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Nontuberculous mycobacteria strains isolated from patients between 2013 and 2017 in Poland. Our data with respect to the global trends

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Abstract

Introduction: During the last decades the prevalence of NTM infections has increased, especially in developed countries. The aim of the study was to provide an overview on all NTM isolated from clinical samples in Poland between 2013 and 2017.

Material and methods: The study comprised 2799 clinical specimens, mostly respiratory accessed in the reference laboratory of National Tuberculosis and Lung Diseases Research Institute in Warsaw and in the Wielkopolska Center of Pulmonology and Thoracic Surgery, Poland, 2013–2017.

Results: During the study period 35 species of NTM were isolated. The number of isolates increased almost 1.6-fold: from 420 in 2013 to 674 in 2017. *M. kansasii*, *M. avium*, *M. xenopi*, *M. gordonae* and *M. intracellulare* were the most common species. This NTM pattern was rather stable over the time. If the aggregated amount of all MAC species was taken into account they dominated over *M. kansasii* from 2015. *M. avium* and *M. intracellulare* were more often isolated from women, while *M. kansasii*, *M. gordonae* and *M. xenopi* predominated in men. Men and women were infected almost with the same frequency. In older patients 65+ women were in majority, quite opposite to those aged 25 to 64 years.

Conclusion: In Poland, like in other countries increased frequency of isolated NTM. *M. kansasii* and *M. avium* were the most frequently identified species from clinical samples. Men and women were infected with NTM with the same frequency.

Key words: NTM, *M. kansasii*, *M. avium*, infection

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Introduction

An increased isolation as well as the prevalence of nontuberculous mycobacteria (NTM) diseases has been noticed during the last decades [1, 2]. In the US, the prevalence of nontuberculous mycobacterial lung disease was calculated at 47 cases per 100,000 population in 2007, with an

annual increase of 8.2% per year from 1997 to 2007 [2]. Interestingly, high geographic variability was noticed: the highest prevalence in Hawaii (396/100,000) and the lowest in some Midwestern states (< 50/100,000). Moreover, the prevalence varied by ethnicity, with the highest rate in Pacific and Asian Islanders and the lowest in blacks. However, opposite to tuberculosis (TB), NTM

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diseases are not reportable conditions in many countries worldwide. Thus, epidemiological data are usually incomplete or even unknown.

NTMs or mycobacteria other than tuberculosis (MOTT) are diverse environmental organisms widespread in water and soil. Up to now more than 150 NTM species have been identified [3, 4]. NTM have a broad spectrum of virulence, about 20 has a known pathogenicity. These pathogens may cause lung disease, the most common complication, less frequently lymphadenitis, skin, soft tissue infections, and disseminated disease. The most widespread species causing lung infection are the slow-growing (SGM): *M. avium* complex (MAC; consisting of *M. avium*, *M. intracellulare* and *M. chimera*), *M. kansasii*, *M. malmoense*, *M. xenopi* and the rapid-growing (RGM): *M. abscessus*, *M. chelonae* and *M. fortuitum* [5]. The new phenomenon is the increase of NTM infections not only in immunocompromised patients but also in ostensibly immunocompetent population. Some NTM strains have evolved over the years, while the new ones have emerged. Also, the patterns of the most common NTM strains differ between the regions of the world.

In Poland, there are two laboratories that identify the species of NTM: the laboratory in the National Tuberculosis and Lung Diseases Research Institute in Warsaw, from which most of the results were sourced, and the laboratory in the Wielkopolska Centre of Pulmonology and Thoracic Surgery in Poznan. So the aim of our study was: 1) to provide an overview on the types of NTMs isolated from patients in Poland over the period 2013–2017, 2) to compare the present isolates with those from the past, 3) to assess our situation with respect to the global trends.

Material and methods

All, mostly respiratory (i.e. sputum and bronchoaspirate), clinical samples of patients culture positive for NTM, which were sent to the laboratory in Warsaw and to the laboratory in Poznan between 2013 and 2017 were included in the study. Detailed numbers of examined samples per year are presented in Table 1.

The significance (Si) of the differences in proportions (distribution of species by sex) was assessed with chi-square test. $P < 0.05$ was regarded as statistically significant.

Processing of clinical samples

Clinical samples were processed in all laboratories according to the standard procedure.

Briefly, clinical samples were digested and decontaminated by adding N-actetyl-L-cysteine-sodium hydroxide solution. Then, the mixture was naturalized with buffered phosphate saline and centrifuged. Sediments of each sample were cultured in Lowenstein-Jensen and Stonebrink mediums, as well as in liquid Middlebrook medium of Bactec MGIT 960 system (Becton-Dickinson-BD), according to previously described method [6].

Then, using TBc ID MGIT (TBc ID, Becton Dickinson, Sparks, MD) test, mycobacteria were assigned to *Mycobacterium tuberculosis complex* (MTC) group or to NTM.

For identification of NTM species GenoType Mycobacterium CM ver. 1.0 and 2.0 (Hain, Lifescience, Nehren, Germany) was performed according to the manufacturer's instructions [4]. This test can identify fourteen most common NTMs as well as MTC, *Mycobacterium abscessus complex* (MABC) and MAC. Detailed specification was performed using GenoType MTBC (for MTC species), GenoType NTM-DR (for MABC and MAC species) and GenoType Mycobacterium AS assay for identification of the rest infrequent mycobacteria [7–9].

The study was approved by the Ethic Committee of the National Tuberculosis and Lung Diseases Research Institute — approval no. 9/2015.

Results

A total of 2799 specimens were included in the study. 1438 clinical samples belonged to men and 1361 to women. Overall, thirty five NTM species were isolated from the clinical specimens during five years. The number of NTM increased from 420 in 2013 to 674 in 2017 (Table 1). *M. kansasii*, *M. avium*, *M. xenopi*, *M. gordonae* and *M. intracellulare* were identified the most frequently.

These five species accounted for 85.8% of all examined specimens in the study period (range from 84.7% (2015 and 2016) to 87.0% (2014)). The rest of isolates, except *M. fortuitum* were observed very infrequently.

The order of all the most common species was almost stable during the study, changing in 2015–2017, where isolates of *M. xenopi* outnumbered isolates of *M. gordonae* and in 2016, in which *M. avium* dominated instead of *M. kansasii* (Fig. 1, Table 2).

If the aggregated amount of all MAC species is given, since 2015 they have dominated over *M. kansasii* (in 2013 — MAC 108, *M. kansasii* 134; in 2014–130 vs. 166; in 2015–185 vs. 155; 2016–167 vs. 129; 2017–213 vs. 177).

Table 1. Nontuberculous mycobacteria (NTM) species isolated from clinical samples in Poland, between 2013 and 2017

NTM species	2013	2014	2015	2016	2017	Total
<i>M. abscessus</i>	2	4	6	11	8	31
<i>M. aurum</i>	0	0	1	0	0	1
<i>M. avium</i>	89	99	149	134	145	616
<i>M. celatum</i>	0	4	1	1	1	7
<i>M. chelonae</i>	2	3	5	5	5	20
<i>M. chimaera</i>	0	0	0	2	12	14
<i>M. flavescens</i>	3	0	0	2	0	5
<i>M. fortuitum</i>	24	27	52	28	35	166
<i>M. genavense</i>	0	0	0	2	1	3
<i>M. gordonae</i>	66	82	70	92	96	406
<i>M. heckeshornense</i>	0	0	1	1	2	4
<i>M. interjectum</i>	1	0	0	2	0	3
<i>M. intracellulare</i>	19	31	36	31	56	173
<i>M. kansasii</i>	134	166	155	129	177	761
<i>M. lentiflavum</i>	0	2	1	2	5	10
<i>M. mageritense</i>	8	0	0	0	2	10
<i>M. malmoense</i>	0	9	5	7	0	21
<i>M. marinum</i>	1	1	2	0	0	4
<i>M. monacense</i>	0	0	0	0	2	2
<i>M. mucogenicum</i>	2	8	6	12	7	35
<i>M. neoaurum</i>	0	0	5	1	0	6
<i>M. nonchromogenicum</i>	4	0	1	1	0	6
<i>M. novocastrense</i>	0	0	0	0	1	1
<i>M. parafortuitum</i>	0	0	1	0	0	1
<i>M. parascrofulaceum</i>	0	0	0	1	0	1
<i>M. peregrinum</i>	5	3	2	2	5	17
<i>M. scrofulaceum</i>	0	1	2	0	1	4
<i>M. simiae</i>	2	0	0	1	0	3
<i>M. shimoidei</i>	0	0	1	0	1	2
<i>M. smegmatis</i>	0	0	0	1	0	1
<i>M. szulgai</i>	0	5	1	3	3	12
<i>M. tokaiense</i>	0	0	0	2	0	2
<i>M. triviale</i>	1	0	0	1	0	2
<i>M. ulcerans</i>	0	0	0	0	1	1
<i>M. xenopi</i>	57	74	106	103	108	448
Total	420	519	609	577	674	2799

There were only few species which had not been isolated before 2017 like *M. monacense*, *M. novocastrense* and *M. ulcerans*.

NTM species distribution was only slightly higher in men than in women ($p > 0.05$) (Fig. 2, Table 3).

Figure 1. Distribution of the most common nontuberculous mycobacteria (NTM) species by year, 2013–2017

Table 2. Number of the most common nontuberculous mycobacteria (NTM) species in Poland, 2013–2017

NTM species	<i>M. kansasii</i>	<i>M. avium</i>	<i>M. xenopi</i>	<i>M. gordonae</i>	<i>M. intracellulare</i>
2013	134	89	57	66	19
2014	166	99	74	82	31
2015	155	149	106	70	36
2016	129	134	103	92	31
2017	177	145	108	96	56
Total	761	616	448	406	173

Figure 2. Nontuberculous mycobacteria (NTM) species distribution by sex in Poland, 2013–2017

Distribution of NTM isolates by sex and age was available in 2017 only.

Except for the youngest groups: 0–14 year-old and 15–24 year-old men predominated,

but among those > 65 year-old women were in majority (Fig. 3).

Two species: *M. avium* (359 vs. 257), *M. intracellulare* (99 vs. 74) were more often isolated

Table 3. Distribution of nontuberculous mycobacteria (NTM) species by sex and number in Poland, 2013–2017

Year	Female	Male	Total
2013	207	213	420
2014	247	272	519
2015	292	317	609
2016	282	295	577
2017	333	341	674

Discussion

Our investigation is a laboratory-based study in which the large number of NTM strains isolated from clinical samples have been assessed. We did not provide any data about clinical relevance of isolated strains. It is known that NTM can cause progressive lung disease or can reside within the lungs representing colonization. It can be assumed that doctors then asked for species identification, if they suspected a disease. On

Figure 3. Distribution of NTM isolates in female and male according to the age groups in 2017 **Figure 4.** Distribution of most common nontuberculous mycobacteria (NTM) species by sex in Poland, 2013–2017; * $p < 0.001$

from women, while *M. kansasii*, *M. gordonae* and *M. xenopi* predominated in men (393 vs. 368; 223 vs. 283, and 274 vs. 174, respectively). Only the differences according *M. avium* and *M. xenopi* were statistically significant ($p < 0.0001$) (Fig. 4).

the other hand, in Poland, there is a statutory obligation to report cases of mycobacteriosis and growth of NTM. According to the National Institute of Public Health — National Institute of Hygiene, having available aggregated data, a total of 1114 cases of mycobacteriosis were registered in the years 2013–2017 [10]. By our study, the number of patients yielding NTM isolates from the respiratory tract increased 1.6-fold between 2013 and 2017, from 420 to 674. Also, high NTM species diversity was found. Over the study period 35 species were isolated from clinical specimens. The most common species were *M. kansasii*, *M. avium*, *M. xenopi*, *M. gordonae* and *M. intracellulare*.

The first study trying to analyze NTM in pulmonary specimens in our country was conducted by Janowiec *et al.* [11] at the beginning of the 1970's. They found that 3.98% out of 106,182 culture-positive specimens isolated from patients registered in pulmonary clinics between 1971 and 1974 were NTM. As in that time NTM were classified according to Ruynion — most of them

— 68.1% belonged to rapidly growing mycobacteria (RGM), followed by the species from the III (15.9%) and the II group (13%). The situation was quite opposite to that in the present study, where slowly growing mycobacteria (SGM) were predominated. Twenty years later Ślupek and coworkers [12] basing on similar material demonstrated that 1% (267) of all culture — positive specimens were NTM. However, in that study only 57% of isolated mycobacteria were identified as species. Interestingly, like nowadays, *M. kansasii*, MAC and *M. xenopi* were the most common species [12]. Of note, 77% of NTM were associated with pulmonary mycobacteriosis (the diagnosis did not have to meet the criteria currently recommended).

According to current results, in Poland NTM were isolated only slightly more often in men than in women. Similar epidemiological situation, but with greater men predominance (61.8%), was reported in the previous century [11]. However, we found also that in older group > 65 year-old women predominated. In our study, *M. avium* and *M. intracellulare* were found in more women than men; *M. kansasii*, *M. gordonae* and *M. xenopi* — in men. In line with the data reported from other countries, the number of isolated NTM increased with the population's age, i.e.: 15–24 yr — 12 isolates, 25–34 yr — 50 isolates to 316 in those older than 65.

Similar trend was reported also in other countries in our region [13–15]. In England, Wales and Northern Ireland, the number of examined NTM specimens rose from 459 in 1995 to 1608 in 2006 [13]. Moreover, like in our study men gained predominance (60%). Nevertheless, in some settings situation is reversed (2,16). The recent study from Japan revealed that NTMs were isolated mainly from individuals older than 70 years of age, mainly women (65.5%) [16]. Also in the US, the majority of subjects tended to be women in older age like in Lady Windermere syndrome [17]. It should be stressed that all authors agreed that patients with NTM infection were older than those with tuberculosis and were usually 60+. Comparable NTM pattern to our current results was also observed in the retrospective study conducted in Bordeaux, France over 12 years (2002–2013) [18]. However, such stable trend among mycobacterial species over the years is not a typical phenomenon. Santin *et al.* [19] studying NTM infection in Barcelona region between 1994 and 2014 revealed that *M. kansasii* was the most common in the first half of the period, while MAC in the second one.

Looking on global geographical distribution of different NTM species, high diversity can be

seen. However, some trends across the regions are noticed. In North America, in Ontario, Canada, the most common are: MAC, followed by *M. xenopi* and RGM [20], while in the US — MAC, *M. abscessus*/*M. chelonae* and *M. xenopi* dominate [17]. Few recent studies from South America have revealed that MAC is generally the most common there, and *M. kansasii* is also frequent [17–21]. Similarly, MAC is predominant in South Asia and in Queensland, Australia, whereas MAC with *M. fortuitum* and *simiae* in the Middle East [22, 23].

In the European Union, data provided by the NTM — Network European Trials Group in 2008 revealed that MAC (47%), *M. gordonae* (11%), *M. xenopi* (8%), *M. fortuitum* (7%) and *M. kansasii* (4%) were the most frequently identified [24]. However, there are still substantial differences between south and north regions. Although MAC was isolated with the highest frequency in northern and southern Europe (44% vs. 31%), *M. xenopi* was more prevalent in southern Europe (21% vs. 6%), in contrast to *M. bohemicum*, which was almost exclusively isolated in northern Europe. *M. kansasii*, common in Poland but losing its dominance over MAC as a whole, predominated in Slovakia, while *M. xenopi* was especially frequent in Hungary [24]. High prevalence of *M. kansasii* in eastern Europe, South America as well as in metropolitan centers of London, Paris and Johannesburg is probably related to the mining activities [25]. Moreover, the study from Queensland (Australia) found that increased soil bulk density positively correlated with *M. kansasii* disease [26]. Likewise in Poland, where in the previous century *M. kansasii* dominated in mine regions [11], but nowadays this species is more typical of urban areas.

In this context, very interesting issue are the species-specific environmental niches with subsequent transmission to humans. Nevertheless, only scarce published data dealt with this problem. Of note, it should be stressed that there is no simple association between environmental NTMs and those revealed in clinical samples. Velayati *et al.* [27] studying water and soil from suburban areas of Tehran and clinical samples of patients living there demonstrated that *M. farcinogenes* and *M. fortuitum* were the most common environmental inhabitants, while *M. simiae* and *M. chelonae* the most frequent species isolated from patients. There are some explanations of these discrepancies. Firstly, abilities of NTM species to cause the disease in humans differ. Secondly, the development of infection or mycobacteriosis

depends on host risk factors like co-morbidities (GERD, COPD, bronchiectases), taken drugs (immunosuppressive, immunomodulatory), low BMI or thoracic skeletal deformation. Surprisingly, more and more often idiopathic mycobacteriosis with no predisposing conditions occur. Such situation takes place in the US among older women who suffer from mycobacteriosis even more often than men with COPD [28]. Unfortunately, there are no such data from our country.

Such chronic conditions like mycobacterial infections, sometimes even lifelong can be better characterized by the prevalence than the incidence. However, we could not provide data about the prevalence of NTM infection in Poland because the later history of the patients in whom NTMs have been detected and identified is not known. Looking on the data from high-income countries worldwide, such a tendency can be seen: as the prevalence and incidence of tuberculosis are decreasing, the prevalence of NTM infections as well as mycobacteriosis increases [29, 30].

In conclusion, as in the 20th century *M. tuberculosis* was considered a global threat, in the 21st century — an era of End TB, as was announced by the WHO, NTM infections are becoming a discernible problem. Although NTMs are not transmissible organisms among humans, with very rare exceptions, taking into account ageing of the European population and its increased comorbid conditions, this problem in our region will be greater than in developing countries.

In Poland, *M. kansasii* and *M. avium* were the most frequently identified NTM species from clinical samples. As in many other countries, there were more samples taken from men, however, in those 65+ women dominated. *M. avium* and *M. intracellulare* were more often isolated from women, while *M. kansasii* and *M. xenopi* predominated in men.

Conflict of interest

The authors declare no conflict of interest.

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