4.5 / 100,000 (95%CI: 3.3 – 5.6, figure 1).

Hospitalization database

Between 2014 and 2017 there 150 patients in the Hospitalisation Database of the PHARMO Database Network and 86 patients in the Radboudumc center of expertise. This means that there were between 0.4 (95% CI 0.3 – 0.4) and 0.51 (95% CI 0.44-0.58) NTM-PD hospital admissions per 100,000

population per year, using the conservative and liberal estimation methods. Annual prevalence estimates were then extrapolated by correcting for the estimated hospitalization rate, yielding an annual projected NTM-PD prevalence of between 2.4 (95% CI 1.8 – 3.0) and 3.48 (95% CI 3.0 – 4.0) patients per 100,000 inhabitants, shown in figure 1.

Pulmonologist survey
The survey was completed by 66 pulmonologists (42.9% response rate) of which 64 indicated they spent >80% of their time in a clinical setting. Of the remaining 64 pulmonologists, 40 (62.5%) had treated NTM-PD patients and >10 bronchiectasis patients over the past 12 months and were therefore eligible for inclusion in the analysis. In addition, of these 64 pulmonologists, (65%) indicated they had treated NTM-PD cases, with an estimated average of 4 NTM-PD patients per year. The conservative prevalence estimate yielded an annual prevalence of 6.2 / 100,000, while the liberal prevalence estimate was 9.9 / 100,000 (fig 1).

Discussion

This is the first study on NTM epidemiology in the Netherlands using hospital, pharmacy and diagnostic codes databases as well as a physician survey; the extrapolated prevalence estimates of each database query and the survey are shown in figure 1. Overall, we estimate the mean annual prevalence to be between 2.3 and 5.9 / 100.000 inhabitants per year. The strength and limitations and the overall conclusion of each of the approaches are summarized in table 2.

Using the drug dispensing databases of both the PHARMO institute and IQVIA we recorded 0.64 (95% CI: 0.48-0.80) and 0.50 (95% CI 0.39 – 0.62) patients per 100,000 inhabitants per year receiving NTM-PD treatment applying the lenient definition thereof. However, both databases underestimate prevalence as they do not cover all pharmacies within the Netherlands and drug prescription databases only detect patients receiving treatment with the predefined antibiotics. To estimate the projected prevalence of NTM-PD in the Netherlands, we extrapolated our findings using database coverage data, inclusion of untreated NTM-PD patients and inclusion of *M. abscessus* patients. Based on the respective coverage percentages of both databases and acknowledging low compliance with guidelines [(14)],the number of patients receiving the “possible NTM-PD” and “probable NTM-PD” definitions of NTM-PD treatment was extrapolated. In addition, previous studies have shown that for a significant portion of NTM-PD patients the decision is made to not treat

We corrected for untreated patients (48%, average of findings in previous studies) and M. abscessus/rapid growers (20% of NTM-PD caseload in most EU countries)[(10, 12-14)] amounting to a total projected mean annual NTM-PD prevalence of 5.9 / 100,000 (95%CI: 4.9 – 7.0) and 2.3 / 100,000 (95%CI: 1.9 – 2.7) for PHARMO and the IQVIA LRx database, respectively. The relatively large difference in prevalence estimated from each drug database is likely due to two factors. First, within the IQVIA database, patients simultaneously receiving pyrazinamide treatment were excluded, as these are likely tuberculosis patients and not NTM-PD. Due to the absence of data on pyrazinamide use this was not possible in the PHARMO database. Therefore, the relatively small amount of tuberculosis patients receiving ethambutol treatment for >30 days likely remain within our selection, leading to an overestimation of NTM-PD patients. The second being the difference in coverage between the two databases. Overall, the IQVIA database has a much higher coverage, meaning extrapolation likely introduces less error. In addition, coverage of certain areas within the Netherland differs between each database, possible influencing prevalence estimates, and although the total period included for each database is equal (5 years), the specific years included differs meaning estimates can be influenced by annual fluctuations in prevalence.

Based on the diagnostic codes database the annual prevalence of the ICD-10 code A31.0 for NTM-PD after correction for coverage and low sensitivity of ICD-10 codes was at 4.5 / 100,000 (95%CI: 3.3 – 5.6)[15]. While extrapolation of Dutch hospitalization rates to total NTM-PD prevalence amounted to an annual prevalence between 2.4 (95% CI 1.8 – 3.0) and 3.5 (95% CI 3.0 – 4.0) patients per 100,000 inhabitants. However, due to the possible presence of tuberculosis patients and relatively low coverage of dispensing pharmacies in the Netherlands, the PHARMO institute dispensing database estimate is likely less reliable than the others. Therefore, the lower estimates of mean annual prevalence, between 2.3 and 4.5 / 100,000, are deemed more probable.

There are important limitations inherent to assessments of disease prevalence from prescription, disease code and hospitalization databases and physician estimates. Our criteria to query the drug dispensing databases were strict, given the well-known poor compliance (10% in five EU countries) with NTM-PD treatment guidelines[14]. The projections, too, are biased as they were based on studies from other countries and health systems[6, 12, 13, 15-17]. Nonetheless, we do provide a first assessment of NTM-PD annual prevalence in the Netherlands, which is between 2.3 and 5.9 patients / 100,000 inhabitants in the study period. This is in line with previous studies in neighbouring Germany and the United Kingdom[3-6]. We did not see an increase during the studied period. This finding is in line with data from the national database in Denmark that also show a stable prevalence of NTM-PD over a 25-year period but in contrast with multiple studies that claim NTM-PD prevalence is increasing[1, 3-5, 16, 18]. National surveillance of NTM-PD would be valuable to better characterize disease burden over time. Laboratory-based surveillance could be a first step and has been successfully implemented before.[19] A previous lab-based prevalence estimate of NTM-PD in the Netherlands found an annual prevalence of 5.5 patients per 100,000 inhabitants.[6] This finding falls within the 2.3 and 5.9 patients / 100,000 prevalence estimate but is slightly higher than the more probable estimate of between 2.3 and 4.5 / 100,000.

In conclusion, after extrapolation of data retrieved from each database the estimated annual prevalence of NTM-PD using databases is between 2.3 and 5.9 patients / 100,000 inhabitants, as shown in figure 1. However, due to the possible presence of tuberculosis patients and relatively low coverage of dispensing pharmacies in one dispensing database, a prevalence of between 2.3 and 4.5 / 100,000 is deemed more probable. This is lower than the annual prevalence estimated in the pulmonologist survey, which was between 6.2 and 9.9 / 100,000 inhabitants annually, indicating physicians likely overestimate prevalence. Our databases show that annual prevalence remains relatively stable over the period included in our survey. This disease prevalence does show that we need to increase effort to understand this disease, its risk factors and optimize its treatment.

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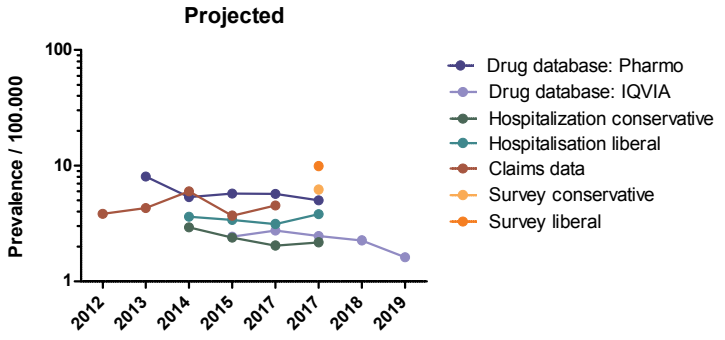
Figures and Tables

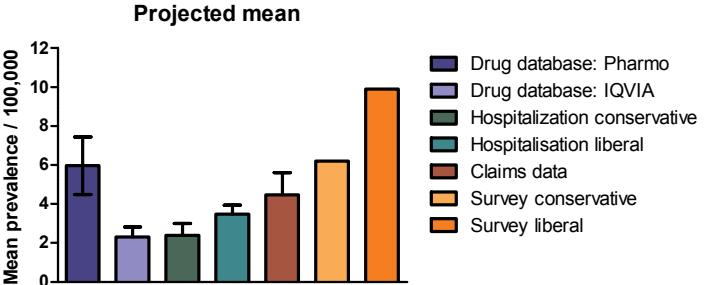
Table 1 - NTM-PD treatment definitions

Definition of Likelihood of NTM-PD treatment	Drug combination
Probable	Rifampicin-ethambutol-azithromycin
Probable	Rifampicin-ethambutol-clarithromycin
Probable	Rifabutin-ethambutol-azithromycin
Probable	Rifabutin-ethambutol- clarithromycin
Probable	Clofazimine-ethambutol-azithromycin
Probable	Clofazimine-ethambutol- clarithromycin
Possible	Rifampicin-ethambutol
Possible	Rifampicin-azithromycin
Possible	Rifabutin-clarithromycin
Possible	Rifabutin-ethambutol
Possible	Rifabutin-azithromycin
Possible	Rifabutin-clarithromycin
Possible	Ethambutol-azithromycin
Possible	Ethambutol-clarithromycin

Table 2 - Overview of data sources, outcomes, strengths and limitations

Data source	Estimated prevalence / 100,000 (95% CI)	Range conservative-liberal / 100,000	Major strength of this approach	Major limitation of this approach	Overall conclusion
Pharmacy dispense data: antibiotics specific for NTM-PD treatment	**IQVIA** *2.3 (1.9 – 2.7)* **PHARMO** 5.9 (4.9 – 7.0)	N/a	These antibiotics are specific for NTM-PD, so the data is reliable.	Not all antibiotics that are used for NTM-PD are included. However, the indication of the other AB is not specific enough to use in this context.	Likely underestimation, because for many NTM-PD patients not treatment is initiated and not all NTM-PD antibiotics were included.
Healthcare insurance data: ICD-10 codes	4.5 (3.3 – 4.6)	N/a	ICD-10 codes are specific for NTM-PD and therefore reliable.	Previous studies have shown that ICD-10 codes have limited sensitivity when detecting NTM-PD cases as the ICD-10 code for NTM-PD is often not assigned.	Likely underestimation, because many patients are not assigned the ICD-10 code for NTM-PD.
Hospitalisation data: based on ICD-10 codes	3.5 (3.2 – 4.0)	2.4 – 3.5	ICD-10 codes are specific for NTM-PD and therefore reliable.	The majority of patients with NTM-PD are never hospitalized.	Likely underestimation, as outpatient treatment is not represented.
Expert opinion: pulmonologists estimating number of patients with bronchiectasis and NTM-PD under their responsibility	6.2	6.2 – 9.9		Vert subjective, can be biased by personal experience of pulmonologist. Lower estimate does not account for NTM-patients treated by pulmonologist that see < 10 bronchiectasis patients while upper estimate likely over extrapolated as physicians treating less bronchiectasis patients likely also treat less NTM-PD	Overestimation.


Projected
Prevalence / 100.000
100
10
1
2012
2013
2014
2015
2017
2017
2018
2019
Drug database: Pharmo
Drug database: IQVIA
Hospitalization conservative
Hospitalisation liberal
Claims data
Survey conservative
Survey liberal


Projected mean
Mean prevalence / 100,000
12
10
8
6
4
2
0
Drug database: Pharmo
Drug database: IQVIA
Hospitalization conservative
Hospitalisation liberal
Claims data
Survey conservative
Survey liberal

Supplementary Table 1 – an overview of all extrapolation data used and reasoning behind their use.

	IQVIA	PHARMO	Hospitalization	Claims	Explanation
Database coverage estimates	57%	28,3	N/a	N/a	Coverage of database as reported by each company.
Percentage untreated patients	48%	48%	N/a	N/a	Percentage of NTM-PD patients not treated with antibiotics determined as the average of previous differing findings in Germany and the UK[12-13].
Percentage NTM-PD treatment not captured	20%	20%	N/a	N/a	Patients receiving treatment for rapidly growing NTM are not captured in included regimens. Proportion of NTM-PD patients with rapidly growing NTM based on previous estimates in 5 European countries[14].
Percentage of patients hospitalized	N/a	N/a	14.7%	N/a	The percentage of patients hospitalized is extrapolated from findings in Germany. Where two studies showed a hospitalization rate of 0.91 / 100,000 (2005-2011) and disease prevalence of 6.2 / 100.000 (2016)[6,16].
Sensitivity of ICD-10 codes	N/a	N/a	N/a	50%	Sensitivity of ICD-10 coding was based on previous findings specific to ICD-10 code A31.0 (NTM-PD) in the US[15].