INT J TUBERC LUNG DIS 17(6):836–841
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http://dx.doi.org/10.5588/ijtld.12.0843

Geographical distribution and clinical relevance of non-tuberculous mycobacteria in Croatia

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SUMMARY

SETTING: The clinical relevance of non-tuberculous mycobacteria (NTM) in Croatia is unknown.

OBJECTIVE: To estimate the isolation rate of NTM, record geographical differences and assess the burden of pulmonary NTM disease in Croatia.

DESIGN: Nationwide retrospective cohort study of all Croatian residents with NTM isolated by culture in the period from 2006 to 2010. Microbiological criteria of the American Thoracic Society were used to establish a laboratory-based case definition of possible and probable NTM disease.

RESULTS: Of 1187 individuals with pulmonary NTM isolates, 8.6% met the possible and 5.5% met the probable disease criteria. We estimated an annual incidence of probable pulmonary NTM disease of 0.23 per 100 000 population. This estimated annual incidence was 0.35/100 000 in the coastal region and 0.17/100 000 in the continental region. Species distribution differed between coastal and continental Croatia. NTM isolation frequency increased over the study period.

CONCLUSION: Geography plays an important role in NTM species distribution and possible disease. The overall burden of NTM pulmonary disease in Croatia is still low compared to that of tuberculosis, but it is higher in the coastal region compared to the continental region.

KEY WORDS: atypical mycobacteria; epidemiological study; geographical diversity; pulmonary NTM disease

NON-TUBERCULOUS mycobacteria (NTM) encompass all *Mycobacterium* species other than *Mycobacterium tuberculosis* complex and *M. leprae*. There are currently more than 140 species of these environmental, mostly opportunistic pathogens.[1] These organisms have recently attracted growing attention, due to increases in the isolation frequency of NTM.[1–5] This increase is thought to be most pronounced in countries where the incidence of tuberculosis (TB) is declining.[1,6] The exact epidemiology of pulmonary NTM disease has been difficult to determine because reporting is not mandatory in most countries and identification of true disease is often difficult.[1,7] Laboratory-based surveillance may be the most cost-effective method for estimating the NTM disease burden over time.[8,9]

A systematic review of NTM epidemiology as well as an estimation of the disease burden in countries with an intermediate TB burden, such as Croatia,[10] are lacking. In the current study, we have aimed to calculate the population-based frequency of NTM, examine geographical differences in species distribution and estimate the burden of pulmonary NTM disease in Croatia.

METHODS

Study design

We conducted a retrospective cohort study using laboratory data on all Croatian residents with NTM isolated from respiratory samples by culture in the period from 2006 to 2010. Gastric lavage was excluded from further analysis. Only one isolate per individual was taken into account when calculating NTM isolation rate frequency. For disease incidence, we only took into account the first time that the defined disease criteria were met. For individuals meeting those criteria, we looked into the data from the year 2005 to exclude those with previously isolated NTM from disease incidence calculation. If multiple NTM species were cultivated from samples of one individual, each species was counted as a separate isolate.

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Article submitted 31 October 2012. Final version accepted 15 January 2013.

Data collection

In Croatia, all NTM isolates are sent to the National Reference Laboratory (NRL) in Zagreb for identification. We obtained information on every Croatian resident with NTM isolated in the study period from the archive of the NRL. For each isolate, we recorded the patient's age, address, zip code, specimen collection date and source and the NTM species isolated. Using the zip code, patients were grouped into two larger areas according to the proximity of the sea, into coastal and continental regions of Croatia. The Croatian population data, which included population by region, age and sex, were obtained from the statistical office of the European Union (Eurostat)[11] and were used for crude and age-standardised (European standard population) rate estimations.

Identification of non-tuberculous mycobacteria

All NTM were identified by molecular methods (GenoType® CM/AS; Hain Lifescience GmbH, Nehren, Germany) supplemented with phenotypic methods, using previously published guidelines.[12] NTM unidentifiable to species level were sent to a Supranational Reference Laboratory (Forschungszentrum Borstel, Germany or Emerging Pathogens Institute, Milan, Italy) for further identification by 16S rRNA gene sequencing.

Pulmonary non-tuberculous mycobacteria disease case definition

Due to the lack of clinical data, we used the American Thoracic Society (ATS) and Infectious Diseases Society of America (IDSA) microbiological criteria[1] to establish a laboratory-based case definition of probable, possible and unlikely NTM disease. We defined possible NTM disease as two positive sputum samples or one positive bronchoalveolar lavage (BAL) or brush. Probable NTM disease was defined as more than two positive sputum samples or one positive BAL/brush and one or more positive sputum samples.

Data analysis

Microsoft Excel (Microsoft, Redmond, WA, USA) was used to calculate frequencies, percentages, median age, and crude and standardised rates. The χ^2 and χ^2 test for trend as well as rate comparisons were done using MedCalc (MedCalc Software, Ostend, Belgium).

RESULTS

During the study period, the total number of samples of pulmonary origin sent to the NRL for analysis decreased from 57 209 samples in 2006 to 42 223 in 2010. The total numbers of all isolated *Mycobacterium* spp (TB and NTM combined), as well as the number of NTM isolates of pulmonary origin, are shown in Figure 1. The average population of Croatia during the study period was 4 437 538, two thirds of whom were living in the continental region.

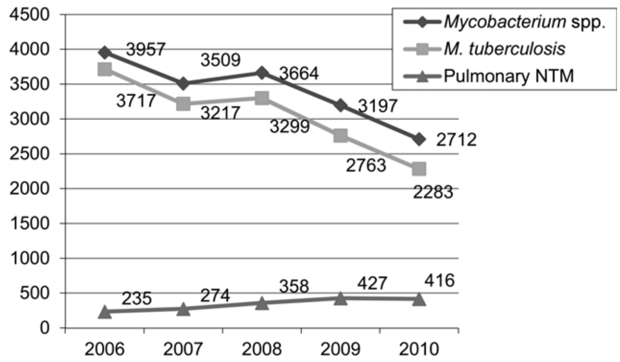

Figure 1 Total number of *Mycobacterium* spp., *M. tuberculosis* and pulmonary NTM isolates submitted to the National Reference Laboratory during the study period. NTM = non-tuberculous mycobacteria.

Pulmonary isolates

The NRL identified a total of 1710 pulmonary NTM isolates of 24 species from 1187 individuals, among whom *M. gordonae* was the most frequent isolate, followed by *M. xenopi*, *M. fortuitum*, *M. terrae* and *M. avium* (Table 1). Over 80% of all NTM isolates originated from patients in continental Croatia (Table 1). The species distribution differed between coastal and continental Croatia: *M. vaccae* (P = 0.05), *M. terrae* ($P < 0.001$), *M. fortuitum* (P = 0.012), *M. gordonae* ($P < 0.001$) and rapidly growing mycobacteria (RGM) as a group ($P = 0.003$) were significantly more frequent in continental Croatia, while *M. xenopi* ($P < 0.001$), *M. lentiflavum* ($P < 0.001$) and *M. avium* ($P < 0.001$) were associated with the coastal region (Figure 2).

Of 1187 patients with NTM isolates, 59% were men and 41% were women, with median ages of 64 and 66 years, respectively. *M. avium* was found more often in women ($P = 0.031$), while *M. xenopi* appeared to be less common in women than in men ($P = 0.002$; Table 1). Among patients aged >50 years, NTM isolation rates were significantly higher in men than in women ($P < 0.001$; Figure 3). After age stratification, the increasing trend of NTM isolation incidence was observed in the population aged >50 years living in the continental region of Croatia (data not shown). The annual isolation frequency of the most common NTM species (⩾30 individual isolates in a 5-year period) is shown in Figure 4.

Pulmonary disease

The most frequently isolated NTM species that met the defined microbiological criteria for probable or possible disease are shown in Table 1. Of 1187 patients with NTM pulmonary isolates, respectively 102 (8.6%) and 65 (5.5%) met the possible and probable disease criteria. The demographic characteristics of these two groups are shown in Table 2. Whereas *M. xenopi* disease was seen most frequently, clinical relevance (i.e., the percentage of patients meeting the

Table 1 NTM isolation frequency in Croatia according to geographic region, sex and microbiological criteria

		Geographic region		Sex		Microbiological criteria		
NTM species	Total *n* (%)	Continental *n* (%)	Coastal *n* (%)	Female *n* (%)	Male *n* (%)	Probable disease *n* (%)*	Possible disease *n* (%)*	Unlikely disease *n* (%)*
M. gordonae	509 (42.9)	437 (45.5)	72 (32)	219 (45)	290 (41.5)	5 (7.7)	29 (28.4)	475 (46.6)
M. xenopi	184 (15.5)	108 (11.2)	76 (33.8)	57 (11.7)	127 (18.2)	21 (32.3)	26 (25.5)	137 (13.4)
M. fortuitum	136 (11.5)	121 (12.6)	15 (6.7)	48 (9.9)	88 (12.6)	3 (4.6)	16 (15.7)	117 (11.5)
M. terrae	93 (7.8)	89 (9.3)	4 (1.8)	47 (9.7)	46 (6.6)	0	4 (3.9)	89 (8.7)
M. avium	42 (3.5)	23 (2.4)	19 (8.4)	24 (4.9)	18 (2.6)	14 (21.5)	10 (9.8)	18 (1.8)
M. abscessus	30 (2.5)	26 (2.7)	4 (1.8)	13 (2.7)	17 (2.3)	3 (4.6)	5 (4.9)	22 (2.2)
M. intracellulare	23 (1.9)	16 (1.7)	7 (3.1)	10 (2)	13 (1.9)	8 (12.3)	1 (1)	14 (1.4)
M. kansasii	10 (0.8)	6 (0.6)	4 (1.8)	4 (0.8)	6 (0.9)	4 (6.2)	1 (1)	5 (0.5)
Other NTM	159 (13.5)	135 (14)	24 (10.7)	65 (13.3)	94 (13.4)	7 (10.8)	10 (9.8)	142 (13.9)
Total	1186 (100)	961 (100)	225 (100)	487 (100)	699 (100)	65 (100)	102 (100)	1019 (100)
Probable disease*	65 (100)	33 (51)	32 (49)	31 (47.7)	34 (52.3)			
Possible disease*	102 (100)	77 (75.5)	25 (24.5)	44 (43.1)	58 (56.9)			
Unlikely disease*	1019 (100)	851 (83.5)	168 (16.5)	412 (40.4)	607 (59.6)			

* Possible disease: two positive sputum samples or one positive BAL or brush. Probable disease: more than two positive sputum samples, one positive BAL/brush and one or more positive sputum samples.
NTM = non-tuberculous mycobacteria; BAL = bronchoalveolar lavage.

criteria for either possible or probable disease, per species) was higher for *M. intracellulare* (9/23; 60.9%), *M. avium* (24/42; 57.1%), *M. kansasii* (5/10; 50%) and *M. lentiflavum* (2/5; 40%). Of the RGM, *M. abscessus* was noted as having the highest clinical relevance (8/30; 26.7%). Taking into account only those isolates that met the probable disease criteria, the clinical relevance was highest for *M. kansasii* (4/10; 40%), *M. intracellulare* (8/23; 34.8%), *M. avium* (14/42; 33.3%) and *M. xenopi* (21/184; 11.4%). The clinical relevance of *M. gordonae* isolates was low, with only 1% of all patients with *M. gordonae* isolates meeting the criteria for probable disease.

The overall estimated age-standardised annual incidence of pulmonary NTM disease amounts to 0.60 per 100 000 population. Taking into account only the

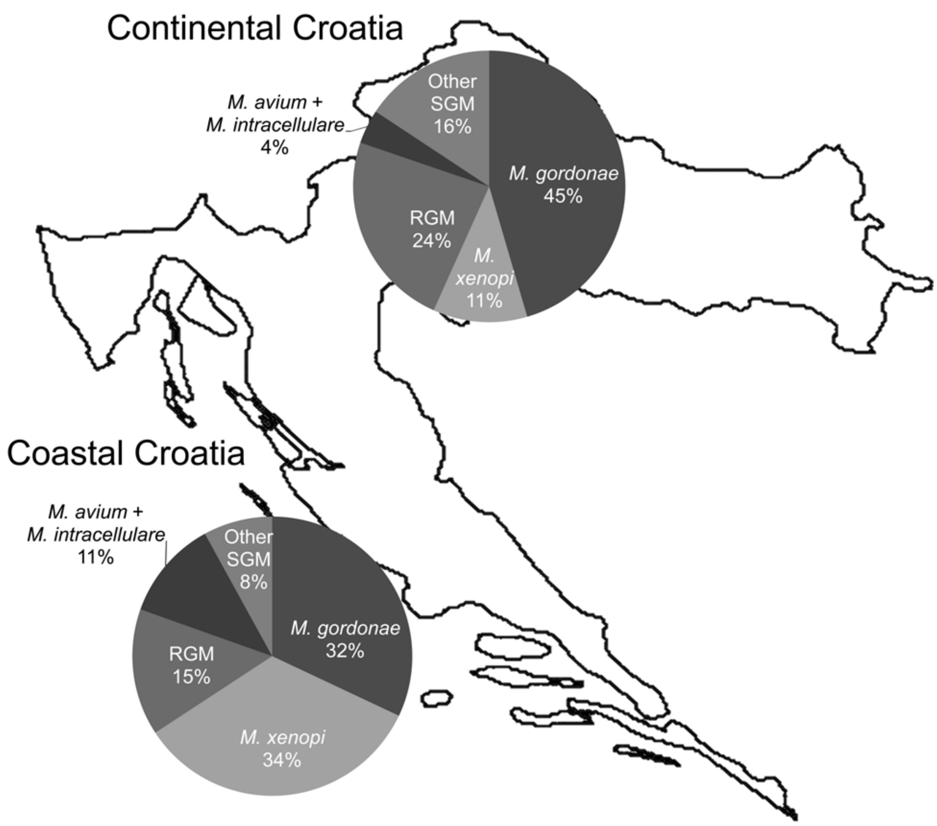

Figure 2 Distribution of NTM species isolated from pulmonary samples in the coastal and continental regions of Croatia. NTM = non-tuberculous mycobacteria.

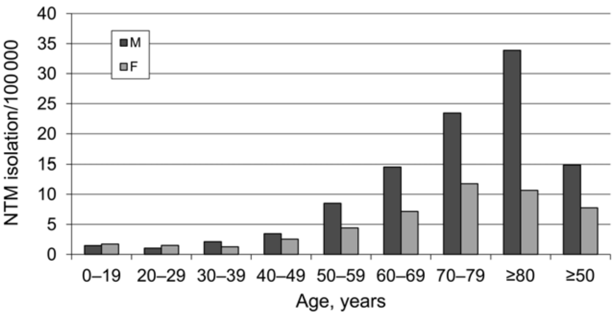

Figure 3 Crude NTM isolation frequency rate per 100 000 population stratified by age and sex. M = male; F = female; NTM = non-tuberculous mycobacteria.

probable disease group, the estimated annual incidence would be 0.23/100 000. The incidence of true pulmonary NTM disease differs between the coastal and continental regions of Croatia: the percentage of patients meeting either possible or probable disease criteria was 25.3% in the coastal region and 11.4% in the continental region; the percentage of people meeting the probable disease criteria was 14.2% in the coastal region, compared to only 3.4% in the continental region; and the incidence and prevalence of probable pulmonary NTM disease were 0.35 and 1.11/100 000 in the coastal region, but only 0.17 and 0.23/100 000 in the continental region.

After age stratification, 56 (86.2%) of all probable disease cases and 81 (79.4%) of all possible disease cases belonged to the group aged ⩾50 years (Table 2). The annual incidence of combined possible and probable disease in this age group was estimated at 1.69/100 000, with an increasing trend observed over the study period.

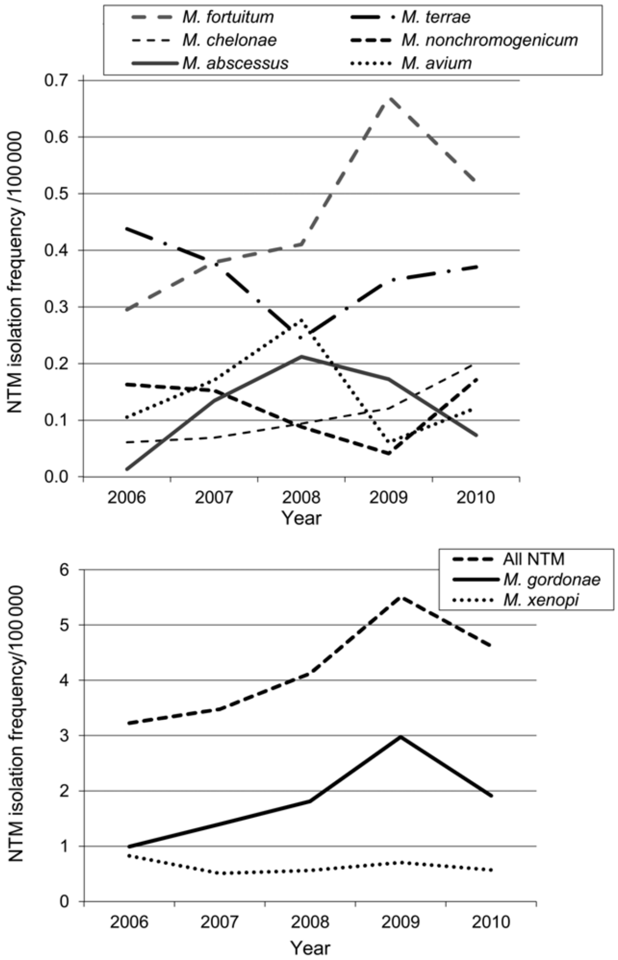

Figure 4 Isolation frequency rate of the most common NTM species in Croatia per year per 100 000 population. NTM = non-tuberculous mycobacteria; M = male; F = female.

DISCUSSION

This is the first study to show the isolation frequency of NTM species from pulmonary samples in Croatia and estimate the nationwide incidence of pulmonary NTM disease through the use of comprehensive laboratory data. This is also one of the rare studies on NTM incidence in a country with an intermediate TB burden. Croatia's TB incidence rates were respectively 26 and 17/100 000 in 2006 and 2010.[10]

Pulmonary isolates

The NTM species distribution differed between the coastal and continental regions. An increase in NTM isolation frequency was observed for the study period, with a peak in 2009. This increase was mostly based on increased isolation of *M. gordonae* and *M. fortuitum* (Figure 3), and the peak in 2009 could be explained by a subsequently established contamination of tap water (presumably consumed by patients before giving sputum samples), with *M. gordonae* in a single centre (VKJ, personal communication). Furthermore, the increasing trend of NTM isolation frequency was observed only in the population aged ⩾50 years living in the continental region of Croatia (data not shown). This increase thus involves mainly clinically irrelevant isolates.[1,13]

Several recent studies from North America and Western Europe have shown a significant increase in total NTM isolation rates.[2–5] In a study from the Netherlands, the increase was caused mainly by a rise in *M. avium* and *M. gordonae* isolates from pulmonary samples, and it was most pronounced in patients aged >40 years.[3] A study from the United Kingdom showed that the increase in NTM reports was mainly in pulmonary specimens and people aged >60 years, with *M. gordonae* showing the biggest increase but *M. avium* complex remaining the most commonly reported species.[14] In Denmark, the rising trend in NTM isolation was less obvious, but the incidence of NTM disease had increased, especially in the elderly.[4]

The NTM species cultured from clinical samples differ strongly by region,[6] and we found interesting regional differences. Although the majority of the NTM isolates came from continental Croatia, most

Table 2 Demographic characteristics of patients meeting the microbiological criteria for probable and possible pulmonary NTM disease per year per 100 000 population in Croatia

	Probable disease*			Possible disease*			
Cases	Value *n* (%)	Median age years	Annual incidence /100 000	Value *n* (%)	Median age years	Annual incidence /100 000	Average population *n*
All cases	65 (100)	66	0.23†	102 (100)	65	0.38†	4 436 265
Sex							
Female	31 (47.7)	66	0.20†	44 (43.1)	62	0.33†	2 297 905
Male	34 (52.3)	64.5	0.21†	58 (56.9)	65.5	0.37†	2 138 360
Age, years							
0–9	0	0		4 (3.9)	4.5	0.18	432 458
10–19	0	0		4 (3.9)	14	0.15	517 389
20–29	2 (3.1)	21	0.07	2 (2)	27	0.07	607 393
30–39	2 (3.1)	33	0.07	5 (4.9)	37	0.17	597 061
40–49	3 (4.6)	49	0.09	6 (5.9)	44.5	0.19	641 701
50–59	16 (24.6)	56.5	0.51	20 (19.6)	55.5	0.63	632 411
60–69	15 (23.1)	66	0.65	25 (24.5)	66	1.08	461 805
70–79	17 (26.2)	73	0.89	28 (27.5)	74	1.46	383 530
⩾80	8 (12.3)	85	1.12	8 (7.8)	82	1.12	143 306
Unknown	2 (3.1)			0			
⩾50	56 (86.2)	68	0.69	81 (79.4)	68	1	1 621 052
Geographical location							
Continental	33 (50.1)	69	0.17†	77 (75.5)	60	0.44†	2 971 550
Coastal	32 (49.9)	64.5	0.35†	25 (24.5)	68	0.25†	1 464 715

*Possible disease: either two positive sputum samples, or one positive BAL or brush. Probable disease: more than two positive sputum samples; one positive BAL/brush and one or more positive sputum samples.
† Age-standardised incidence rates.
NTM = non-tuberculous mycobacteria; BAL = bronchoalveolar lavage.

were species that are generally considered of low virulence.[1,13] In contrast, clinically relevant NTM isolates were found significantly more often in the coastal region. The species distribution in pulmonary samples is shown in Figure 4. Some of the factors that might promote these observed regional differences in Croatia include the climate, the rate of urbanisation and TB incidence.[15] The urbanised coastal region has a wetter, warmer climate and relies on larger municipal water supplies compared to the more rural, continental part of Croatia, where more households use well water. Furthermore, the incidence of TB was lower in the coastal region than in the continental region of Croatia (21.2 vs. 30.1/100 000) in 2006.[10]

Pulmonary disease

We relied solely on microbiological criteria to assign patients with isolated NTM to three groups—probable, possible and unlikely disease. We used this approach because it had previously been shown that microbiological criteria were highly predictive of disease and were useful for laboratory-based NTM disease surveillance.[8,9]

The data observed in this study are consistent with the previously described epidemiology of *M. xenopi* infection in Croatia.[16] However, despite the high frequency of *M. xenopi* isolation, *M. avium*, *M. intracellulare* and *M. kansasii* were more strongly associated with pulmonary NTM disease compared to *M. xenopi*. This differs from observations in the Netherlands, where, applying the full ATS diagnostic criteria,[1] *M. xenopi* and *M. kansasii* were more strongly associated with disease than *M. avium* and *M. intracellulare*.[13] The reason for such apparent regional differences remains unknown.

Taking into account all individuals who met the microbiological criteria, we estimated the annual incidence of NTM pulmonary disease at 0.60/100 000. However, the number of cases of *M. gordonae* disease is probably overestimated, as it is known to rarely cause true disease.[1,13] Excluding all of the *M. gordonae* cases, therefore, the annual incidence would be 0.38/100 000. Furthermore, taking into account the probable disease group only, the annual incidence decreases to 0.23/100 000, with most of the cases due to *M. xenopi*, *M. avium*, *M. intracellulare*, *M. kansasii* and *M. abscessus*.

The incidence of NTM pulmonary disease in Croatia is low compared to its TB incidence and to NTM data from North-Western Europe. In the Netherlands, the incidence of NTM disease was estimated at 1.7/100 000 in 2008,[17] while in Denmark the incidence of true disease reached 1.08/100 000.[4] A study from New Zealand using methodology similar to ours estimated pulmonary NTM disease incidence to be 1.2/100 000, and found the majority (79%) of cases to be women.[18] We found no significant sex differences in NTM pulmonary disease cases (Table 2).

The incidence of TB in Croatia is higher than in North-Western Europe and New Zealand, and bacille Calmette-Guérin (BCG) vaccination is still mandatory. This may explain the lower NTM isolation and disease rates, as there is speculation that infection with TB and BCG vaccination may provide cross-immunity to NTM infection.[19]

We observed that a higher percentage of patients living in coastal Croatia met the defined disease criteria compared to those living in continental Croatia. Moreover, the estimated annual incidence in the coastal region is twice as high as in the continental region. This might reflect the species distribution in these two regions, but further research is needed to fully understand the observed differences. A recent study in the USA showed that regional environmental factors related to soil and differences in daily evapotranspiration levels are associated with pulmonary NTM disease, but that both host susceptibility and environmental factors should be considered in explaining disease development.[20]

A limitation of this study is the lack of clinical and radiological data. The methodology used could cause disease overestimation (e.g., for *M. gordonae*). On the other hand, disease incidence could also be underestimated if only one sputum sample is sent to the laboratory for identification, with no follow-up testing. We applied the criteria 'possible' and 'probable' disease to reinforce the effectiveness of the microbiological criteria alone. Furthermore, it is possible that the incidence of NTM disease is slightly overestimated, given that some of the patients classified as 'incident' cases in 2006 might have had NTM isolated before the study period. We tried to minimise this error by looking into the available data from the year 2005 and excluding the recurrent cases from the calculation of disease incidence.

In conclusion, we have shown that the distribution of NTM species and the incidence of pulmonary NTM disease differ significantly between the coastal and continental regions of Croatia. Pulmonary NTM disease is strongly associated with age and more often affects males, but the burden of disease remains low compared to TB. The annual incidence amounts to 0.60/100 000, or 0.23/100 000 if restricted to probable disease only. The isolation frequency rose slightly throughout the study period.

Acknowledgements

This research was supported by the Croatian National Institute of Public Health and University Hospital Centre Zagreb, without any additional funding.

Conflict of interest: none declared.

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RÉSUMÉ

CONTEXTE : On ignore en Croatie la signification clinique des mycobactéries non-tuberculeuses (NTM).

OBJECTIF : Estimer le taux d'isolement des NTM, enregistrer les différences géographiques et évaluer le fardeau des maladies pulmonaires dues aux NTM en Croatie.

SCHÉMA : Etude rétrospective de cohorte au niveau national chez tous les résidants Croatiens où des NTM ont été isolées par culture dans la période de 2006 à 2010. On a utilisé les critères microbiologiques de l'American Thoracic Society pour élaborer une définition des cas basée sur le laboratoire concernant les maladies NTM possibles et probables.

RÉSULTATS : Sur 1187 personnes où des isolats de NTM d'origine pulmonaire ont été observés, 8,6% répondaient aux critères de maladie possible et 5,5% à ceux de maladie probable. Nous avons estimé l'incidence annuelle des maladies pulmonaires NTM probables à 0,23/100 000 habitants. Cette incidence annuelle estimée a été de 0,35/100 000 dans la région côtière et de 0,17/100 000 dans la région continentale. La distribution des espèces a été différente entre la Croatie côtière et la Croatie continentale. La fréquence d'isolement des NTM a augmenté pendant la période d'étude.

CONCLUSION : Les facteurs géographiques jouent un rôle dans la répartition des espèces de NTM et peut-être aussi dans la répartition de la maladie. Le fardeau global des maladies pulmonaires dues aux NTM est toujours faible en Croatie par comparaison avec celui de la tuberculose ; il est plus élevé dans la région côtière que dans la région continentale.

RESUMEN

MARCO DE REFERENCIA: Se desconoce la importancia clínica de las infecciones por micobacterias atípicas (NTM) en Croacia.

OBJETIVO: Calcular la tasa de aislamiento de NTM, registrar las diferencias geográficas y evaluar la carga de morbilidad por enfermedad pulmonar causada por NTM en Croacia.

MÉTODOS: Se llevó a cabo un estudio retrospectivo de cohortes de alcance nacional de todos los residentes de Croacia en quienes se habían aislado NTM mediante cultivo entre el 2006 y el 2010. Con el fin de establecer la definición de casos posibles o probables de enfermedad por NTM con base en las pruebas de laboratorio, se aplicaron los criterios microbiológicos de la American Thoracic Society.

RESULTADOS: De las 1187 personas con aislados pulmonares de NTM, el 8,6% cumplió con los criterios de diagnóstico posible y el 5,5% con las condiciones de diagnóstico probable de la enfermedad. Se calculó una incidencia anual de enfermedad probable por NTM de 0,23 por 100 000 habitantes. Esta incidencia anual fue 0,35 por 100 000 en la zona costera y 0,17 por 100 000 en la zona continental. La distribución de las especies difirió en ambas regiones de Croacia. La frecuencia de aislamiento de NTM aumentó durante el período de estudio.

CONCLUSIÓN: La geografía influye en la distribución de las especies de NTM y probablemente de la enfermedad. La carga de morbilidad global por NTM en Croacia sigue siendo baja en comparación con la de tuberculosis y es más alta en la región costera que en la región continental del país.