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Epidemiology of Kawasaki disease before and after universal Bacille Calmette-Guérin vaccinations were discontinued

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Short title: Kawasaki disease and the Bacille Calmette-Guérin vaccine

Abstract

Aim: Bacille Calmette-Guérin (BCG) vaccine (BCG) has been suggested to induce the primary immunity needed for the subsequent Kawasaki disease (KD). We studied the epidemiology of KD before and after the universal BCG vaccination ended in Finland in September 2006.

Methods: KD cases were retrieved from national health registries from 1996-2016 for annual incidence rates. We then compared 612433 children born in the BCG vaccination era, from 1 January 1996 to 30 August 2006, to 604163 born after BCG era, from 1 September 2006 to 31 December 2016.

Results: The annual incidence rates did not change after the BCG vaccination stopped. We found 370 first visits for KD by children born in the BCG era and 341 after universal BCG vaccination ended. The mean age at diagnosis increased from 2.6 years to 3.0 years (95% CI -0.64 to -0.012, p=0.04) and the proportion of children with Kawasaki disease under five years decreased from 87% to 81% (95% CI 1%-12%, p=0.02).

Conclusion: Discontinuing the universal BCG vaccination programme did not change the incidence rates of KD. The increased age at diagnosis could suggest that the pathogenesis of KD may be associated with the immunological pathways primed by BCG immunisation.

Keywords: Aetiology, Bacille Calmette-Guérin vaccine, epidemiology, immunisation, Kawasaki disease

KEY NOTES

- We studied the epidemiology of Kawasaki disease before and after the universal Bacille Calmette-Guérin (BCG) vaccination ended in Finland in September 2006 using national health registry entries for 711 children.
- Discontinuing the universal BCG vaccination programme did not change the incidence rates of Kawasaki disease.
- However, the mean age at diagnosis increased, which could suggest that the pathogenesis of Kawasaki disease may be associated with the immunological pathways primed by BCG immunisation.

INTRODUCTION

Kawasaki is a systemic vasculitis disease that mainly affects children under five years of age (1,2). The incidence is slowly increasing in many countries (3-7), probably because of better

awareness among paediatricians. Its aetiology remains unknown and this means that specific diagnostic tests and prevention methods are lacking (1,8). This may lead to a delay in diagnosis and thus increase the possibility of severe complications, such as coronary artery aneurysms (8).

Bacille Calmette-Guérin (BCG) vaccination protects children from *Mycobacterium tuberculosis* and environmental mycobacterial infections (2,9,10). One of the earliest signs of Kawasaki disease in children who have received a BCG vaccination is reactivity at the vaccination site (2,11). Interestingly, one animal model study showed that BCG vaccinations induced the onset of symptoms that were similar to Kawasaki disease in mice (12). Furthermore, it has been suggested that common microbes that are immunogenically related to BCG, such as other environmental mycobacteria, may induce immunological reactions and trigger Kawasaki disease (13). Therefore, BCG might induce the primary immunity needed for the subsequent Kawasaki disease immune reactions stimulated by other environmental mycobacteria (13). However, limited data are available on any connections between BCG and Kawasaki disease in humans.

When the universal BCG vaccination of newborn infants came to an end in Finland on 1 September 2006 (9,10,14) we hypothesised that this could change the epidemiology of Kawasaki disease, given that BCG vaccination may play a role in the pathogenesis of Kawasaki disease. We therefore set out to study the epidemiology of Kawasaki disease for a number of years before and after universal BCG vaccination ended in Finland.

PATIENTS AND METHODS

Study design

We conducted a register-based, nationwide study on the epidemiology of Kawasaki disease in Finland from 1996-2016, which covered the periods before and after the discontinuation of universal BCG vaccination on 1 September 2006. First, we calculated the annual incidence rates and incidence rates for five-year periods. Then, we compared the epidemiology of Kawasaki disease in two birth cohorts in Finland. The first was 612433 children born between 1 January 1996 and 31 August 2006, in the BCG vaccination era. The second was 604163 children born between 1 September 2006 and 31 December 2016, after vaccination ended. We identified children under 16 years of age with Kawasaki disease during the study period from the Finnish Care Register for Health Care. Our research was approved by the Review Board of the National Institute for Health and Welfare, Helsinki, Finland (decision number THL/875/5.05.00/2017).

Registers

The Finnish Care Register for Health Care is maintained by the National Institute for Health and Welfare, Helsinki, and includes data on patients discharged from inpatient care. It also provides additional information from healthcare centres and outpatient care. We identified all patients aged 0-16 years with Kawasaki disease, using the International Classification of Diseases , 10^{th} revision diagnosis code M30.3. The data contained in the register included the patient's name, the personal identity number used in all databases throughout the country, the date of onset of the disease, the date of diagnosis and the hospital or healthcare district where the patient was treated.

Statistics Finland maintains a register that consists of population data for the whole of Finland and we used the number of children born from 1996 to 2016 to calculate the annual incidence rates of Kawasaki disease in Finland.

We evaluated the diagnostic criteria for Kawasaki disease at Oulu University Hospital over the period of 1996-2016, going through the medical records of paediatric patients diagnosed with Kawasaki disease.

Statistical analyses

The child's first Kawasaki disease visit was identified and subsequent or duplicate visits were excluded. Annual numbers of Kawasaki disease cases were calculated. The annual incidence rates with a 95% confidence interval (95% CI) were calculated for all children in Finland. We then carried out separate calculations for children younger than five years. We also calculated the incidence rates for four longer time periods so that we could carry out comparisons that minimised the impact of annual epidemiological fluctuations. These were: 1 January 1996 to 31 December 2000 and 1 January 2001 to 30 August 2006, during the vaccination era, and 1 September 2006 to 31 December 2011 and 1 January 2012 to 31 December 2016, when vaccination had stopped. The epidemiology of Kawasaki disease was compared between the two birth cohorts born before (1January 1996 to 30 August 2006) and after (1 September 2006 to 31 December 2016) the end of universal BCG vaccination. The mean ages at the onset of Kawasaki disease were compared and the statistical significance of the difference was tested using the Student's t-test. The normal standard deviation test was used to compare the difference between the two proportions. The statistical analyses were performed using IBM SPSS Statistics 25 (IBM Corp, New York, USA) and StatsDirect statistical software 3 (StatsDirect Ltd, Merseyside, England).

RESULTS

We identified 5676 Kawasaki disease patients with the M30.3 diagnosis code from 1 January 1996 to 31 December 2016. After excluding 589 duplicates and 3932 follow-up visits, there were 1155 patients with a first visit for Kawasaki disease (Figure 1). Children under five years had higher annual incidence rates than older children aged 5-16 years: 6.7 to 17.9 per 100 000 (Figure 2) versus 0.8 to 5.3 per 100 000.

The annual incidence rates of Kawasaki disease did not change before and after the discontinuation of the universal BCG vaccination (Table 1). In addition to annual incidence rates (Table 1), we calculated the occurrence of Kawasaki disease for longer time periods and these are presented as rates per 100 000 and 95% CIs. There were 215 children aged 0-15 years from 1 January 1996 to 31 December 2000 (21.1, 95% CI 18.4 - 24.1), 300 from 1 January 2001 to 30 August 2006 (30.5, 95% CI 27.2 - 34.2), 336 from 1 September 2006 to 31 December 2011 (35.1, 95% CI 31.5 - 39.1) and 304 from I January 2012 to 31 December 2016 (31.9, 28.4 to 35.7). When we looked at children under the age of five for the same periods there were 144 (47.2, 95% CI 39.8 - 55.5), 198 (69.5, 95% CI 60.2 - 79.9), 207 (69.6, 95% CI 60.5 -o 79.8) and 166 (55.7, 47.6 - 64.9), respectively.

We compared the mean age at onset of the disease in the two birth cohorts: 612 433 children born between 1 January 1996 and 31 August 2006, during universal BCG vaccination, and 604 163 born between 1 September 2006 and 31 December 2016, after universal BCG vaccination ceased (Figure 3). There were 370 with Kawasaki disease patients in the first cohort and 341 in the second. The mean age at the onset of Kawasaki disease was higher in the post BCG vaccination cohort, 3.0 (SD 2.2), than during the vaccination era, 2.6 (SD 2.0) (95% CI -0.64 to -0.012, p=0.04). We then looked at children who were younger than five years at the time of diagnosis and found that 323/370 children (87%) had Kawasaki disease in the first cohort and there were 276/341 (81%) in second cohort. The difference was 6% (95% CI 1%-12%, p=0.02) (Figure 3).

We were able to review 93 of the original medical records and this showed that 76 patients (82%) met the fever criterion and at least four of the other principal clinical criteria for Kawasaki disease.

DISCUSSION

Discontinuing universal BCG vaccination in Finland did not change the overall incidence rates of Kawasaki disease in this register-based, nationwide study covering 1996-2016. Children diagnosed with Kawasaki disease after the end of universal BCG vaccination tended to be slightly older than children in the vaccination era.

The aetiology and pathogenesis of the Kawasaki disease should be better understood if we are to develop effective methods for preventing it. In animal models, BCG vaccination primes immunity until Kawasaki disease-like disease is induced later by microbes related immunogenically to BCG, for example environmental mycobacteria (12,13). Our results show that the cancellation of the universal BCG vaccination program resulted in a shift towards older age at diagnosis. Our epidemiological data thus suggest that BCG vaccination may have primed the immunological pathways in children as well, resulting in the earlier occurrence of KD earlier in children who had received BCG vaccination. This suggests that BCG immunisation may be one of the primers of the immune system before a later cross-reactive immune response leads to Kawasaki disease in some children.

Several microbial agents are thought to be involved in the pathogenesis of Kawasaki disease (15). For example, earlier studies, have suggested *Yersinia*, *Staphylococcus* and *Streptococcus* as possible triggers for Kawasaki disease (13,16). A viral aetiology could also be involved in the pathogenesis of Kawasaki disease (17). This would explain the seasonality of the disease

(15,18,19), with the highest peaks in winter in many countries and the lowest occurrence usually in autumn (18,20). Regional differences in Kawasaki disease seasonality could indicate that the microbial triggers of Kawasaki disease have different epidemiological patterns in different countries (18,20). The nationwide epidemics reported especially in Japan and Finland in the 1980s, suggest that epidemic microbial agents are triggers for Kawasaki disease (20,21). In our study, we observed marked year-to-year fluctuations, with the highest annual incidence rates for Kawasaki disease in 2005 and 2015. Furthermore, genetics is believed to have an effect on the development of this disease, as it is more common in Asian populations, especially in Japan (8,17,20). Host susceptibility is supported by the much higher risk of Kawasaki disease if a sibling or parent has had Kawasaki disease (17,20). This could suggest that microbial antigens act as triggers in genetically susceptible children and lead to the onset of Kawasaki disease (20).

The strength of this study was that we were able to collect comprehensive nationwide data from high-quality national registers for more than 20 years, covering periods before and after the cessation of universal BCG vaccination in 2006. Our study was based on earlier reports of a role for BCG in priming immunity in Kawasaki disease in animal models and the well-known reaction of the BCG immunisation site in children with Kawasaki disease. The main limitation of our study was that, due to the register-based study design, we were not able to analyse any individual data concerning environmental or medical factors. For example, not all children received the BCG vaccine before 2006 and risk groups were still immunised after 2006.

CONCLUSION

This nationwide register-based study covering more than 20 years of the epidemiology of Kawasaki disease in Finland showed that the incidence rates did not change during the immunisation period and after vaccination had ceased. However, there was a slightly older age at diagnosis after universal BCG vaccination was discontinued. This suggests that BCG immunisation may be one of the primers of the immune system before a later cross-reactive immune response leads to Kawasaki disease in some children.

ABBREVIATION

BCG, Bacille Calmette-Guérin; KD, Kawasaki disease

FINANCE

This study did not receive any specific funding.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

REFERENCES

1 Garrido-García LM, Castillo-moguel A, Vázquez-Rivera M, Cravioto P, Fernando G. Reaction of the Bcg Scar in the Acute Phase of Kawasaki Disease in Mexican Children. *Pediatr Infect Dis J* 2017; 36(10): e237-e241.

2 Uehara R, Igarashi H, Yashiro M, Nakamura Y, Yanagawa H. Kawasaki disease patients with redness or crust formation at the Bacille Calmette-Guérin inoculation site. *Pediatr Infect Dis J* 2010; 29(5): 430-433.

3 Lue H, Chen L, Lin M, Chang L, Wang J, Lee C, et al. Epidemiological Features of Kawasaki Disease in Taiwan, 1976–2007: Results of Five Nationwide Questionnaire Hospital Surveys. *Pediatrics & Neonatology* 2014; 55(2): 92-96.

4 Saundankar J, Yim D, Itotoh B, Payne R, Maslin K, Jape G, et al. The epidemiology and clinical features of Kawasaki disease in Australia. *Pediatrics* 2014; 133(4): 1009-14.

5 Pinto FF, Laranjo S, Carmo MM, Brito MJ, Ferreira RC. Twelve Years of Kawasaki Disease in Portugal: Epidemiology in Hospitalized Children. *Pediatr Infect Dis J* 2017; 36(4): 364-368.

6 Kim GB, Park S, Eun LY, Han JW, Lee SY, Yoon KL, et al. Epidemiology and Clinical Features of Kawasaki Disease in South Korea, 2012–2014. *Pediatr Infect Dis J* 2017; 36(5): 482-485.

7 Makino N, Nakamura Y, Yashiro M, Sano T, Ae R, Kosami K, et al. Epidemiological observations of Kawasaki disease in Japan, 2013-2014. *Pediatr Int* 2018; 60(6): 581-587.

8 Singh S, Vignesh P, Burgner D. The epidemiology of Kawasaki disease: a global update. *Arch Dis Child* 2015; 100(11): 1084-1088.

9 Salo E, Renko M, Koivunen P, Heiskanen-Kosma T, Mertsola J, Nokso-Koivisto J, et al. Lymphadenitis caused by nontuberculous mycobacteriae. *Duodecim* 2011; 127(10): 979-986.

10 Kontturi A, Soini H, Ollgren J, Salo E. Increase in Childhood Nontuberculous Mycobacterial Infections After Bacille Calmette-Guérin Coverage Drop: A Nationwide, Population-Based Retrospective Study, Finland, 1995–2016. *Clin Infect Dis* 2018; 67(8): 1265-1261.

11 Kuniyuki S, Asada M. An ulcerated lesion at the BCG vaccination site during the course of Kawasaki disease. *J Am Acad Dermatol* 1997; 37(2): 303-304.

12 Chun J, Jeon BY, Kang D, Kim DS. Bacille Calmette Guérin (BCG) can induce Kawasaki disease-like features in programmed death-1 (PD-1) gene knockout mice. *Clin Exp Rheumatol* 2011; 29(4): 743-750.

13 Nakamura T, Yamamura J, Sato H, Kakinuma H, Takahashi H. Vasculitis induced by immunisation with Bacillus Calmette-Guerin followed by atypical mycobacterium antigen: a new mouse model for Kawasaki disease. *FEMS Immunol Med Microbiol* 2007;49(3): 391-397.

14 Salo E. BCG in Finland: changing from a universal to a selected programme. *Euro Surveill* 2006; 11(3): 18-20.

15 Kitano N, Suzuki H, Takeuchi T. Patient Age and the Seasonal Pattern of Onset of Kawasaki's Disease. *N Engl J Med* 2018; 378(21): 2048-2049.

16 Matsubara K, Fukaya T. The role of superantigens of group A streptococcus and staphylococcus aureus in Kawasaki disease. *Curr Opin Infect Dis* 2007; 20(3): 298-303.

17 Rowley AH, Shulman ST. The Epidemiology and Pathogenesis of Kawasaki Disease. *Front Pediatr* 2018; 6: 374.

18 Burns JC, Herzog L, Fabri O, Tremoulet AH, Rodó X, Uehara R, et al. Seasonality of Kawasaki Disease: A Global Perspective. *PLoS ONE* 2013; 8(9): e74529.

19 Burns JC, Cayan DR, Tong G, Bainto EV, Turner CL, Shike H, et al. Seasonality and Temporal Clustering of Kawasaki Syndrome. *Epidemiology* (Cambridge, Mass.) 2005; 16(2): 220-5.

20 Nakamura Y. Kawasaki disease: epidemiology and the lessons from it. *Int J Rheum Dis* 2018; 21(1): 16-19.

21 Salo E, Pelkonen P, Pettay O. Outbreak of Kawasaki Syndrome in Finland. *Acta Paediatr* 1986; 75(1): 75-80.

Table 1 Annual incidence rates, with 95% confidence intervals, of Kawasaki disease per 100 000 persons younger than 16 years and in children younger than five years in 1996-2016. Universal BCG immunisation was stopped on September 1, 2006.

Year	Incidence < 16 years	95 % CI	Incidence < 5 years	95% CI
1996	3.3	2.4 to 4.7	9.1	6.1 to 13.0
1997	3.2	2.2 to 4.5	6.7	4.2 to 10.3
1998	4.8	3.6 to 6.4	7.2	4.5 to 10.9
1999	4.8	3.5 to 6.3	11.8	8.2 to 16.4
2000	5.0	3.7 to 6.6	12.7	8.9 to 17.5
2001	5.7	4.3 to 7.4	12.2	8.5 to 17.0
2002	4.5	3.2 to 6.0	8.5	5.4 to 12.6
2003	4.2	3.0 to 5.6	8.5	5.4 to 12.6
2004	5.1	3.8 to 6.7	13.7	9.8 to 18.8
2005	7.4	5.8 to 9.3	17.7	13.2 to 23.3
2006*	5.5	4.1 to 7.2	12.5	8.8 to 17.3
2007	6.9	5.3 to 8.7	14.4	10.4 to 19.5
2008	7.1	5.5 to 9.0	13.9	10.0 to 18.9
2009	7.8	6.1 to 9.7	16.8	12.4 to 22.1
2010	5.7	4.3 to 7.4	10.9	7.5 to 15.4
2011	6.0	4.5 to 7.8	9.9	6.7 to 14.1
2012	5.5	4.1 to 7.2	9.9	6.7 to 14.1
2013	5.0	3.7 to 6.7	8.3	5.3 to 12.2
2014	6.0	4.5 to 7.7	9.7	6.5 to 13.9
2015	8.9	7.1 to 11.0	17.2	12.7 to 22.6
2016	6.5	5.0 to 8.3	11.1	7.6 to 15.7

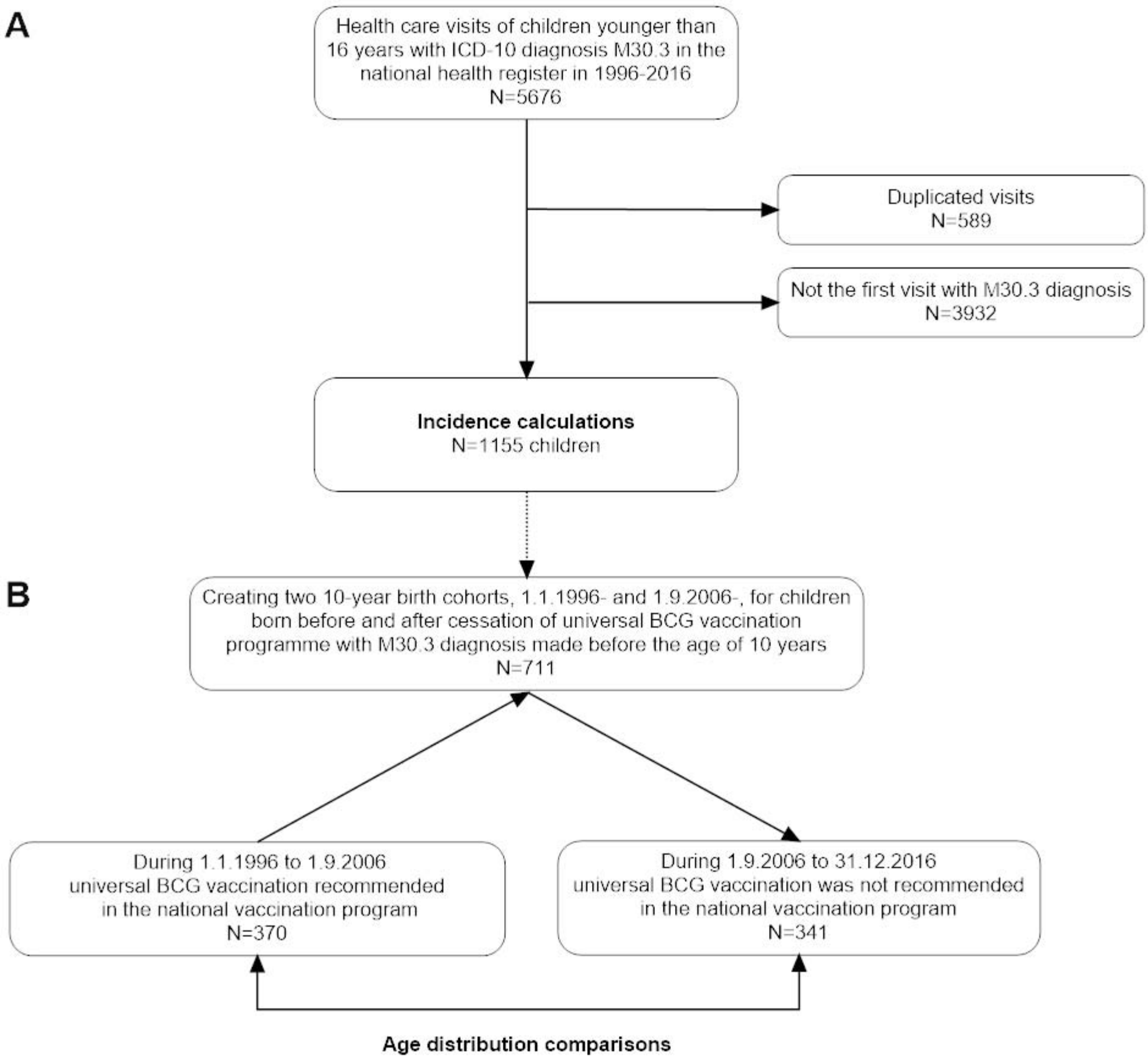
* Universal BCG immunisation program stopped.

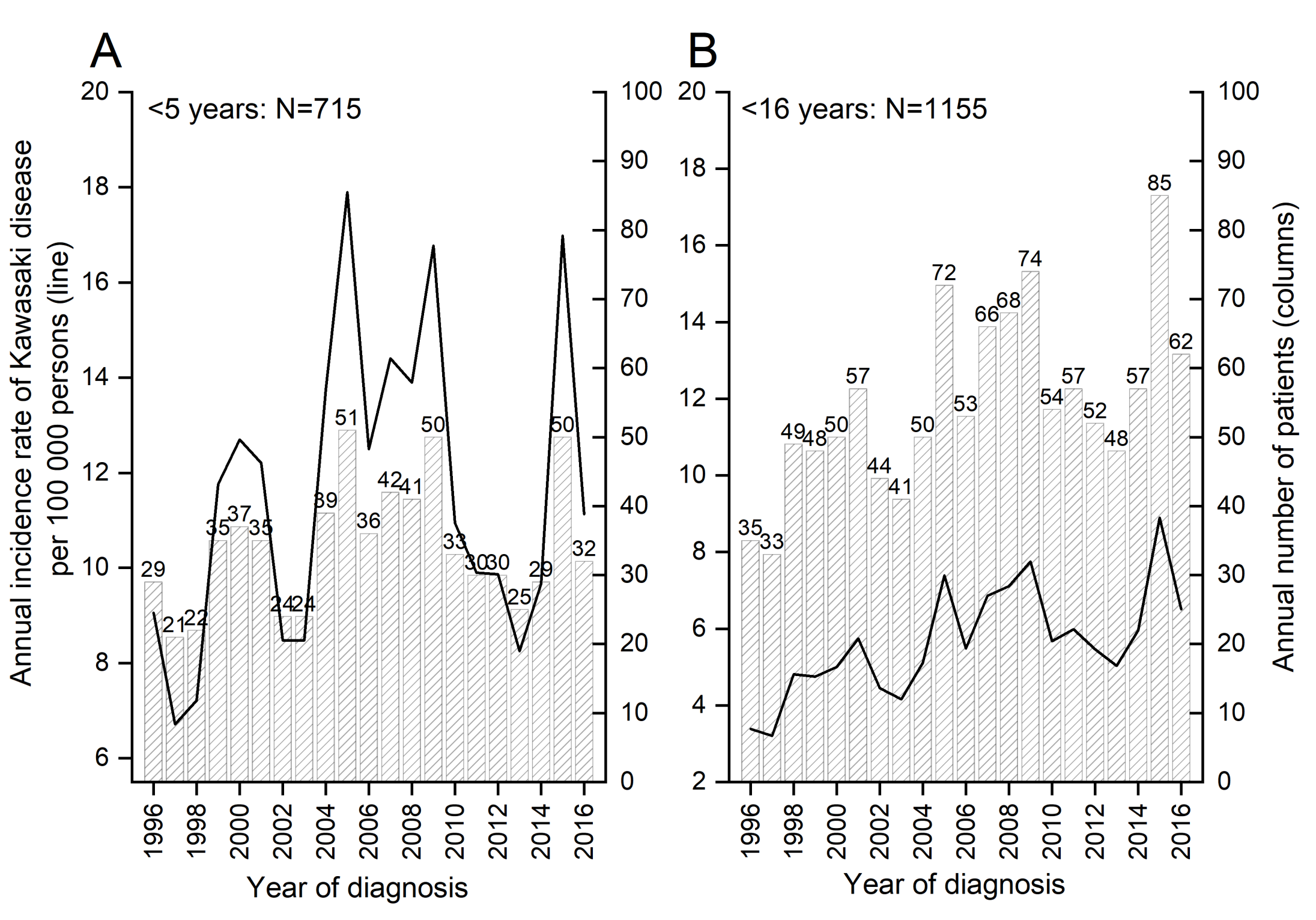
FIGURE LEGENDS

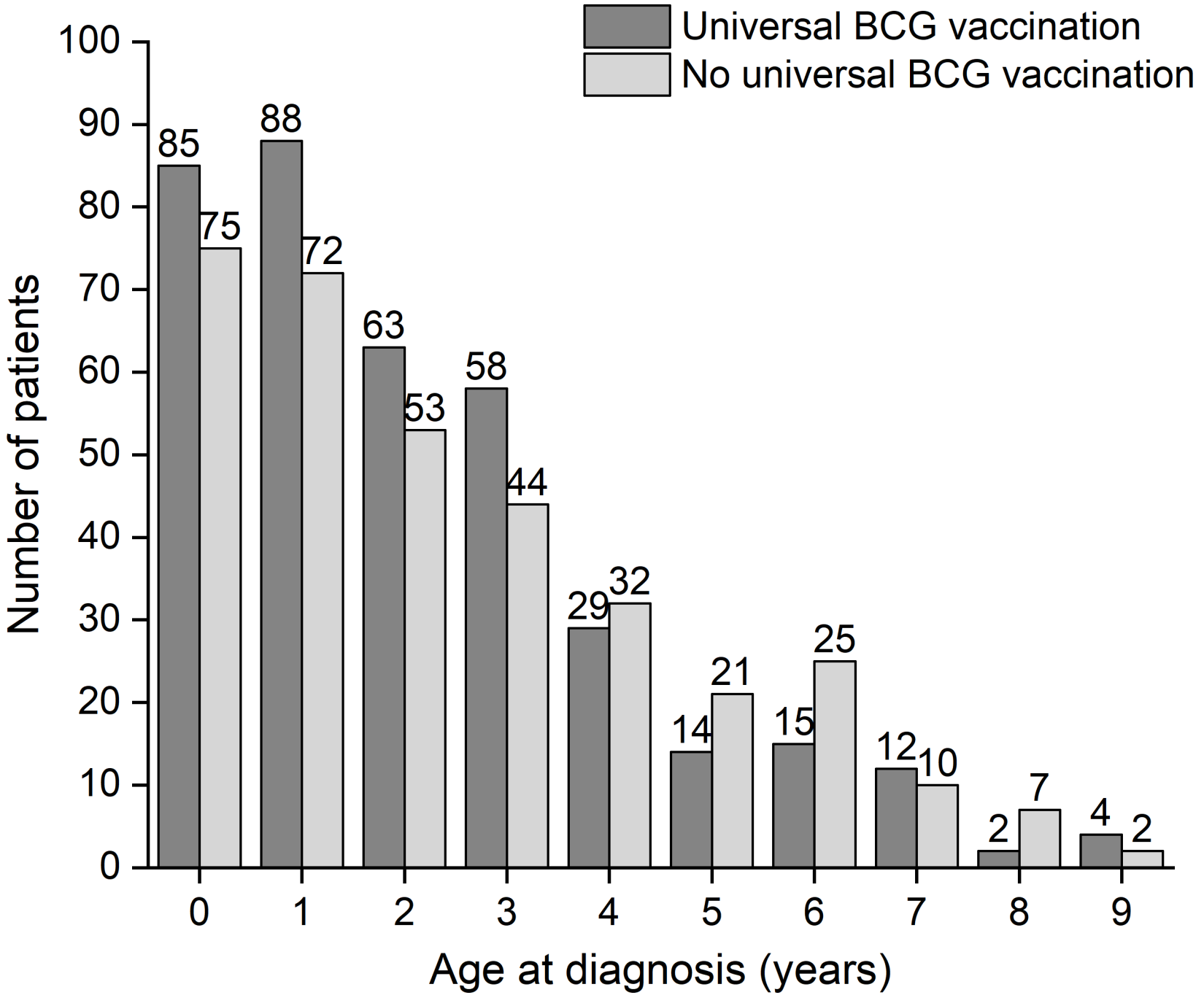
Figure 1. Study design.

Figure 2. Annual incidences of Kawasaki disease per 100 000 children under five years of age (A) and under 16 years (B) from 1996 to 2016. The solid line indicates the annual incidence rates and the grey bars the number of annual cases.

Figure 3. Age at the diagnosis of Kawasaki disease in two birth cohorts: In children born in the BCG immunisation era and in children born after the cessation of universal BCG vaccination.


A
Health care visits of children younger than 16 years with ICD-10 diagnosis M30.3 in the national health register in 1996-2016
N=5676
Duplicated visits
N=589
Not the first visit with M30.3 diagnosis
N=3932
Incidence calculations
N=1155 children
B
Creating two 10-year birth cohorts, 1.1.1996- and 1.9.2006-, for children born before and after cessation of universal BCG vaccination programme with M30.3 diagnosis made before the age of 10 years
N=711
During 1.1.1996 to 1.9.2006
universal BCG vaccination recommended in the national vaccination program
N=370
During 1.9.2006 to 31.12.2016
universal BCG vaccination was not recommended in the national vaccination program
N=341
Age distribution comparisons


A
<5 years: N=715
Annual incidence rate of Kawasaki disease per 100 000 persons (line)
Annual number of patients (columns)
Year of diagnosis
29
21
22
35
37
35
24
24
39
51
36
42
41
50
33
30
30
25
29
50
32
B
<16 years: N=1155
Annual number of patients (columns)
Year of diagnosis
35
33
49
48
50
57
44
41
50
72
53
66
68
74
54
57
52
48
57
85
62


Universal BCG vaccination
No universal BCG vaccination
Number of patients
Age at diagnosis (years)
0
10
20
30
40
50
60
70
80
90
100
0
1
2
3
4
5
6
7
8
9
85
75
88
72
63
53
58
44
29
32
14
21
15
25
12
10
2
7
4
2