Increase in Childhood Nontuberculous Mycobacterial Infections After Bacille Calmette-Guerin Coverage Drop : A Nationwide, Population-Based Retrospective Study, Finland, 1995-2016

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Increase in childhood nontuberculous mycobacterial infections after BCG coverage drop – a nationwide population-based retrospective study, Finland, 1995 to 2016

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Keywords: nontuberculous mycobacteria, NTM, lymphadenitis, BCG, vaccination coverage

Summary: In 2006 the universal BCG vaccinations in Finland discontinued. In our population based retrospective study childhood NTM infections increased drastically after the BCG policy change suggesting that BCG offers protection against childhood NTM infection.

Abstract

Background

Epidemiological data on childhood nontuberculous mycobacterial (NTM) disease is scarce and the protective effect of Bacillus Calmette-Guérin (BCG) vaccination remains debated. In 2006 the BCG policy in Finland changed from universal to selective. We aimed to study the effect of the BCG coverage decrease on the incidence of childhood NTM infections in Finland.

Methods

We conducted a nationwide, population-based, retrospective study of NTM notifications recorded to the National Infectious Diseases Register between 1995 and 2016 and identified native-born children aged 0–4 years infected with NTM. Poisson log linear model was used to estimate the change in the incidence rate of cohorts born during universal or selective BCG policy between 1995 and 2015.

Results

We identified 97 native-born children infected with NTM under the age of five (median age 27 months, female to male ratio 2:1). The most common species was *Mycobacterium avium* (N=69; 71%). The estimated incidence rates of NTM in universal-BCG and selective-BCG cohorts were 0.2 and 3.9 per 100,000 person-years, respectively. The incidence rate ratio of selective-BCG cohorts compared to universal-BCG cohorts was 19.03 (95% CI, 8.82–41.07, $p<0.001$).

Conclusions

After the infant BCG coverage in Finland decreased, childhood NTM infections increased drastically. Since there is no other apparent cause for the increase, this indicates that BCG offers protection against childhood NTM disease. This observation adds to the understanding of childhood NTM epidemiology and might explain why the disease is emerging in some countries.

Text

Nontuberculous mycobacteria (NTM) represent a large fraction of the genus *Mycobacterium [1]*. Other *Mycobacterium, M. tuberculosis* (MTB) and *M. leprae,* cause tuberculosis (TB) and leprosy, respectively. Although NTM are mostly non-pathogenic, some can cause disease in humans. NTM are ubiquitous in the environment that is the likely source of infection [1]. In children infection predominantly presents as a cervicofacial lymphadenitis between 1 and 5 years of age [2, 3]. Although those with impaired immunity are especially susceptible, most affected children are immunocompetent [2, 4].

Mycobacterium species share many antigens and cellular immunity is essential for the immune response to both MTB and NTM [1]. Bacillus Calmette-Guérin (BCG) vaccine contains attenuated strains of *M. bovis* and is used for TB prevention. In animal models BCG has also shown a protective effect against certain NTM infections [5-7]. Furthermore, BCG has additional nonspecific or heterologous effects independent of vaccine-specific immunity that are beneficial [8, 9]. After cessation of universal BCG vaccinations in Sweden in 1975 childhood NTM infections increased [10]. While the universal BCG vaccinations in Finland continued, childhood NTM infections remained rare [11].

National surveillance studies and published data on childhood NTM epidemiology are scarce, and in some developed countries NTM infections seem to have emerged even without change in BCG coverage [1, 12, 13]. As recent observations after BCG coverage change have not been published, the protective effect of BCG against NTM remains debated [1]. Therefore, to understand the role of BCG and the burden of childhood NTM disease better further epidemiological data is required.

On September 1, 2006 the BCG policy in Finland changed from universal to a risk group-based approach, and consequently the BCG coverage of infants dropped from >98% to estimated

6% [14]. Such a recent and drastic change in BCG coverage has not been observed anywhere else. Furthermore, NTM isolates in Finland have been mandatorily notifiable since 1995 to the National Infectious Diseases Register (NIDR) [15].

Our aim was to study the effect of the BCG coverage change in Finland on the incidence of childhood NTM infections.

Methods

We conducted a nationwide, population-based, retrospective study of NTM notifications recorded to the NIDR between January 1, 1995 and December 31, 2016 (accessed April 5, 2017). The NIDR collects information on the informant (source and date of notification), patient (personal identity code, gender, nationality, date and country of birth), specimen (source, type and date of specimen) and culture results. From the registry data, we identified native-born children infected with NTM under the age of five. We defined a case of NTM infection as having ≥ 1 isolate from any site and considered cases to be incident at the time of specimen collection.

As a part of national surveillance and control, clinical microbiology laboratories are obligated to notify new NTM isolates directly to the NIDR. In clinical laboratories that perform primary detection of mycobacteria, the NTM isolates obtained from patient specimens are isolated according to standard laboratory procedures: acid-fast smear with the auramin and Ziehl-Neelsen methods, culture on solid (Lövenstein-Jensen) and liquid media (BACTEC 480 and since 2000 BACTEC MGIT 960, Becton Dickinson, Franklin Lakes, NJ). Since 2010 direct detection of mycobacteria has also been performed with the GeneXpert MTB/RIF assay (Cepheid, Sunnyvale, CA) and with the GenoType Mycobacteria Direct assay (Hain Lifescience, Nehren, Germany). Isolates are further submitted to the Mycobacterial Reference Laboratory at the National Institute for Health and Welfare where the identification of mycobacterial species is performed with the

GenoType Mycobacterium CM/AS assays (Hain Lifescience, Nehren, Germany) and with sequencing of the 16S rRNA gene.

Population data was obtained from the Statistics Finland population database (accessed March 29, 2017) [16]. Based on the registry and population data, we estimated the annual incidence of NTM infection in native-born children aged 0-4 years. The BCG status of individual patients was not available from the NIDR or National Vaccination Register and we did not contact the patients or families directly. To assess the effect of the BCG coverage change, we estimated the incidence rates of NTM infection per 100,000 person-years among birth cohorts born in Finland between 1995 and 2015. The children born in 2006, however, were further divided into two birth cohorts: those born during universal BCG policy from January to August and those born during risk-group-based BCG policy from September to December. All birth cohorts born before September 2006 were denominated as "universal-BCG" and those born thereafter as "selective-BCG" cohorts. We assumed that the birth-rate was equal year-round, so that for example all children born during 2015 and registered until December 31, 2016 were observed for 1.5 years. Birth cohorts that turned five before December 31, 2016 were observed for the maximum of five years. The estimated incidence rate per 100,000 person-years was calculated by dividing the number of NTM cases per cohort with the number of live-born children per cohort multiplied by the number of years of observation per cohort, and then multiplying the whole number with 100,000.

Poisson log-linear model was used to estimate the incidence rate ratio (IRR) and relative risk reduction (RRR) between cohorts. Goodness of fit criteria was examined so that the ratio of the deviance to degree of freedom (value/df) was less than 1.50. A p-value < 0.05 was considered statistically significant. Data were collected and analysed with Microsoft Excel (Version 15, Microsoft Corporation, Redmond, WA, US) and IBM SPSS Statistics (Version 24, IBM Corporation, Armonk, NY, US).

Data in this study were analysed within the epidemiological research purposes authorized by the Finnish Communicable Diseases Act 1227/2016, 42 §. Therefore, ethical approval was deemed unnecessary.

Results

A total of 100 children under the age of five were identified from the NIDR. After excluding foreign-born children (N=3), the rest were included in the data analysis (N=97). The female to male ratio was 2:1 (65 female and 32 male). The age at the time of specimen collection ranged from 4 to 59 months with a median age of 27 months (interquartile range, 13). Due to the small number of cases in the universal-BCG cohorts, we did not compare demographic characteristics between the groups. The most common isolated NTM species was *M. avium* (N=69; 71%) and culture specimen was a needle aspirate or tissue biopsy (N= 78; 80%). The sources of the culture specimens and isolated species are presented in Table 1.

Between 1995 and 2016 the native-born under-five population ranged from 280,049 to 322,369. The annual number of NTM infections and estimated annual incidence of NTM infection in native-born children aged 0–4 ranged from 0 to 20 per year and 0 to 6.7 per 100,000 children, respectively (figure 1).

Altogether, the universal-BCG cohorts contained 678,221 children observed for 3,391,105 person-years and selective-BCG cohorts contained 549,000 children observed for 2,290,820.5 person-years. The percentage of native-born children with foreign-born mothers in the birth cohorts increased from 3.0% to 11.5%. The sex ratio (males/females) of the birth cohorts remained relatively constant between 1.04 and 1.06. Key characteristics and the estimated incidence rates for individual birth cohorts are detailed in Table 2.

The incidence rate of NTM infection in native-born children aged 0–4 years was estimated at 0.2 per 100,000 person-years for the combined universal-BCG cohort and 3.9 per 100,000

person-years for the combined selective-BCG cohort. The IRR of the selective-BCG cohorts compared to the universal-BCG cohorts was 19.03 (95% confidence interval {CI}, 8.82–41.07, p<0.001, value/df 1.4). The RRR from the 2006 to 2015 and 2006 to 2013 selective-BCG cohorts was 0.10 (95% CI, 0.02–0.18, p<0.05, value/df 0.45) and 0.08 (95% CI, -0.02–0.17, p=0.11, value/df 0.47), respectively.

Discussion

After the BCG policy in Finland changed from universal to selective, childhood NTM infections increased drastically. As the BCG policy change resulted in decreased coverage of infants, the increase indicates that non-BCG-vaccinated children are more susceptible to NTM infections.

National surveillance studies and published data on childhood NTM epidemiology are scarce [1, 17]. To our knowledge, our study represents the only one examining the effect of BCG coverage change on the incidence of NTM infection in over 20 years. The only two previously published studies are from Sweden and the Czech Republic, where BCG policy changed in 1975 and 1986, respectively [10, 18]. The incidence of NTM presented in our study and other published studies compare well when BCG policy is taken into consideration (table 3) [2, 10, 11, 19, 20]. In our study, the difference observed between selective-BCG and universal-BCG cohorts was clear (IRR 19.03 [95% CI, 8.82–41.07]). Compared to the ratio between non-BCG-vaccinated and BCG-vaccinated presented by Romanus et al. from Sweden (5.9 [95% CI, 1.6–48.5]), it is well within the confidence interval. In the Czech Republic, protective effect of BCG against childhood NTM infections was also previously observed [18]. In some studies childhood NTM infections have increased without significant change in BCG coverage, but none of these show a sharp increase [12, 13].

In our study, there was a slight decreasing trend in the selective-BCG cohorts born between 2006 and 2015 (RRR 0.10, 95% CI, 0.02–0.18). However, the 2014 and 2015 birth cohorts were observed only up to 2.5 and 1.5 years of age, respectively, and children who develop disease at a later age are missing from these birth cohorts. After excluding these birth cohorts from the model, there was no decreasing trend between the selective-BCG cohorts (RRR 0.08, 95% CI, -0.02–0.17).

In our study and the previous study from Finland there was a clear female predominance (female to male ratio of 2:1 and 3:1, respectively) [11]. Slight female predominance in adults with pulmonary NTM disease and children with any NTM infection has also been observed elsewhere [10, 12, 18, 21-24]. It is unclear why the female predominance in Finnish children seems to be more distinct.

In Finland BCG vaccinations generally take place in maternity hospitals at infancy most likely before first NTM exposure. After the policy change, the BCG coverage of birth cohorts is estimated to have decreased rapidly from >98% to 6% allowing comparison between BCG-vaccinated and non-BCG-vaccinated children living in otherwise relatively similar settings [14]. Other explanations that might be considered to cause the NTM to emerge are changes in one or more of the following: detection, notifications, investigations, exposure, pathogenicity, or host susceptibility.

During the study period detection of mycobacteria from primary specimens has remained largely the same. Liquid culture methods have been used in Finland since the 1990s, first the radiometric BACTEC 480 system and since 2000 the BACTEC MGIT 960 system. Direct detection of mycobacteria became available in Finland in 2010, yet childhood NTM infections had clearly emerged earlier and all registered cases were culture positive. Notifying a positive NTM culture to the NIDR has been mandatory since 1995 and thus allows for a reliable examination of nationwide notifications during the complete retrospective period.

The number of all requested mycobacterial cultures during the retrospective period is unknown. Heightened clinical awareness could increase investigations and diagnosed cases. Due to the previous experience from Sweden, the National Public Health Institute of Finland (predecessor of the National Institute for Health and Welfare) anticipated a rise in NTM infections when the BCG policy changed [25]. However, the decision to change the BCG policy was made precipitatedly [26], and the medical community was not largely informed to expect an increase of NTM infections. Furthermore, the current estimated incidence corresponds well with the incidence reported from other countries [2, 10, 20]. Therefore, in our opinion heightened awareness explaining the radical increase is unlikely.

Suggested sources for NTM reservoirs are broad [27]. NTM species have widely been found in Finnish environment since the 1990s and early 2000s [28, 29], and we are not aware of any significant changes that may have increased occurrence of mycobacteria in the environment since. Corresponding to previous studies most cases were caused by *M. avium*. Interestingly in our data *M. lentiflavum* was the second most common isolate (N=7; 7%) that first appeared in 2008. A study from Madrid noted that around the same time *M. lentiflavum* isolates increased [30]. In other studies, *M. lentiflavum* isolates have been scarce [4]. Swimming pools and potable water have been suggested as a possible source for *M. lentiflavum* infections [30, 31]. However, *M. lentiflavum* was common in Finnish drinking water systems even before the BCG policy changed [29]. Although the exact place of transmission for our cases is not known, the *M. lentiflavum* isolates came from five different health care districts without any specific region standing out. It is uncertain whether, regardless of BCG coverage, *M. lentiflavum* is emerging or the concurrence is coincidental. We are not aware of any data suggesting an increase in the pathogenicity of *M. avium* that represented majority of the increase. In fact, simultaneous studies from other European countries show that *M. avium* isolates in children have not increased, indicating pathogenicity has not changed [20, 32].

Many factors affecting host susceptibility are recognised in adults with NTM infection [24]. However, previous studies have found that most children with NTM infection are otherwise healthy and immunocompetent [2]. In Finland, primary immunodeficiency diseases and Mendelian susceptibility to mycobacterial diseases are rare. Although immunosuppressive medications have become more available, in children under the age of five they remain rare. HIV prevalence in children is very low in Finland and only one native-born pediatric case has been reported to the NIDR since 1995. Therefore, significant changes between cohorts that would affect host susceptibility under the age of five, other than BCG, have not occurred.

Our retrospective study holds some limitations. Information on medication, HIV and vaccination status was not available. The BCG coverage of infants, however, has decreased considerably and coincides with the clear increase in childhood NTM infections excellently. Since the date when symptoms started was not available, we could not examine the seasonal distribution of infections. We accepted all cases based on an isolation from any site and acknowledge that an isolation of NTM may also indicate colonization. However, most of the culture samples were from needle aspiration, tissue biopsy, or purulent or other discharge (N=89; 92%) that would likely represent relevant specimen and disease especially in children under five years of age. Furthermore, a study in Denmark found that positive NTM cultures among children represented definite disease in 95% of the cases [20]. Because NTM cultures have low-yield (~50%), all NTM cases are not captured in the registry and actual disease burden might be higher. Also, a novel blood based IGRA method for diagnosing childhood NTM lymphadenitis has recently been introduced in Finland and cultures may be considered unnecessary [33]. This may have decreased the number of cases in the selective-BCG cohorts only.

The burden of NTM disease in high TB incidence countries, where environmental exposure to NTM, BCG coverage and HIV prevalence are likely higher, is largely unknown [1]. Evidence suggests that prior NTM exposure affects the efficacy of BCG vaccine against TB and tuberculin

skin test as a diagnostic test for TB [2, 34, 35]. Furthermore, prior NTM exposure may provide some protection against TB [35]. BCG has also shown nonspecific or heterologous effects influencing the immune response to other vaccines and reduced all-cause mortality in resource limited countries [8, 9]. Thus, understanding the interactions between the immune system, BCG, NTM and TB will advance the development of new vaccines and diagnostic tests in the future. As the non-BCG-vaccinated cohorts mature, it is possible to examine whether NTM infections in adolescents and adults in Finland will increase. As the efficacy of BCG against tuberculosis is highest in young children, who are also the main risk group for NTM disease, a remarkable increase in older age groups is unlikely.

In Finland, during universal vaccinations with Statens Serum Institut vaccine the incidence of lymph node abscesses caused by BCG from 2002 to 2004 was 150 per 100,000 vaccinated [36]; far higher than the estimated incidence of childhood NTM infections currently. Furthermore, serious complications, such as osteitis, arthritis and generalized BCG, were observed in 14 per 100,000 vaccinated [36]. Though other BCG strains may be less reactogenic, BCG remains a live vaccine which may cause serious adverse effects. Considering these and the self-limiting nature of NTM lymphadenitis, it is our opinion that utilizing BCG merely for NTM prevention is not advisable.

Our study presents a large retrospective population-based cohort with complete capture of culture confirmed childhood NTM infections nationwide over a 21-year period including a major change in BCG coverage. We observed a drastic increase in childhood NTM infections after infant BCG coverage decreased which supports the hypothesis that BCG offers protection against childhood NTM disease. This observation adds to the understanding of NTM epidemiology and might explain why the disease is emerging in some developed countries.

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Conflict of interest. All authors: No conflict.

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Tables/figures

Table 1. The source of the culture specimens and isolated species of 97 native-born children aged 0–4 years with nontuberculous mycobacterial infection registered between 1995 and 2016 to the National Infectious Diseases Register in Finland.

Culture specimen[a]	**n (%)**
Needle aspiration or tissue biopsy from	
lymph node	7 (7)
cervicofacial mass or anomaly	6 (6)
unspecified abscess	4 (4)
unspecified source	61 (63)
Purulent or other discharge material	11 (11)
Skin	2 (2)
Nasopharynx	1 (1)
Unknown	5 (5)
Isolated species	**n (%)**
M. avium	69 (71)
M. lentiflavum	7 (7)
M. malmoense	6 (6)
M. intracellulare	3 (3)
M. bohemicum	2 (2)
M. interjectum	2 (2)
M. fortuitum	1 (1)
M. abscessus	1 (1)
M. gordonae	1 (1)
M. scrofulaceum	1 (1)
M. simiae	1 (1)
M. kansasii	1 (1)
NTM, unspecified	2 (2)

NOTE.
[a]Based on data reported to the registry.

Table 2. Characteristics of Finnish birth cohorts born from 1995 to 2015 and estimated incidence rates per 100,000 person-years of non-tuberculous mycobacterial infection in children under the age of five.

BCG policy	Birth cohort	Cohort population	No. (%) with foreign-born mother	Total person-years[c]	No. of cases	Incidence rate[d]
universal	1995	63 067	1 881 (3.0)	315 335	0	0.0
	1996	60 723	1 989 (3.3)	303 615	0	0.0
	1997	59 329	2 133 (3.6)	296 645	0	0.0
	1998	57 108	2 267 (4.0)	285 540	2	0.7
	1999	57 574	2 382 (4.1)	287 870	0	0.0
	2000	56 742	2 381 (4.2)	283 710	0	0.0
	2001	56 189	2 633 (4.7)	280 945	0	0.0
	2002	55 555	2 696 (4.9)	277 775	1	0.4
	2003	56 630	2 825 (5.0)	283 150	1	0.4
	2004	57 758	2 959 (5.1)	288 790	0	0.0
	2005	57 745	3 220 (5.6)	288 725	0	0.0
	I/2006[a]	39 801	2 378 (6.0)	199 005	3	1.5
selective	II/2006[b]	19 039	1 138 (6.0)	95 195	5	5.3
	2007	58 729	3 690 (6.3)	293 645	16	5.4
	2008	59 530	3 923 (6.6)	297 650	14	4.7
	2009	60 430	4 290 (7.1)	302 150	11	3.6
	2010	60 980	4 760 (7.8)	304 900	16	5.2
	2011	59 961	4 969 (8.3)	299 805	9	3.0
	2012	59 493	5 415 (9.1)	267 719	7	2.6
	2013	58 134	5 625 (9.7)	203 469	8	3.9
	2014	57 232	6 219 (10.9)	143 080	3	2.1
	2015	55 472	6 363 (11.5)	83 208	1	1.2

NOTE.
[a]Born from January to August 2006.
[b]Born from September to December 2006.
[c]Total person-years in cohort observed up until December 31, 2016 or five years of age.
[d]Number of cases per 100,000 person-years.

Table 3. Reported incidence of non-tuberculous mycobacterial infection in children under the age of five in published studies and the Bacillus Calmette-Guérin policy of the cohort population or in the respective countries during the study period [19].

Study	Country	Study period	BCG policy	Age group (years)	Measure of disease frequency	Frequency/ 100,000
our study	Finland	1995–2016[a]	universal	0–4	Annual incidence rate of infection[c]	0.2
Katila et al (1987)	Finland	1977–86	universal	1–4	Annual incidence rate of cervical adenitis	0.6
Romanus et al (1995)	Sweden	1969–74	universal	0–4	Annual incidence of extrapulmonary infection	0.06
our study	Finland	2007–2016[b]	selective	0–4	Annual incidence rate of infection[c]	3.9
Romanus et al (1995)	Sweden	1975–80	selective	0–4	Annual incidence of extrapulmonary infection	2.5
Romanus et al (1995)	Sweden	1981–85	selective	0–4	Annual incidence of extrapulmonary infection	5.7
Romanus et al (1995)	Sweden	1986–90	selective	0–4	Annual incidence of extrapulmonary infection	4.5
Hermansen et al (2017)	Denmark	1991–2015	selective	0–4	Annual incidence rate of infection	5.4
Haverkamp et al (2004)	The Netherlands	2001–03	selective	0–4	Annual incidence of extrapulmonary infection	2.3

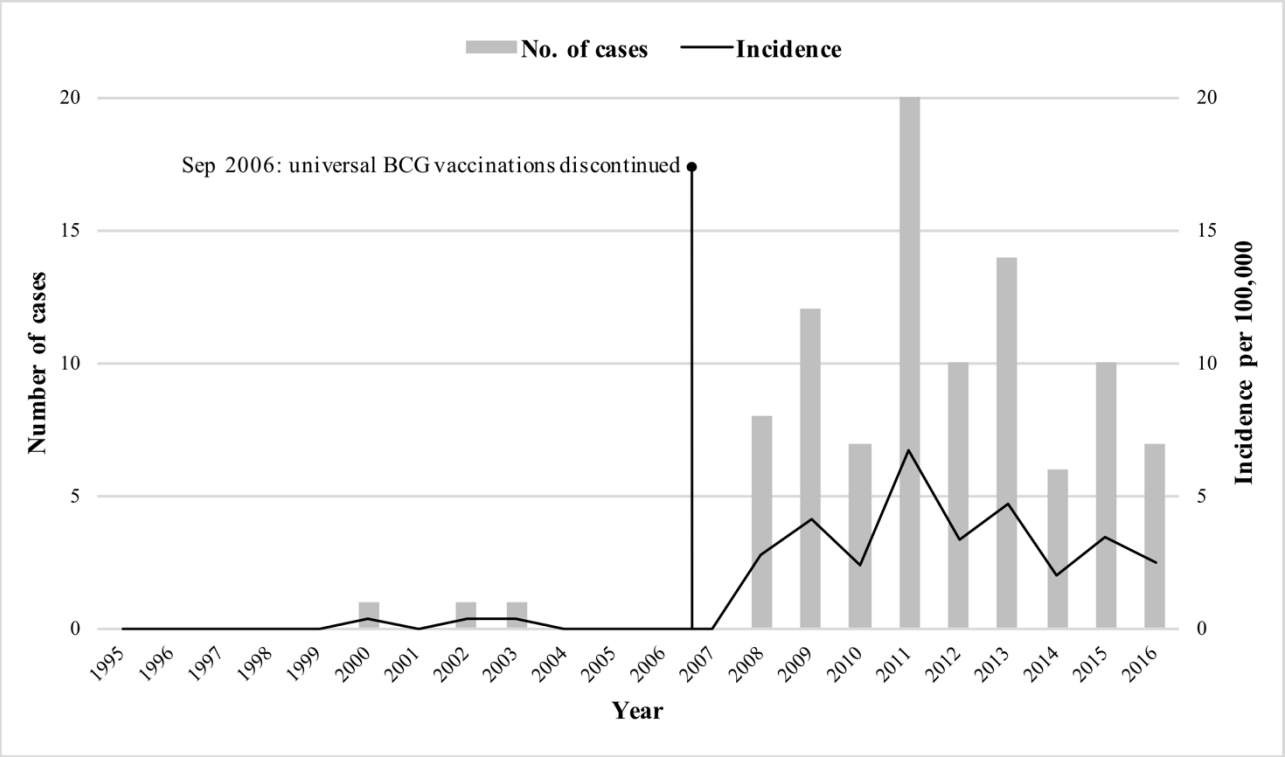
NOTE.

[a]Birth cohort from January 1995 to August 2006.

[b]Birth cohort from September 2007 to December 2015.

[c]The annual incidence rate presented is for native-born children.

Figure 1. Annual number of infections and estimated annual incidence per 100,000 persons of nontuberculous mycobacterial infection in native-born children under the age of five registered between 1995 and 2016 to the National Infectious Diseases Register.


No. of cases
Incidence
Sep 2006: universal BCG vaccinations discontinued
Number of cases
Incidence per 100,000
Year
0
5
10
15
20
1995
1996
1997
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016