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Incidence rate of nontuberculous mycobacterial disease in immunocompetent children a prospective nationwide surveillance study in Germany

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An increasing incidence in disease caused by nontuberculous mycobacteria is being reported. We investigated the burden of disease in immunocompetent German children in a prospective nationwide study from April 2003 to September 2005. Ninety-seven percent of children presented with lymphadenitis; median age was 2.5 years. Using the capture-recapture method, we estimated a cumulative incidence rate of 3.1/100000 children.

Humans are extensively exposed to natural sources of environmental mycobacteria (eg, water, soil). Nontuberculous mycobacterial (NTM) disease develops predominantly in immunocompromised individuals but can also present a major problem for immunocompetent children.1 Various publications report increasing incidence rates of NTM disease in children in developed countries but few nationwide studies have been carried out.2–5 Nontuberculous mycobacteria are not included in mandatory reporting in Germany and thus, the burden of NTM disease is unknown. The Robert Koch Institute and the German Pediatric Surveillance Unit undertook a prospective nationwide study to investigate the epidemiology of NTM infections in children and determine the burden of NTM disease. Clinical data on NTM cases were provided by pediatric hospitals. To detect further cases, laboratories of a surveillance network reported NTM isolates. Availability of 2 data sources allowed the use of the capture-recapture technique.6 This method has repeatedly been applied in Germany for estimation of the number of cases missed by surveillance systems.7,8

Methods

All 370 pediatric hospitals and pediatric wards in Germany participate in a notification system for conditions that require hospitalization. A total of 480 clinicians monthly reported per notification card if they had managed a case of NTM disease. Any positive report prompted a detailed questionnaire about clinical presentation and demographic characteristics. In case questionnaires were not returned, hospitals were contacted by telephone. All microbiologic laboratories serving pediatric hospitals and laboratories specialized in detection of mycobacteria (on average 305 institutions) reported mycobacterial isolates. Laboratories that failed to report were contacted by telephone. Details on laboratory diagnosis and demographic characteristics were recorded. Clinical cases were defined as immunocompetent children<15 years with symptoms consistent with NTM disease, no prior history of NTM disease, and admission to hospital between October 2002 and September 2005. NTM infection had to be laboratory confirmed by positive culture or positive PCR plus typical mycobacterial histology. Inclusion criteria for 2-source capture-recapture analysis were admission to hospital or receipt of sample in the laboratory between April 2003 and September 2005, age <15 years and laboratory confirmation of NTM by positive culture or positive PCR plus typical mycobacterial histology. Because of data protection the collected data allowed no patient identification. To identify cases reported by both hospitals and laboratories, matching was performed using 10 criteria. Assuming independence of sources, the number of cases missed by both sources was estimated.6,9 Data were analyzed with STATA software (version 10.0; StataCorp LP, College Station, TX). Information on cases with lymphadenitis due to tuberculosis (“TB adenitis”) was obtained by the mandatory reporting system.10 Incidence rates were calculated using population statistics.11

Results

Participation rates were high for both hospitals (97.2%) and laboratories (95.8%). One hundred two cases and 173 isolates fulfilled our case definition. No trend or seasonal differences were observed.

Demographic Characteristics. The majority of cases reported by hospitals belonged to the youngest age groups 0 to 4 years (93.1%) with the highest total number of cases in the second year of life (30.4%); median age was 2.5 years. In comparison, median age of TB adenitis cases was 3 years. Female to male ratio was 1.27. Statistical analysis showed no higher probability for female sex to be affected by NTM disease. There was no association between geographic location of living (at level of German Federal state) and risk to develop NTM disease. Nintyeight percent cases originated from Germany and had never lived abroad.

Clinical Presentation. Ninety-seven percent of children reported by hospitals presented with lymphadenitis (Table 1), most frequently with unilateral cervical lymphadenitis (75.5%). Of the remaining children, one child had an infected wound, one child presented with bronchitis, and for one child no further information was provided. Based on our data, we found no evidence for differences in clinical manifestation between cases reported by hospitals and those reported by laboratories. Clinical symptoms included fever (20.8%), pain (42.7%), and development of fistula (16.7%). Stratification of symptoms revealed that fever occurred more often in children <4 years (80%) than in children ≥4 years (20%) of age. Two children were reported to be BCG vaccinated. Details on clinical

presentation and symptoms of TB adenitis cases were not available. *Diagnosis.* Seventy-two children (82.8%) reported by hospitals showed positive reactions following tuberculin skin test (indurations of >5 mm). Forty-nine children (56.3%) had indurations of >10 mm with 16 children (19.5%) showing a strong reaction >15 mm. Among those 16 children, 2 had received BCG vaccination. Details on skin testing of TB adenitis cases were not available. Most often, lymph node material was used for establishing the diagnosis (88.7%). Culture isolation was used for NTM isolation (88.2%), often combined with histopathologic examination (68.6%). The great majority of isolated species were slow-growing mycobacteria, predominantly *M. avium*. Two children had coinfection with *M. tuberculosis complex*. Their clinical presentation did not differ from other cases.
Treatment. The planned treatment regimen for children with lymphadenitis included surgery only (42%), chemotherapy only (17%), a combination of both surgery and chemotherapy (39%), and a wait-and-see strategy (2%). However, we have no information on the final type of drug treatment.
Capture-Recapture Analysis. Thirty-seven cases were reported by both the sources, 133 cases by laboratories only and 43 cases by hospitals only. An estimated 155 cases were missed by both sources, resulting in a total number of 368 NTM cases (95% CI, [255; 514 cases]). Stratification by age and sex confirmed validity of the estimated total number. Thus, the estimated cumulative incidence rate of NTM cases was 3.3/100000 children (95% CI, [2.3; 4.6]) from April 2003 to September 2005. Incidence rate of children <4 years was 11.3 (95% CI, [8.2; 15.6]) and incidence rate of children ≥4 years was 1.4 (95% CI [0.9; 1.6]) per 100000. In comparison, the cumulative incidence rate of all TB adenitis cases in children was 0.5/100000 (95% CI [0.3; 0.6]) from April 2003 to September 2005. Incidence rate of TB adenitis in children <4 years was 0.9 (95% CI [0.5;1.4]) and 0.4 (95% CI, [0.3; 0.5]) in children ≥4 years. Completeness of reporting of hospitals was 22% and completeness of laboratory reporting was 46%.'

Discussion

We investigated the epidemiology of NTM disease in German children with 2 established and representative prospective nationwide surveillance systems and present the first estimate of NTM incidence rate in Germany adjusted for underreporting.
Characteristics of Clinical Cases. The majority of reported children was between 2 and 4 years old, an age-distribution also reported by other authors.2,3,5 We did not find statistical evidence of differences between genders. However, there are reports about preponderance of female cases.2–5 In agreement with other publications, the majority of children presented with cervical lymphadenitis.4,5 Positive tuberculin reactions were observed in 84% of cases. This confirms the diagnosis of NTM disease in immunocompetent children.12 The frequency and distribution of mycobacterial species varies greatly in different geographic regions of the world. In developed countries, *M. avium complex* is the most common mycobacterial species causing disease.1 The results of our study are in line with this. Sensitivity of the culture method was reported to be 50% to 80%, even if material is obtained from lymph nodes showing NTM-typical histopathology.1 Because of our strict case definition for laboratory confirmed cases, we may have precluded some true NTM cases due to a lack of positive culture result. These false-negative diagnoses could result in an underestimation of total NTM cases.

Estimation of Incidence Rate. Traditional approaches to analyze surveillance data do not take into account the number of cases missed by sources. Therefore, estimates of disease burden are often biased. Using the capture-recapture approach, we estimated a cumulative incidence rate of NTM cases of 3.3/100000 children <15 years between April 2003 and September 2005 (average yearly incidence rate is 1.3/100000 children). A prospective study in the Netherlands showed an annual incidence of children of 0.8/100000, but the complementary Dutch Chirurgie versus Medicatie (CHIMED) study suggested a likely higher incidence of 1.2/100000 children.2 We found that the 2-source model gives a valid estimate. Consequently, cases present in both samples are appropriately matched. However, there could be false-positive case ascertainment in laboratories because of primary diagnosis of NTM in another laboratory. Some degree of positive dependency of sources likely exists in our study. Yet, the effect of “capture bias” is considered to be limited because reporting laboratories received samples from different hospitals. Our study revealed that many NTM patients are not seen in pediatric hospitals. This finding indicates that NTM cases—particularly older age-groups—are also treated in surgical or otolaryngologic units or by general practitioners. We assume that clinicians in pediatric hospitals are more likely to send samples from NTM cases to laboratories for further analysis than clinicians in other hospitals. The CHIMED study has also shown that inclusion of specialists like ear, nose, throat physicians, and oral-maxillofacial surgeons increases completeness of notification.2

Conclusion

Acknowledging potential limitations of the capture-recapture model, our study defines the burden of NTM disease in immunocompetent children in Germany. Assuming similarity of all cases reported, adenitis in children <4 years is 13 times more likely caused by NTM than by TB.

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Table 1. Clinical Characteristics of Cases With NTM Disease Reported by Pediatric Hospitals.

Clinical Characteristic	No. (%) of cases
Lymphadenitis (n = 102)	99 (97.1)
Cervical	75 (73.5)
Cervical plus parotid	10 (9.8)
Cervical plus preauricular	2 (2.0)
Parotid	3 (2.9)
Other locations	9 (8.8)
Species (n = 102)	
M. avium	85 (83.3)
M. intracellulare	4 (6.9)
M. kansasii	5 (4.9)
>1 species	7 (6.9)
Unilateral (n = 95)	89 (93.7)
Symptoms	
Fever* (n = 96)	20 (20.8)
Pain (n = 89)	38 (42.7)
Fistula (n = 84)	14 (16.7)
BCG vaccination (n = 88)	2 (2.3)

*Temperature >38.5°C.