Burden of non-tuberculous mycobacterial pulmonary disease in Germany

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Newly diagnosed NTM-PD causes substantial healthcare costs and has high mortality
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ABSTRACT The objective of this study was to estimate the burden of disease in incident patients with non-tuberculous mycobacterial pulmonary disease (NTM-PD).

A sample of 7 073 357 anonymised persons covered by German public statutory health insurances was used to identify patients with NTM-PD. In total, 125 patients with newly diagnosed NTM-PD in 2010 and 2011 were matched with 1250 control patients by age, sex and Charlson Comorbidity Index, and followed for 39 months.

The incidence rate for NTM-PD was 2.6 per 100 000 insured persons (95% CI 2.2–3.1). The mortality rate for patients with NTM-PD and the control group in the observational period was 22.4% and 6%, respectively ($p<0.001$). Mean direct expenditure per NTM-PD patient was €39 559.60 (95% CI 26 916.49–52 202.71), nearly 4-fold (3.95, 95% CI 3.73–4.19) that for a matched control (€10 006.71, 95% CI 8907.24–11 106.17). Hospitalisations were three times higher in the NTM-PD group and accounted for 63% of the total costs. Attributable annual direct costs and indirect work-loss costs in NTM-PD patients were €9093.20 and €1221.05 per control patient, respectively. Only 74% of NTM-PD patients received antibiotics and nearly 12% were prescribed macrolide monotherapy.

Although NTM-PD is considered rare, the attributable mortality and financial burden in Germany are high. Efforts to heighten awareness of appropriate therapy are urgently needed.

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Introduction

Non-tuberculous mycobacteria (NTM) have been isolated worldwide and comprise more than 160 validly described species, partly divided into several subspecies [1]. Pulmonary disease due to NTM (NTM-PD) is a rare, chronic and slowly progressive disease; patients present mostly with cavitary lesions and/or nodules and bronchiectasis [2]. The development of NTM-PD from inapparent infection to clinical manifestation is, aside from underlying genetic factors and the virulence of the NTM pathogen [3], predisposed by inflammatory lung diseases. In particular, cystic fibrosis, bronchiectasis and chronic obstructive pulmonary disease (COPD) are responsible [4, 5]. The diagnosis of NTM disease requires the combination of a patient's symptoms, radiographic findings and microbiological criteria, *e.g.* two or more sputum cultures for well-described respiratory pathogens such as *Mycobacterium avium* complex, *M. kansasii* or *M. abscessus* [6, 7]. Because NTM-PD is debilitating in the long term due to lung damage, the need for treatment should be carefully evaluated and it is recommended that patients receive a pathogen-adapted treatment with a multidrug regimen over a period of at least 12 months after sputum culture conversion [6, 8].

The incidence of NTM-PD is considered to be on the increase worldwide. In Oregon, USA, the incidence of NTM-PD increased from 4.8 per 100 000 in 2007 to 5.6 per 100 000 population in 2012 [9]. In a study of notified NTM-PD cases in Queensland, Australia, the incidence rose from 2.2 in 1999 to 3.2 in 2005 per 100 000 persons at risk [10]. Shah *et al.* [11] observed an increase in pulmonary NTM isolates from 4.0 per 100 000 in 2007 to 6.1 per 100 000 in 2012 in England, Wales and Northern Ireland. Ringshausen *et al.* found a significant increase of 5.9% per year in overall age-adjusted NTM-PD-associated hospitalisations in Germany [12]. However, estimates of the cost of treatment for patients with newly diagnosed NTM-PD are currently not available for any European country.

The objective of the current study was to estimate the burden of illness associated with newly diagnosed (incident) NTM-PD in Germany, with a follow-up of 3 years after the first quarter in which the diagnosis was made.

Methods

Setting and data collection

This study was a population-based cohort study with a nested case–control design based on administrative data from more than 80 German company statutory health insurances (SHI). Privately insured patients are not included in this database. The German health claims database used comprises anonymised billing data from longitudinally linked records of 7 073 357 members. Patients with NTM-PD were identified based on the International Classification of Diseases German Modification (ICD-10 GM) code A31.0. Because in Germany patient data are pooled and transferred to the SHI on a quarterly basis, patients classified as having newly diagnosed NTM-PD were identified in the years 2010 and 2011 and tracked over 3 years after the first (index) quarter in which A31.0 was coded.

Patients were classified as having incidental NTM-PD if they met the following criteria: 1) at least one medical claim with a documented ICD-10 GM code A31.0 as an inpatient or, to avoid clerical errors as suggested by the German coding guidelines, at least two as an outpatient in 2010 or 2011; and 2) no documented diagnosis code A31.0 in the four quarters prior to the first diagnosis in 2010 or 2011. NTM-PD patients were not considered for inclusion in the analysis if data were not available either in the four quarters prior to their first diagnosis in 2010/2011 or in the 12 quarters (3 years) after their index quarter, unless they were deceased (figure 1). The incidence rate refers to a total of 4 807 692 members of the database who could be followed comprehensively for that period of 39 months.

In order to calculate the sum of not only all-cause healthcare costs for patients with NTM-PD but also disease-specific incremental costs, which estimate the excess attributable primarily to the presence of NTM-PD, control patients without NTM-PD were randomly assigned an index quarter according to the distribution of index quarters in NTM-PD patients and followed for a total of 39 months, or until death. The control group was matched to the group of NTM-PD patients with regard to age and sex and, given the major impact of a variety of co-existing diseases on the use of medical resources with a high prognostic potential for mortality, in terms of their burden of comorbidity. Therefore, patients' comorbid conditions were measured using the Charlson Comorbidity Index (CCI) score, a claims-based measure of overall disease burden based on the occurrence of at least one of more than 30 comorbid conditions identified using the ICD-10 GM coding manual [13, 14]. Considering that NTM-PD is a rare disease, a 10-to-one matching with NTM-PD patients was run based on age, sex and CCI category for each patient, so that the characteristics of the non-NTM-PD sample were comparable with those of NTM-PD patients (table 1). Some diseases are known to undermine a patient's compliance and/or adherence to treatment or to be extraordinary cost drivers. Therefore NTM-PD patients as well as control patients meeting at least one of the following criteria were *a priori* excluded to avoid potential confounders for seeking and maintaining healthcare or for extensive resource use: Alzheimer's disease (ICD-10 GM code G30–32), dementia (F00–03), delusional

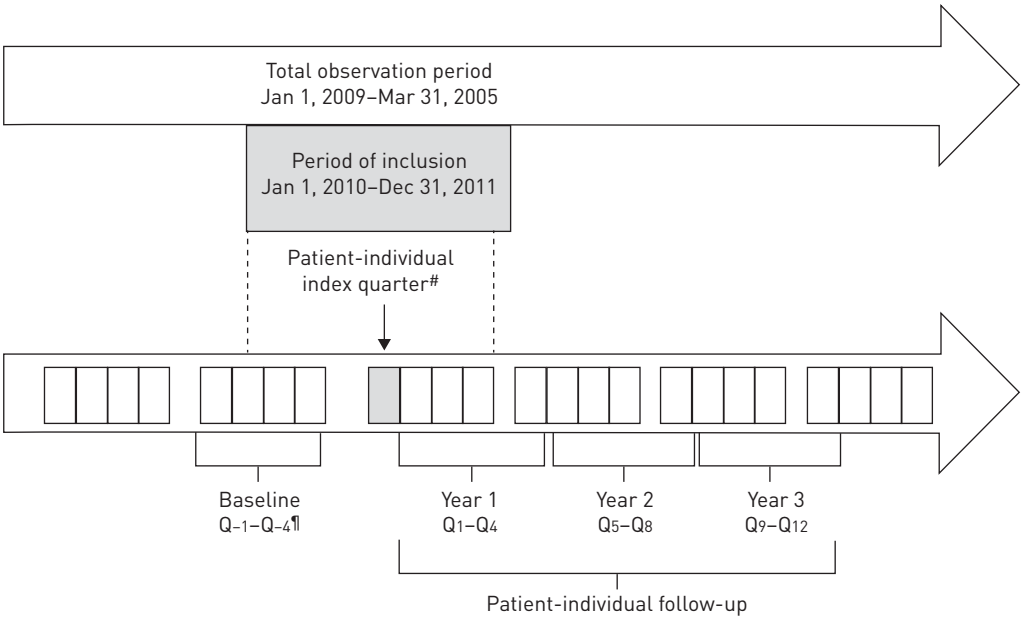

FIGURE 1 Patient-individual observation periods. #: example of a quarter of the first non-tuberculous mycobacterial pulmonary disease diagnosis in 2010/2011; ¶: all quarterly information refers to the patient-individual follow-up period relative to the index quarter.

disorders (F22), severe depression (F32.2, F32.3, F31.4, F31.5, F33.2, F33.3), mental retardation (F71–78), chronic alcohol abuse (F10, K70) or other drug addictions (F11–19), eating disorders (F50), multiple sclerosis (G.35) and haemophilia (D66–68).

Mortality was determined separately between both groups per quarter, yearly and at the end of the study period. We generated a Kaplan–Meier survival plot and used a log-rank test to prove whether the difference in survival times between the NTM-PD and the non-NTM-PD group was statistically significant. Cox regression adjusted to group membership (NTM-PD or non-NTM-PD) was employed to calculate the hazard ratio (HR) of all-cause mortality. Costs over the entire follow-up period were retrieved for six different categories: inpatient care (hospitalisation), outpatient visits and diagnostics, prescribed pharmaceuticals according to German national drug (ATC) codes, remedies, medical aids, and sick pay. In Germany, at the end of continued wage payments by the employer, sick pay is paid out in the SHI as a substitute wage from day 43 of the sick leave according to §44 of the 5th German Social Code (SGB V). Furthermore, drug regimens prescribed for NTM-PD management were analysed.

Calculation of loss of productivity due to NTM-PD (indirect costs)

In accordance with the human capital approach, indirect costs refer to the production loss for the national economy caused by absence from the workplace on sick leave. According to the Hanover Consensus [15], the productivity losses caused by sickness should be evaluated without consideration of differences in the types of jobs, age or sex, with the average gross income from non-self-employed employment as employee compensation. The per-day average productivity loss to cover the self-employed as well is calculated as sick leave days × (gross income from non-self-employed work for the respective year/365 days).

TABLE 1 Patient characteristics for the non-tuberculous mycobacterial pulmonary disease and matched control groups

Variable	NTM-PD group	Control group
Subjects n	125	1250
Age years	49.8 (45.5–54.0)	49.8 (48.4–51.1)
Female	62 (49.6)	620 (49.6)
Male	63 (50.4)	630 (54)
Charlson Comorbidity Index	1.9 (1.5–2.3)	1.8 (1.6–1.9)

Data are presented as mean (95% CI) or n (%), unless otherwise indicated. NTM-PD: non-tuberculous mycobacterial pulmonary disease.

The follow-up time period amounts to a maximum of 39 months. However, the exact calendar years within the observation period in which an individual NTM-PD patient or a matched control was on sick leave were not assessed. As a consequence of the timeline of the research, the cost-generating process (*i.e.* lost working days) could have begun in January 2010 and stretched to April 2013 or could also have stretched into March 2015 if the patient's NTM-PD disease was not diagnosed before December 2011. Moreover, cost data are time-dependent, as per-day employee compensation in Germany increased slightly but continuously between 2010 and 2015 from €96.14 to €108.95 (see table S1 in the supplementary material). Accordingly, we performed a Monte Carlo simulation, running 10 000 first-order simulation trials for each group considering different times of infection, empirical mortality rates, changing cost over time of lost working days, and variance in lost working days per NTM-PD and control patient. The model is described in detail in the supplementary material.

Statistical analysis

Frequency and percentages were reported for categorical variables. For descriptive analyses, mean, standard deviation, 95% confidence interval, median and interquartile ranges (IQR) were reported for all continuous variables. To compare NTM-PD patients and matched controls, appropriate univariate tests (*i.e.* Chi-squared test of independence for categorical variables and the Wilcoxon–Mann–Whitney test for continuous variables) were used. A log-rank test and Cox's regression analysis were performed as described above. Differences were considered significant if the two-sided p-value was less than 0.05. Ratios of the mean (RoM), including 95% confidence intervals, were calculated for continuous outcomes as well as the standardised mean difference (SMD).

All costs are reported in Euros (€) in the respective follow-up year in which they were incurred. Because the base case value of the German diagnosis-related groups' (DRGs) payment system [16] and the point values of the uniform assessment standard (Einheitlicher Bewertungsmaßstab (EBM)) catalogue [17] for outpatient services are continuously adjusted in national budget contracts, a correction according to the medical component of the consumer price index was not required.

Results

After exclusion of 19 of the initial 144 NTM-PD patients due to predefined comorbidities, a total of 125 cases and 1250 matched controls met the study criteria and were included in the analysis. The excluded 19 patients did not differ with respect to age and sex from those 125 deemed eligible ($p>0.05$). The mean age of NTM-PD patients was 49.8 years (95% CI 45.5–54.0), and 50.4% were female (table 1). Incidence rate before exclusion was 3.0 (95% CI 2.5–3.48) per 100 000 insured population at risk. For our 125 included NTM-PD patients the cumulative incidence rate was 2.6 (95% CI 2.16–3.1) per 100 000; 2.67 for men (95% CI 2.05–3.42) and 2.53 for women (95% CI 1.94–3.24) (table 2). Yearly incidence rates were 1.12 (95% Cl 0.87–1.12) in 2010 and 1.48 (95% CI 1.19–1.48) in 2011.

Direct costs

Overall, drug and hospital costs, average duration of hospital stay and average number of hospitalisations were lower for control patients compared with NTM-PD patients.

TABLE 2 Incidence rate of non-tuberculous mycobacterial pulmonary disease for patients included in the study

Age group years	Sex	Patients n	Incidence (95% CI)[#]
<15	Female	8	2.12 (0.92–4.18)
15–65	Female	39	2.40 (1.71–3.28)
>65	Female	15	3.31 (1.85–5.46)
Total	Female	62	2.53 (1.94–3.24)
<15	Male	13	3.32 (1.77–5.67)
15–65	Male	31	1.93 (1.31–2.74)
>65	Male	19	5.24 (3.16–8.18)
Total	Male	63	2.67 (2.05–3.42)
<15	Total	21	2.73 (1.69–4.17)
15–65	Total	70	2.17 (1.69–2.74)
>65	Total	34	4.17 (2.89–5.82)
Total	Total	125	2.60 (2.16–3.10)

[#]: per 100 000 persons at risk. Incidence rate refers to a population of 4 807 692 insured members who could be followed for the entire period of 39 months.

For patients with NTM-PD, the total direct expenditure over the follow-up period was €39 559.60 (95% CI 26 916.49–52 202.71), which was 3.95 (95% CI 3.73–4.19) times the expenditure for a matched control (€10 006.71, 95% CI 8907.24–11 106.17) (table 3). Accordingly, total direct cost attributable to a NTM-PD patient (*i.e.* difference *versus* a matched control) was €29 552.90 (95% CI 24 290.50–34 815.30), or €9093.20 per year.

With the exception of the costs of remedies, technical aids and dialysis (in patients who developed chronic renal failure throughout the observation period), all differences were statistically significant ($p<0.01$ or $p<0.001$) in the respective cost categories.

About 63.2% of the total costs (€18 689.90, 95% CI 15 294.20–22 085.59) could be attributed to costs accrued in the hospital sector. Hospital costs were three times higher in the NTM-PD group (RoM 3.02, 95% CI 2.94–3.11, $p<0.0001$).

On average, NTM-PD patients spent 36.6 more days in hospital during the observation period (table 4). Hospital stays in NTM-PD patients started on average with 14.5 days (95% CI 12.8–16.3) during the quarter of diagnoses and decreased in the following 3 years of follow-up to 10.9 days (95% CI 8.6–13.1) in the first year, 8.9 days (95% CI 6.5–11.4) in the second year, and 5.3 days (95% CI 3.0–7.6) at the end of the third year of follow-up when more than one fifth (22.4%) of patients in the initial NTM-PD cohort had already died.

The major part of the remaining direct total costs were drug costs, accumulating to €6454.7 (95% CI 4209.5–8699.9), which accounted for 21.8% of total direct costs.

On average, NTM-PD patients had nearly 10 additional doctor's appointments (42.1 visits, 95% CI 37.4–46.7) compared with the matched controls (32.4 visits, 95% CI 31.3–33.6) within the 3-year follow-up period, and the frequency of visits to a chest physician was about 12-fold higher (3.8, 95% CI 2.8–4.8, *versus* 0.32, 95% CI 0.24–0.40). Also the number of sick leave days was clearly higher in PNTM patients at 71.2 days compared with 26.6 days, resulting in a mean difference of 44.6 days (95% CI 31.5–57.6).

NTM-PD patients received on average €698.8 (95% CI 223.6–1173.9) more wage compensation than patients in the control group.

Figure 2 presents the costs for each of the main cost categories in the NTM-PD and control groups.

Mortality

Differences in all-cause mortality rates per quarter between the two groups are shown in the Kaplan–Meier curve in figure 3. Of the initial 125 patients in the NTM-PD group, 28 (22.4%) died within the 39-month follow-up period, but only 75 of the initial 1250 patients in the control group died within this period (6.0%; $p<0.0001$, log-rank test). When using Cox's regression and only adjusting for disease group, NTM-PD patients had a nearly fourfold higher risk of death (HR 3.64, 95% CI 2.28–5.77, $p<0.0001$).

Of note, mortality in NTM-PD patients within the first quarter of diagnosis was 10 times higher (3.2% *versus* 0.32%) than that in non-NTM-PD patients in the control group (table 5).

Recently, COPD has been identified as the most frequent pulmonary comorbid cause of death in NTM-PD-related mortality [18, 19]. For that purpose, COPD patients (n=245 218) in the research database were matched with respect to occurrence or non-occurrence of NTM-PD by age, sex and CCI. The mortality rate in those matched COPD patients who had NTM-PD was compared with the rate in patients with COPD but without NTM-PD. In the same observation period, the mortality rate was particularly high in the COPD with NTM-PD group at 41.5% (27 out of 65 patients) but was only 15.9% (62 out of 390) in COPD patients without NTM-PD ($p<0.001$) (figure 4).

Cost due to loss of productivity

The incremental work absence burden for employees with NTM-PD was significantly different from that for matched controls: NTM-PD patients had on average 44.6 (95% CI 31.49–57.64) more sick leave days, or 13.7 days per patient per year ($p<0.001$), and thus were 2.67 (95% CI 2.55–2.81) times more often off work than control patients. As can be seen in table S4 in the supplementary material as a result of our Monte-Carlo simulation, the mean difference in costs attributable to productivity loss per NTM-PD patient compared with control patients was €3968.4±9238.09 in the 39-month period of our study, equivalent to an incremental cost of €1221.05 per year. Annual total direct medical costs amount to €9093.20; work-loss costs in NTM-PD patients are 13.4% of that total.

Notification of sick leave days is generally not provided in a medical certificate for transfer to the employer and to the SHI before 3 days of work absence; thus, short-term disability was not included in that figure.

TABLE 3 Total and incremental (attributable) costs of non-tuberculous mycobacterial pulmonary disease patients compared with matched controls after adjusting for age, sex and Charlson Comorbidity Index scores

	Control group without NTM-PD[#]		Incident NTM-PD patients[¶]		Difference (95% CI)	RoM (95% CI)	p-value[+]	SMD %
	Sum	Mean (95% CI)	Sum	Mean (95% CI)				
Outpatient diagnostic and visiting costs[§]	2 547 747.23	2038.2 (1933.26–2143.14)	345 694.37	2765.55 (2348.16–3182.95)	727.35 (300.93–1153.77)	1.36 (1.34–1.37)	<0.0001	−37.53
Costs of remedies	386 508.3	309.21 (257.43–360.99)	73 430.76	587.45 (303.66–871.23)	278.24 (7.5–563.98)	1.90 (1.67–2.17)	0.34	−27.49
Medical aids costs	413 520.93	330.82 (250.71–410.93)	308 360.53	2466.88 (723.16–4210.61)	2136.06 (407.46–3964.66)	7.46 (5.64–9.46)	0.051	−65.43
Costs of dialysis	137 263.25	109.81 (−22.85–242.27)	84 721.00	677.77 (−663.72–2019.26)	567.96 (−25.08–1161.0)	6.17 (0.41-92-14)	0.39	−17.62
Sick pay costs	523 618.07	418.89 (284.83–552.96)	139 706.54	1117.65 (431.31–1804.0)	698.76 (6.03–1391.49)	2.67 (1.34–5.30)	0.02	−27.06
Hospitalisation costs	4 560 863.73	3648.69 (3053.21–3648.69)	2 792 317.98	22 338.54 (13 294.07–31 383.01)	18 689.85 (9713.75–27 665.95)	6.12 (5.56–6.74)	<0.0001	−101.29
Drug costs (outpatients)	3 938 865.2	3151.09 (2534.76–3767.43)	120 0719.29	9605.75 (6040.61–13 170.9)	6454.66 (1828.42–10 038.37)	3.05 (2.79–3.33)	<0.0001	−52.9
Total costs	12 508 386.71	10 006.71 (8907.24–11 106.17)	4 944 950.47	39 559.6 (26 916.49–52 202.71)	29 552.89 (16 984.84–42 120.94)	3.95 (3.73–4.19)	<0.0001	−103.34

All costs are presented in Euros. NTM-PD: non-tuberculous mycobacterial pulmonary disease; RoM: ratio of the mean; SMD: standardised mean group difference. [#]: n=1250; [¶]: n=125; [+]: two-sided Wilcoxon–Mann–Whitney [§]: outpatient costs comprise reimbursement for outpatient physician's office visits, laboratory diagnostics and imaging.

TABLE 4 Disease-related event numbers for non-tuberculous mycobacterial pulmonary disease patients compared with matched controls

	Control group without NTM-PD[#]		Incident NTM-PD patients[¶]		Difference (95% CI)	RoM (95% CI)	p-value[+]	SMD %
	Sum	Mean (95% CI)	Sum	Mean (95% CI)				
Outpatient treatment cases	40 552	32.44 (31.25–33.63)	5258	42.06 (37.38–46.74)	9.62 (5.59–13.65)	1.30 (1.28–1.31)	<0.0001	−43.86
Outpatient treatment cases (general practitioner)	14 580	11.66 (11.28–12.05)	1670	13.36 (11.97–14.75)	1.70 (0.41–2.99)	1.15 (1.14–1.15)	0.0237	−24.22
Outpatient treatment cases (chest physicians)	399	0.32 (0.24–0.40)	474	3.79 (2.84–4.75)	3.47 (3.09–3.86)	11.88 (11.18–12.62)	<0.0001	−166.71
Inpatient cases	1415	1.13 (1.01–1.25)	428	3.42 (2.71–4.14)	2.29 (1.86–2.73)	3.02 (2.94–3.11)	<0.0001	−96.82
Emergency hospital admissions	484	0.39 (0.34–0.44)	141	1.13 (0.84–1.42)	0.74 (0.55–0.93)	2.91 (2.79–3.04)	<0.0001	−72.88
Sick leave days	33 269	26.62 (22.98–30.25)	8897	71.18 (51.23–91.12)	44.56 (10.25–64.64)	2.67 (2.55–2.81)	<0.0001	−62.72
Sick pay days	10 710	8.57 (5.92–11.22)	3404	27.23 (12.20–42.26)	18.66 (3.55–33.78)	3.18 (2.60–3.89)	0.0137	−35.76
Hospital days	10 035	8.03 (6.84–9.22)	5576	44.61 (31.61–57.60)	36.58 (31.04–42.12)	5.56 (5.27–5.86)	<0.0001	−121.58

NTM-PD: non-tuberculous mycobacterial pulmonary disease; RoM: ratio of the mean; SMD: standardised mean group difference. [#]: n=1250; [¶]: n=125; [+]: two-sided Wilcoxon–Mann–Whitney.

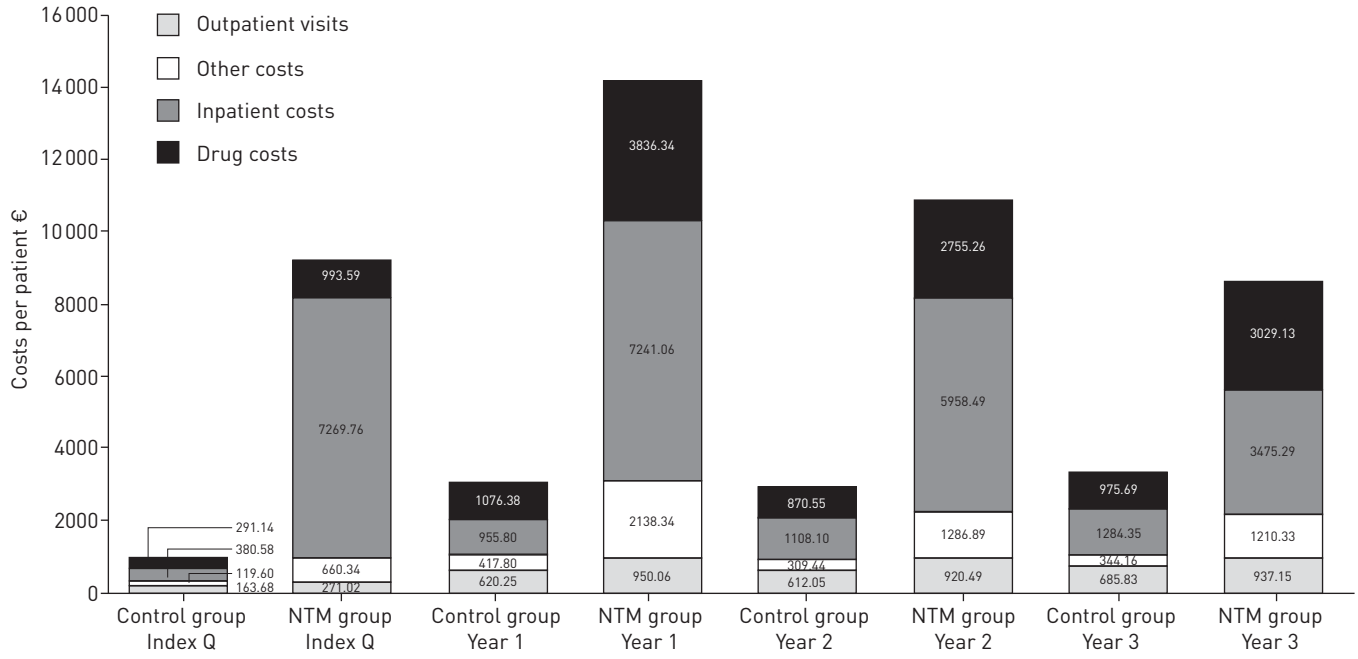

FIGURE 2 Distribution of direct costs separated by main cost types and follow-up years in non-tuberculous mycobacterial (NTM) pulmonary disease and control group patients.

Antibiotic treatment for NTM-PD and associated costs

Of 125 patients with newly diagnosed PNTM, 93 out of 125 (74.4%) received antibiotic therapy of any type during the 3-year follow-up period, but only 68 out of 125 patients (54.4%) had begun treatment at the time of diagnosis, *i.e.* in the quarter of the first NTM-PD diagnosis. Median time between (discharge) diagnosis and therapy initiation was 32 days (IQR 260 days). At any time during follow-up, 29 different drug combinations were prescribed; of those, five regimens were continuously administered over the entire observation period of 39 months (*i.e.* including the quarter in which the diagnosis was retrieved) (table 6). Two of the five continuously prescribed combinations consisted of only two drugs (ethambutol plus clarithromycin or rifampicin). Clarithromycin combined with ethambutol was the most frequently prescribed option in 24 out of 93 (25.8%) of the treated patients, followed by standard treatment clarithromycin plus rifampicin plus ethambutol in 18 out of 93 patients (19.4%) or rifabutin plus ethambutol in 14 out of 93 patients (15.1%). Rifampicin plus ethambutol was continuously administered in 9 out of 93 patients (9.7%).

At least 11 out of 93 patients (11.8%) received monotherapy with clarithromycin for at least two subsequent quarters, indicating that this therapy was administered for treating NTM-PD rather than for treating other respiratory infections. Accordingly, when comparing the frequency of NTM-PD patients receiving a long-term macrolide monotherapy with control patients, the difference (11 out of 125 *versus* 34 out of 1250) was highly significant ($p<0.001$).

Of note, parenteral antibiotics (*e.g.* amikacin, streptomycin, cefoxitin or imipenem) were not prescribed for any NTM-PD patient in the outpatient setting.

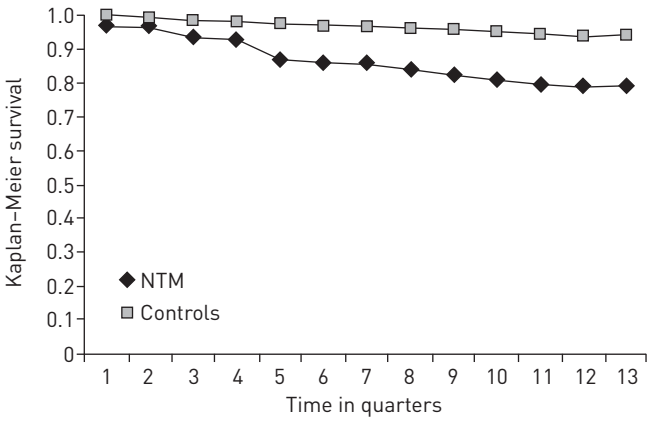

FIGURE 3 Kaplan–Meier curve illustrating the difference in mortality between non-tuberculous mycobacterial pulmonary disease (NTM-PD) and non-NTM-PD patients over a period of 39 months.

TABLE 5 Mortality rates by follow-up years

Group	Time	Patients at risk n	Patients diseased n	Mortality %
Control	Index quarter	1250	4	0.32
	Year 1	1246	25	2.01
	Year 2	1221	21	1.72
	Year 3	1200	25	2.08
	Total	1250	75	6.00
NTM-PD	Index quarter	125	4	3.20
	Year 1	121	12	9.92
	Year 2	109	6	5.50
	Year 3	103	6	5.83
	Total	125	28	22.40

NTM-PD: non-tuberculous mycobacterial pulmonary disease.

Discussion

The objective of this study was to estimate the burden of NTM-PD in Germany in incident patients. This was accomplished by a retrospective observational design comparing medical and productivity-related spending for 125 patients with PNTM to a 1:10 matched comparison group of patients without NTM-PD over a 39-month period. The economic burden attributed to NTM-PD is expected to be great, because it is a chronic disease that can require frequent medical visits, long-term treatment with multidrug regimens and hospitalisations to minimise the risk of further progression.

To date, only a few North American studies have been published presenting detailed cost data for treatment of NTM-PD in a prevalence-based approach: in the US, the total cost for inpatients varied between USD 19 876 [20] (median cost) and USD 37 579 (mean cost) [21] for inpatients, whilst Leber *et al.* [22] reported a median of only CAD 4916 per inpatient in Toronto, Canada.

Mirsaiedi *et al.* [23] calculated an aggregated cost of USD 903 767 292 for 20 048 hospital discharges of NTM-PD patients from 2001 to 2012 in the USA, whereas Strollo *et al.* [24] estimated a mean annual cost of USD 815 million for 86 244 national NTM-PD cases in 2010 alone.

To our knowledge, our study represents the first investigation of healthcare costs brought about by incident NTM-PD and of respective antibiotic prescription patterns in Europe.

Whilst previous studies covered only prevalent costs, our work covers the accumulation of costs that follow diagnosis. These were determined as incremental costs for NTM-PD in excess of those incurred for control patients. Furthermore, it includes, for the first time, both mortality and costs due to lost patient productivity.

In line with the previous studies cited above, we found approximately fourfold higher direct costs in German NTM-PD patients compared with a control group without NTM-PD, and 63% of incremental costs were driven by inpatient stays alone. Despite in-depth analysis, it remains unclear whether the continuously decreasing number of hospital days over the 39 months, from a total 1918 days in the index quarter to 835 days in the third year of observation, is primarily the desired result of successful treatment or, rather, the result of decreasing claims for healthcare services by fewer NTM-PD patients who were still alive.

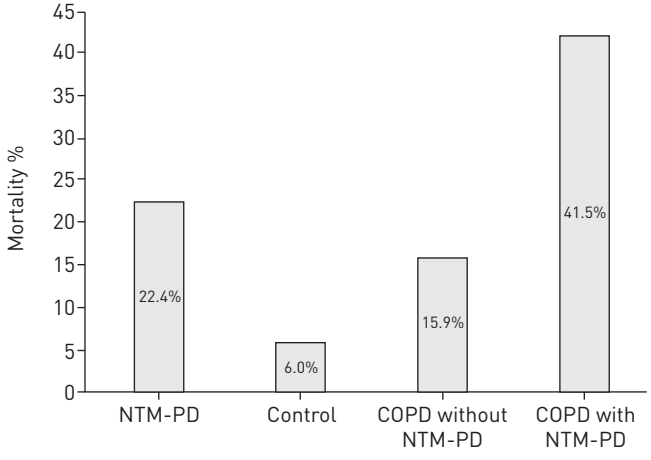

FIGURE 4 Mortality rates among matched non-tuberculous mycobacterial pulmonary disease (NTM-PD), control patients and chronic obstructive pulmonary disease (COPD) patients with and without NTM-PD within 39 months of observation.

TABLE 6 Two- or multidrug regimens prescribed to 93 patients with non-tuberculous mycobacterial pulmonary disease at any time within the total of 13 quarters

NTM-specific drug regimens	Number of quarters prescribed	Number of patients[#]
Azithromycin + rifabutin + ethambutol	13	<5
Clarithromycin + ethambutol	13	24
Clarithromycin + rifabutin + ethambutol	13	14
Clarithromycin + rifampicin + ethambutol	13	18
Rifabutin + ethambutol	13	5
Clarithromycin + rifabutin + prothionamide	11	<5
Clarithromycin + rifabutin	6	10
Clarithromycin + ciprofloxacin	5	<5
Rifampicin + ethambutol	5	9
Rifampicin + isoniazid + ethambutol	5	<5
Moxifloxacin + ethambutol	4	<5
Azithromycin + rifampicin + ethambutol	3	<5
Azithromycin + ethambutol	3	<5
Clarithromycin + moxifloxacin + ethambutol	3	<5
Clarithromycin + prothionamide	3	<5
Clarithromycin + rifampicin	3	5
Moxifloxacin + ethambutol	3	<5
Rifampicin + prothionamide + ethambutol	3	<5
Clarithromycin + ciprofloxacin + ethambutol	2	<5
Clarithromycin + ciprofloxacin + rifabutin	2	<5
Clarithromycin + ciprofloxacin + rifabutin + ethambutol	2	<5
Clarithromycin + levofloxacin + rifampicin + ethambutol	2	<5
Clarithromycin + levofloxacin + ethambutol	2	<5
Clarithromycin + moxifloxacin + rifampicin	2	<5
Clarithromycin + moxifloxacin + rifampicin + ethambutol	2	<5
Clarithromycin + rifampicin + isoniazid + ethambutol	2	<5
Moxifloxacin + rifabutin + ethambutol	2	<5
Levofloxacin + rifabutin + isoniazid + ethambutol	1	<5
Levofloxacin + rifampicin + isoniazid + ethambutol	1	<5

NTM: non-tuberculous mycobacteria. [#]: number of patients does not equal 100% because regimens may have changed from quarter to quarter.

In fact, mortality in our NTM-PD patients was nearly four times higher (3.73%, 95% CI 2.52–5.53) than in the matched patient group without the disease, impressively demonstrating the severity of the disease, and was even higher for NTM-PD patients with associated COPD (6.92%, 95% CI 4.82–9.95). Because mortality was highest at 3.2% within the first 3 months after diagnosis, immediate and appropriate medical treatment should be offered.

However, 25.6% of NTM-PD patients (32 out of 125) did not receive any treatment. In those who were treated, outpatient treatment started with a median delay of 32 days between the date of coding discharge diagnosis to the receipt of an outpatient prescription for drug therapy. A high scatter represented by an interquartile range of 250 days in which 50% of all prescriptions were filled shows that many patients began or continued medical treatment even later.

International guidelines (*e.g.* those described in references [6] and [7]) recommend long-term multidrug treatment until patients achieve 12 consecutive months of negative sputum cultures,. The most recommended treatments mostly comprise a macrolide, rifampicin, and ethambutol, modified according to the phenotypic resistance patterns of the causative strains, if necessary.

Surprisingly, 29 different combinations of drugs were prescribed at least once in the 39 months, and the short number of subsequent intervals in which 23 of the 29 different combinations were prescribed seems to reveal some uncertainty about which basic regimens should be chosen. The most frequently used combination of clarithromycin plus ethambutol alone (used in 26% of the patients) is not sufficient for treatment of NTM-PD, irrespective of the underlying species, and consequently is not recommended in any guideline. Furthermore, a considerable number of patients received an inadequate type of macrolide regimen that could have increased the probability of macrolide resistance during the course of treatment [4] (*i.e.* clarithromycin monotherapy, in 11 out of 93 patients (11.8%), or macrolide plus rifampicin only and/or a macrolide plus a fluoroquinolone) (table 6). No injectable drugs were prescribed in addition to any orally administered drug regimen in outpatients, although this may be indicated in refractory courses of

M. avium Complex-PD and difficult-to-treat species such as *M. abscessus*. Finally, the mortality rate did not differ between those 32 patients who were not prescribed an antibiotic (7 out of 32, 21.9%) and those 93 patients prescribed at least one antibiotic (21 out of 93, 22.6%). Although the sicker patients may have been in the group that started treatment, this observation suggests that medication in the NTM-PD group may have partly been ineffective and thus may have contributed to the poor prognosis within the follow-up period.

Reduced productivity may also have a substantial economic impact on NTM-PD patients: although indirect costs cannot be captured directly from administrative claims, we calculated cost due to absenteeism from work productivity loss by Monte Carlo simulation, which amounted to €1221.05 per NTM-PD patient per year. As this cost is equal to 13.4% of the direct total costs, indirect costs cannot be considered negligible. Because short-term disability with sick leave of <3 days is not captured by the SHI, these costs are probably underestimated in our calculations. Together, annual direct costs of care (€9093.20) plus those indirect costs total €10 314.25 per year from a societal perspective. This figure of societal cost for a NTM-PD patient clearly exceeds the annual per patient cost for many other chronic respiratory diseases, such as COPD (€1013) or asthma (€1950) [25]. When extrapolating the incidence rate of 2.6 per 100 000 (95% CI 2.2–3.1) that we found in our study, on average a total of 2137 (range 1808–2548) newly diagnosed NTM-PD patients per year can be expected in the 2015 German population of 82.2 million [26], and the direct and indirect expenditures attributable to the disease amount to more than €22.04 million (range €18.65–€26.28 million).

Our analysis was limited by several factors. First, we only followed NTM-PD patients for 3 years after the index quarter in which diagnosis was assured and thus did not capture the long-term burden of the disease. Accordingly, future studies of the long-term costs of NTM-PD are warranted. Second, other costly comorbid conditions that were not accounted for *via* the CCI in the matching processes might have influenced the cost burden estimates. Whilst the CCI also addresses COPD and bronchiectasis comorbid conditions, cystic fibrosis is not included. However, because only one patient with both NTM-PD and cystic fibrosis was found in our database in 2010/2011, an overestimation of cost burden due to cystic fibrosis alone appears to be unlikely. Third, although the pool of insured persons from which our sample of NTM-PD patients and their controls were taken was large at more than 7 million, our patients were not formally selected as part of a representative sample. Thus, it is not certain whether our results are generalisable to the entire German population. Nevertheless, the database used has been shown to be representative of the German population in terms of measures of morbidity, mortality and drug usage [27]. Fourth, classification of NTM-PD patients is based on correct diagnostic coding and may thus lead to potential selection bias with unknown NTM-PD cases in the control group that could have affected the cost estimates in favour of the control patients. Accordingly, our approach of billing data may have resulted in an underestimate of the true costs associated with NTM-PD. Therefore, to address concerns of possible underestimation in our outcomes, a validation cohort study assessing the sensitivity and specificity of the ICD-10 code "A31.0" by investigating a random selection of a large number of inpatient medical records should be undertaken in the near future.

Nevertheless, our results not only demonstrate that per patient spending on NTM-PD is high but also suggest that treatment is not based on guidelines in a considerable proportion of cases; thus, appropriate and early guideline-based treatment of NTM-PD may both lower mortality and reduce costs. Improving and expanding the information available about guideline-based treatment options may lead to more effective treatment choices and help to avoid rapid progression of the disease.

Conclusions

Although NTM-PD is considered a rare disease, the attributable mortality and the financial burden in Germany are substantial. Efforts to manage NTM-PD costs may be directed to reducing hospitalisation expenditures, which were the main cost drivers. Providing early and effective therapeutic interventions that can prevent disease progression related to NTM-PD can potentially further reduce the associated economic burden of NTM-PD. Therefore, changes in treatment protocols toward guideline-based treatment are urgently required.

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