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Early Vaccinations Are Not Risk Factors for Celiac Disease

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KEY WORDS

celiac disease, infant, epidemiology, vaccines

ABBREVIATIONS

BCG—bacillus Calmette-Guérin

CD—celiac disease

CI—confidence interval

DT—diphtheria tetanus toxoid (vaccine)

Hib—*Haemophilus influenzae* type b (vaccine)

IPV—inactivated polio vaccine

MMR—measles, mumps and rubella (vaccine)

OR—odds ratio

Pa—acellular pertussis vaccine

T1D—type I diabetes

Drs Ivarsson and Persson, both pediatricians and epidemiologists, and Dr Hernell, pediatrician, were responsible for the original design and data collection. The manuscript was primarily drafted by Dr Myléus, PhD student. The data were analyzed by Dr Myléus, with statistical support from Mr Stenlund, statistician. In addition, Dr Gothefors, pediatrician and former member of the Vaccination Council, Swedish Institute for Infectious Disease Control, and Ms Hammarström, immunologist, contributed substantially with specific knowledge within their respective fields of knowledge. All authors were involved in critical revision of the manuscript and approved its final version.

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WHAT'S KNOWN ON THIS SUBJECT: Celiac disease is an immunologic disorder with autoimmune features. Sweden experienced an epidemic of celiac disease in infants (1984–1996). Early vaccinations might influence the risk for autoimmune diseases, and could potentially have contributed to celiac disease risk and the epidemic.



WHAT THIS STUDY ADDS: Early vaccinations within the national Swedish program are not risk factors for celiac disease, nor do changes over time contribute to explaining the Swedish epidemic. A protective effect by vaccination against tuberculosis (bacillus Calmette-Guérin) is suggested.

abstract

FREE

OBJECTIVES: To investigate if changes in the national Swedish vaccination program coincided with changes in the celiac disease (CD) incidence rate in infants (ie, the Swedish CD Epidemic), and to assess the potential association between these vaccinations and CD risk.

METHODS: All studies were based on the National Swedish Childhood Celiac Disease Register. Using an ecological approach, we plotted changes over time in the national vaccination program in the graph displaying CD incidence rate. A population-based incident case-referent study of invited infants was performed. Exposure information was received through a questionnaire and child health clinic records. Vaccines explored were diphtheria/tetanus, pertussis (acellular), polio (inactivated), *Haemophilus influenzae* type b (conjugated), measles/mumps/rubella, and live attenuated bacillus Calmette-Guérin (BCG) in children with increased tuberculosis risk. Findings were subjected to a birth cohort analysis.

RESULTS: Introduction of pertussis vaccine coincided in time with decreasing CD incidence rates. In the infant case-referent study, however, neither vaccination against pertussis (odds ratio 0.91; 95% confidence interval 0.60–1.4), nor against *Haemophilus influenzae* type b or measles/mumps/rubella was associated with CD. Coverage for the diphtheria/tetanus and polio vaccines was 99%. BCG was associated with reduced risk for CD (adjusted odds ratio 0.54; 95% confidence interval 0.31–0.94). Discontinuation of general BCG vaccination did not affect the cumulative incidence of CD at age 15 years.

CONCLUSIONS: Early vaccinations within the national Swedish program were not associated with CD risk, nor could changes in the program explain the Swedish epidemic. A protective effect by BCG was suggested, which could be subject to further studies. *Pediatrics* 2012;130:e63–e70

Celiac disease (CD) is an immunologic disorder with autoimmune features¹ affecting approximately 0.5% to 2.0% of the general population,^{2,3} and is more common in girls than boys.⁴ In infants, the disease predominantly presents with gastrointestinal symptoms,⁵ whereas in children and adults the clinical spectrum varies from vague to severe symptoms.⁶ Prerequisites for disease development are genetic predisposition (human leukocyte antigen [HLA]-DQ2 or HLA-DQ8) and exposure to wheat gluten proteins and related prolamines in rye and barley. In individuals developing CD, ingestion of these prolamines causes a small intestinal lesion characterized by villous atrophy, crypt hyperplasia, and production of interferon- γ by T cells.^{1,7,8} Production of antibodies to wheat gluten and autoantigens, such as tissue-transglutaminase, is characteristic. On a gluten-free diet, interferon- γ and antibody production ceases and the small intestinal lesion resolves.²

From 1984 to 1996, Sweden experienced an epidemic of symptomatic CD among infants.^{9,10} The epidemic pattern, a rapid fourfold increase in incidence rate, followed by an equally abrupt decline 1 decade later, is unique for an immunologic and autoimmune disease, indicating that not only genetics but also environmental and lifestyle factors have a causal role in disease development. Probable contributing factors should have affected a large proportion of the pediatric population, changed over time, and had the potential to affect the immune system. The cause of the epidemic has partly been attributed to changes in infant feeding practices,¹¹ but among additional contributing factors, 1 possible candidate is early vaccinations.

Most countries worldwide have a national vaccination program for children. In Sweden, the first national program was initiated in the 1940s and today encompasses 9 vaccines for routine use and another 4 are offered to

risk groups.¹² Since initiation of the first program, changes have been made regarding types of vaccines used, age at administration, and number of doses.¹³ Because vaccines modulate the immune system, they have been proposed to be causal risk or protective factors for autoimmune diseases^{14–16} (eg, type 1 diabetes [T1D]). Because CD has autoimmune traits and shares several features with T1D, this may also apply to CD.¹⁷ To our knowledge, the potential association between CD and vaccinations has not been previously analyzed. We hypothesized that immunologic responses to vaccinations may influence the immune reaction toward gluten proteins and thereby affect the risk for CD in genetically predisposed individuals.

The objectives of this study were twofold: to investigate if changes in the national Swedish vaccination program coincided with the changes in CD incidence rate in the beginning and end of the Swedish CD epidemic, and to assess the potential association between early vaccinations and CD risk.

METHODS

Study Design

Different epidemiologic designs were used (Fig 1). The National Swedish Childhood Celiac Disease Register, with quality-controlled data for the period from 1973 to 2003, constituted the basis for all studies. To investigate if changes in the national Swedish vaccination program coincided in time with changes seen in CD incidence rate, an ecological approach was used. To assess the potential association between early vaccinations and CD risk, we used an incident case-referent design. Relevant findings from the infant case-referent study were compared between birth cohorts.

National Swedish Childhood Celiac Disease Register

The incidence register was initiated in 1991 with 14 pediatric clinics, covering

40% of the pediatric population, prospectively reporting all new cases. In 1998, the register became nationwide.^{9,10} For the period 1973 to 1991, 5 units, covering 15% of the pediatric population, reported retrospectively (Fig 1). Included cases were younger than 15 years of age and had biopsy-verified CD, according to criteria set by the European Society of Pediatric Gastroenterology, Hepatology, and Nutrition.¹⁸ Population data were obtained from Statistics Sweden (www.scb.se).

Ecological Approach

The ecological approach focused on changes in the vaccination program starting 4 years before until 4 years after the increase and decrease, respectively, in CD incidence rate. In the graph displaying the incidence rate in infants, we plotted the point in time when new or modified vaccines were introduced and any changes over time in vaccination population coverage. Data on changes in the national vaccination program were obtained from the Swedish Council on Technology Assessment in Health Care¹³ and data on vaccination coverage in children at 2 years of age were obtained from the Swedish Institute for Infectious Disease Control (www.smittskyddsinstitutet.se) and the National Board of Health and Welfare (www.socialstyrelsen.se).

Infant Case-Referent Study

From November 1, 1992, to April 30, 1995, all children reported to the CD register ($n = 714$) were invited to a case-referent study called “Child Health in the 1990s” (Fig 2). Requirements for participation were informed consent with full personal identity number, and biopsy-verified CD according to European Society of Pediatric Gastroenterology, Hepatology, and Nutrition.¹⁸ During this period, 3 consecutive small intestinal biopsies constituted the established routine in Sweden for

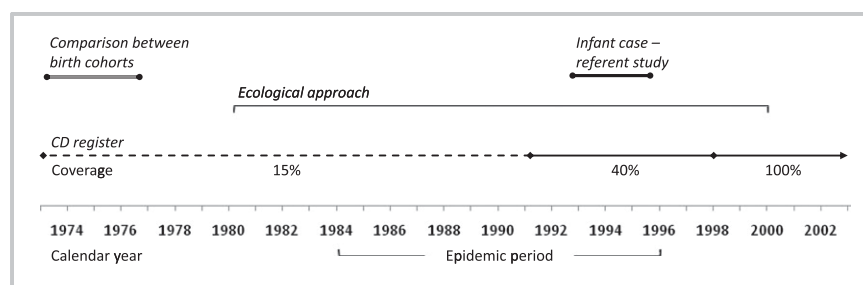


FIGURE 1

Epidemiologic studies based on the Swedish National Childhood Celiac Disease Register (CD register) with coverage (%) of the pediatric population. The dotted line represents retrospectively collected data and the solid line represents prospectively collected data. At indicated time periods, an ecological approach, a case-referent study, and comparison between cohorts were performed.

diagnosis in infants (ie, a first biopsy for diagnosis followed by a second during a gluten-free diet, and a third after gluten challenge).¹⁹ This routine for diagnosis was required for participation, excluding 38 children. Of the eligible children, 475 were infants at diagnosis and included in this study (Fig 2). For

every case, 2 referents were selected from the national population register after matching for date of birth, gender, and residence area. All cases and referents received a questionnaire regarding family characteristics, infant feeding, and the child's general health. The questionnaire did not reveal the special interest in CD. For prospectively recorded data on early vaccinations, we requested the child health clinic records from well-baby clinics, with data on type of vaccinations given and date of administration. Both the questionnaire and the child health clinic record were available for 428 cases and 693 referents. Inclusion criteria were defined as a matched set of 1 case with 1 or 2 referents with complete information on all vaccinations. The final analyses included 1015 infants: 392 cases (83%) and 623 referents (66%) (Fig 2).

Comparison Between Birth Cohorts

Based on the register data, the cumulative incidence of CD at 15 years of age was compared for different birth cohorts to further analyze relevant findings in the infant case-referent study. Information on vaccinations was obtained from the same sources as for the ecological approach.

Vaccines

Vaccinations within the national Swedish program were explored; thus, the study was restricted to vaccines in routine use. The program, at the time of interest,

included diphtheria/tetanus toxoid vaccine (DT), acellular pertussis vaccine (Pa), inactivated polio vaccine (IPV), conjugated *Haemophilus influenzae* type b vaccine (Hib), attenuated measles/mumps/rubella vaccine (MMR), and for children in risk groups, also vaccination against tuberculosis with live attenuated variant of *Mycobacterium bovis* (ie, bacillus Calmette-Guérin vaccine [BCG]).¹³ Further details are given in Table 1.

Definitions

Infant was defined as a child younger than 2 years. The infant's vaccination status was defined as vaccinated for a given vaccine after the date the initial dose was given, and unvaccinated until then. Infants with CD were considered unvaccinated, with respect to their disease, if vaccinated after diagnosis. Age at CD diagnosis was defined as age at the first small intestinal biopsy, and the referents in each matched set received the same cutoff age. As previously described in detail,¹¹ breastfeeding included both exclusive and partial breastfeeding. Breastfeeding at the time of gluten introduction was categorized into discontinued the month before introduction, continued the month during introduction, and continued beyond that time. The amount of gluten-containing flour per day, 2 weeks after introduction, was calculated from questionnaire data and standard recipes.¹¹

Statistical Analyses

The CD incidence rate was calculated as the number of new cases divided by the total person-time at risk, approximated as the midyear population each year. Vaccination coverage was presented as percentages of vaccinated infants per birth cohort, and once with mean value with SD. Cumulative incidence of CD per birth cohort was calculated as the total number of cases per year divided by the number of children in that population

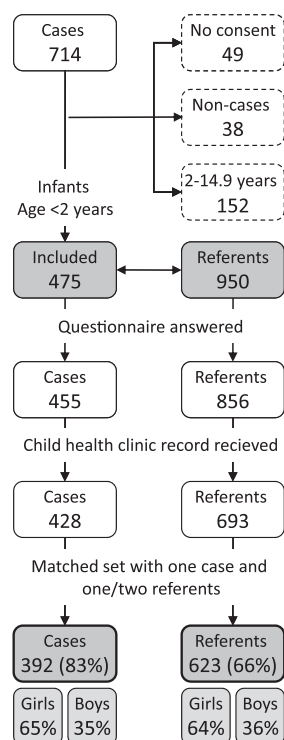


FIGURE 2

Flow chart depicting number of participants in the infant CD case-referent study. Numbers of children and percentages are given in the boxes. Boxes with dotted lines indicate excluded children. Gray shaded areas indicate invited infants and those included in the final analysis.

TABLE 1 Vaccinations Within the National Swedish Vaccination Program During the Epidemic Period

Disease	Vaccine ^a	Type of Vaccine	Age at First Dose, mo	Route	Combinations ^b
Diphtheria	D	Inactivated toxin	3	IM	DT: DTPa during trial and after Pa introduction
Tetanus	T	Inactivated toxin	3	IM	
Pertussis	Pa	Acellular component	3	IM	
Polio	IPV	Inactivated virus	3	IM	IPV: IPV+Hib after introduction
<i>Haemophilus influenzae</i> type b	Hib	Conjugated component	3	IM	
Measles	M	Attenuated virus	18	SC	MMR
Mumps	M	Attenuated virus	18	SC	
Rubella	R	Attenuated virus	18	SC	
Tuberculosis	BCG	Live attenuated	0 or 6	ID	

ID, intradermal; IM, intramuscular; SC, subcutaneous.

^a Abbreviation for vaccine name.

^b Main combinations are presented. They differed depending on time (Fig 3) and geographical area.

birth cohort. A difference in cumulative incidence of CD between birth cohorts was evaluated by using the χ^2 test. In the infant case-referent study, variables were presented by using proportions and, when appropriate, median values with interquartile range. Missing answers for possible confounders were coded as separate categories. Associations between categorical variables were compared for cases and referents, with χ^2 tests and stratified analyses performed, including stratifications for gender. Conditional logistic regression models were developed and evaluated in bivariate and multivariate analyses. Data summarization and statistical analyses were done with PASW Statistics 18 (SPSS Inc, Chicago, IL). Statistical significance was defined as $P < .05$ or an odds ratio (OR) with a 95% confidence interval (CI) not including 1.0.

Ethical Considerations

The research ethics committees of all Swedish medical faculties and the Swedish Data Inspection Board approved the study. All participating families gave informed consent.

RESULTS

Ecological Approach to Celiac Disease and Vaccinations

The incidence rate of CD in infants changed in a pattern resembling an epidemic between 1984 and 1996, and during that period the national vaccination program underwent some changes

(Fig 3). Vaccination with DT and IPV remained unchanged, with coverage of ~99%. In the early 1980s, BCG vaccination coverage increased but remained largely the same during the epidemic period (mean 13.8% $\pm$ 1.2% SD).

In 1982, 2 years before the increase in CD incidence rate, MMR combination vaccine replaced the separate vaccines for measles and rubella, and at the same time, a vaccine against mumps was introduced. This change occurred too early to explain the increase in CD incidence rate. Hib was introduced in 1992, which was in the middle of the epidemic period. In 1996, after years of large clinical trials,¹³ Pa was introduced. The clinical trials and subsequent introduction of Pa coincided in time with the decrease in CD incidence rate (Fig 3).

Characteristics of the Study Subjects in the Infant Case-Referent Study

The study population consisted of 392 infants with CD, whereof two-thirds were girls, and their gender- and age-matched referents ($n = 623$) (Fig 2). Median age at onset of symptoms indicative of CD was 11 months (interquartile range 9–13 months). Median age at diagnosis was 15 months (interquartile range 12–17 months).

Vaccination Against Pertussis (Pa) and CD Risk

From the ecological approach, introduction of Pa could be connected in

time to the decrease in CD incidence rate. In 1996, Pa reached almost complete coverage; however, because the infant case-referent study was performed during the years of the clinical trials, ~25% of the infants were vaccinated (Table 2). In the infant case-referent study, we found no association between Pa and CD risk (OR 0.91; 95% CI 0.6–1.4). Vaccination coverage and separate risk assessments were similar for boys and girls (data not shown).

Vaccination With DT, IPV, Hib and MMR, and CD Risk

We found that both cases and referents received DT, IPV, Hib, and MMR to approximately the same extent (Table 2). Risk assessment in relation to DT and IPV was not feasible owing to 99% vaccination coverage. CD risk was not associated with Hib, or with MMR. Vaccination coverage and separate risk assessments were similar for boys and girls (data not shown).

Vaccination Against Tuberculosis (BCG) and CD Risk

In the infant case-referent study, 4.8% of the CD cases were BCG vaccinated and the corresponding number for the referents was 8.5% (Table 3). Median age for BCG vaccination was 5.3 months among cases and 0.2 months for referents ($P = .02$). Girls received BCG more often than boys (9.3% vs 4.1%, $P = .003$). The decreased risk for CD among

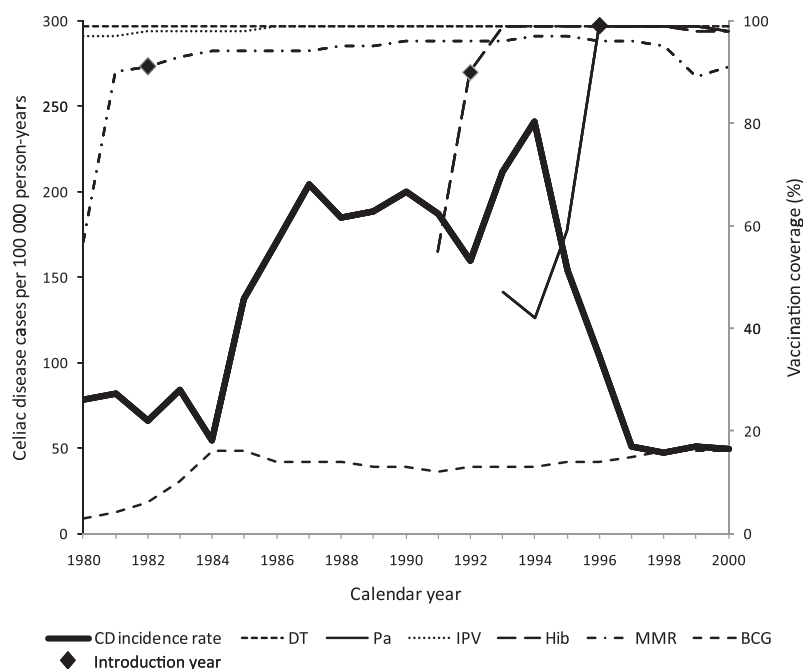


FIGURE 3

Changes over time in CD incidence rate in infants¹⁰ in relation to changes over time in the national Swedish vaccination program, including both introductions of new vaccines and changes in vaccination coverage at 2 years of age. The diamond shape indicates the year when the respective vaccine was introduced into the program.

infants vaccinated with BCG remained significant in the multivariate analysis (adjusted OR 0.54; 95% CI 0.31–0.94), even after adjusting for 2 exposures suggested to affect CD risk (Table 3). Separate assessments showed adjusted OR 0.54 (95% CI 0.29–0.99) for girls, and adjusted OR 0.48 (95% CI 0.11–2.07) for boys. As in our previous reports,¹¹ there was a reduced risk for CD in infants who were breastfed at and beyond introduction of gluten-containing

flour and an increased risk for CD in infants receiving large amounts of flour (Table 3). ORs suggested that BCG vaccination was at least as efficient as breastfeeding in decreasing the risk for CD (Table 3).

BCG and Comparison Between Birth Cohorts

General vaccination against tuberculosis with BCG was replaced with a selective strategy in 1975. This caused

a drop in vaccination coverage from ~95% before 1975 to ~2% in 1976/77.²⁰ The selective strategy involved vaccination of risk groups: (1) children potentially exposed to persons with tuberculosis; (2) children whose parents came from countries with a high occurrence of tuberculosis; and (3) children in families planning to stay for longer periods in an area where tuberculosis is common.^{12,21} This was reflected in the characteristics of the BCG-vaccinated group, most commonly with 1 or 2 parents from a country other than Sweden, for both cases and referents. The change in strategy in 1975 enabled a comparison between different birth cohorts. Children born in 1973/74 had the same cumulative incidence of CD at 15 years of age as children born in 1976/77 ($P = .47$) (Fig 4).

DISCUSSION

In this study, by using different epidemiologic designs, we found no association between early vaccinations and risk for CD. On the contrary, a protective effect by BCG vaccination was suggested. Neither changes over time in the national Swedish vaccination program, nor changes in the population's vaccination coverage contributed to explaining the changes in CD incidence rate (ie, the Swedish CD epidemic).

Vaccinations have long been discussed as potential protective or risk factors for autoimmune diseases. The hypothesis has been that vaccinations, particularly live attenuated vaccines, such as BCG,¹⁵ affect the risk through 1 or more of the following mechanisms: (1) molecular mimicry; (2) impact on the developing immune system (eg, regulatory T cells); or (3) nonspecific immunologic effects (eg, heterologous immunity).^{15,16,22} These mechanisms are partly the same as proposed for how infections and microbiota might affect the risk for autoimmune diseases.^{16,23,24}

TABLE 2 Vaccination Coverage for Cases and Referents and Association with CD

Exposures ^a	Descriptives		Bivariate Logistic Regression ^b OR (95% CI)
	Cases (<i>n</i> = 392) <i>n</i> (%)	Referents (<i>n</i> = 623) <i>n</i> (%)	
Pertussis (Pa)			
Nonvaccinated	291 (74)	457 (73)	1.0
Vaccinated	101 (26)	166 (27)	0.91 (0.60–1.37)
<i>Haemophilus influenzae</i> type b (Hib)			
Nonvaccinated	81 (21)	132 (21)	1.0
Vaccinated	311 (79)	491 (79)	1.01 (0.68–1.52)
Measles/mumps/rubella (MMR)			
Nonvaccinated	320 (82)	512 (82)	1.0
Vaccinated	72 (18)	111 (18)	0.99 (0.58–1.69)

^a Vaccines within the national Swedish program.

^b Conditional logistic regression using matched sets of case and referent(s).

TABLE 3 Vaccination Against Tuberculosis (BCG) and Association With CD, Including Adjustment for Other Exposures Suggested to Affect CD Risk

Exposures ^a	Descriptives		Bivariate Logistic Regression ^b	Multivariate Logistic Regression ^c
	Cases (<i>n</i> = 392) <i>n</i> (%)	Referents (<i>n</i> = 623) <i>n</i> (%)	OR (95% CI)	OR (95% CI)
BCG vaccination				
Nonvaccinated	373 (95)	570 (92)	1.0	1.0
Vaccinated	19 (4.8)	53 (8.5)	0.54 (0.32–0.93)	0.54 (0.31–0.94)
Breastfeeding at introduction of flour				
Discontinued	196 (50)	179 (29)	1.0	1.0
Continued	89 (23)	136 (22)	0.59 (0.42–0.84)	0.62 (0.43–0.88)
Continued beyond	82 (21)	242 (39)	0.33 (0.24–0.46)	0.37 (0.26–0.52)
Nonresponse ^d	25 (6.4)	66 (11)	0.37 (0.22–0.61)	0.56 (0.24–1.27)
Amount of flour per day 2 weeks after the first portion				
Small-Medium	184 (47)	344 (55)	1.0	1.0
Large	174 (44)	189 (30)	1.86 (1.38–2.51)	1.45 (1.05–1.99)
Nonresponse ^d	34 (8.7)	90 (14)	0.75 (0.49–1.16)	0.80 (0.39–1.63)

^a BCG and infant feeding practices. For definitions, see Methods.

^b Conditional logistic regression using 392 matched sets of case and referent(s).

^c Multivariate model including both BCG and infant feeding.

^d The questionnaire was not completely answered.

To our knowledge, there are no previous studies on vaccinations and CD risk. As CD and T1D share several features, we turned to experiences from diabetes research. Although contradictory results have been presented,^{25,26} a large European multicenter study on T1D found no association with early vaccinations.²⁷ In our study, we found no association between Pa, Hib, or MMR and CD risk, which agrees with findings in T1D.

Regarding BCG, most studies that have shown nonspecific effects were performed in low-income countries or investigated the relationship with asthma.^{28,29} Albeit conflicting results, studies have shown effects that cannot be attributed to the protection of tuberculosis and a stronger effect for girls compared with boys.^{29–32} On the contrary, previous studies on BCG and T1D found no association,^{27,33} but the

evidence remains inconsistent.³⁴ In our study, BCG vaccination was significantly associated with decreased risk for CD (adjusted OR 0.54), but with no difference between girls and boys. Referents received BCG at a younger age, which could indicate that to exert a protective effect, BCG has to be given early in life. Conversely, in the birth cohort comparison, we found no significant difference in cumulative incidence of CD at 15 years of age, and comparable results for T1D were shown in Sweden.³⁵ Since 1975, Sweden has a selective BCG vaccination strategy. Therefore, the BCG-vaccinated group constitutes a risk group for tuberculosis and, consequently, the assumption of exchangeability is compromised. A recent Swedish study showed a lower incidence of CD in second-generation immigrants from low-prevalence countries, indicating genetic effects, but could not exclude involvement of environmental factors³⁶ (eg, intestinal microbiota^{37,38}). This is in accordance with our results, because such a strong association between BCG and CD risk (OR = 0.54) probably could not be attributed only to differences in genetics. Overall, a protective effect by BCG was suggested, but the association should be interpreted with caution.

A strength of this study is that it is based on the quality-controlled National Swedish Childhood Celiac Disease Register. The register encompasses the vast majority of all cases, because all suspected cases are referred to a pediatric unit for diagnosis. At each unit, a contact person reports all incident cases to the register and most cases are reported with full personal identity number,³⁹ enabling follow-up. In the infant case-referent study, referents were randomly selected from the national population register, after matching criteria were fulfilled, and invited at the same time as the case. Referents could consequently be considered representative. The vaccination data

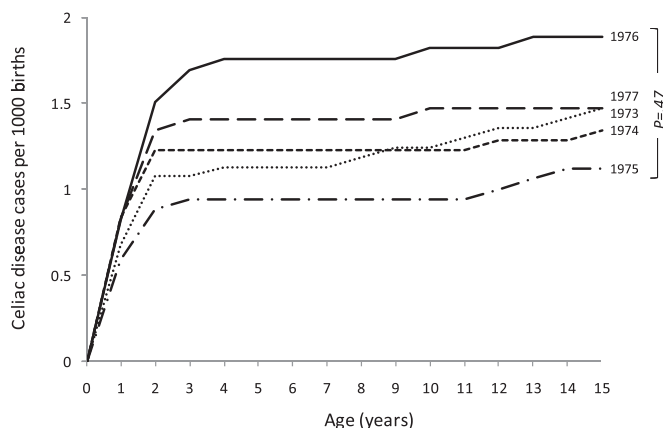


FIGURE 4

Cumulative incidence of CD in birth cohorts before and after a changed strategy for BCG vaccination. In 1975, general BCG was replaced with a selective strategy. Subsequently, BCG coverage dropped from 95% in 1973/74 to 2% in 1976/77. The CD cumulative incidence at 15 years of age remained unchanged.

were well defined, prospectively recorded in the well-baby clinic, and therefore robust. In the national vaccination program, however, MMR is administered at 18 months of age (Table 1), which could be too late to affect CD risk, as most children had not received the MMR before CD diagnosis (median age 15 months). Questionnaire data on possible confounders have been evaluated by using “imputation missing value analysis” without significant impact on results.¹¹ Some questions had nonresponses, but this did not affect the outcome. The cohort analysis was based on the CD register for the period 1973 to 1991, which covered 15% of the pediatric population (Fig 1). At that time, CD was relatively uncommon, which resulted in few cases, yielding a low power for this analysis. In this study, we used different epidemiologic designs; however, in the event of inconsistency between results,

the case-referent design provides the best evidence, as it uses data on the individual level.

One of the consequences of the epidemic was shown by screening children born in 1993 at 12 years of age, revealing a CD prevalence of 3%.⁴ This remarkably high prevalence emphasizes the need to understand what caused the epidemic. The current study excludes 1 possible candidate factor.

CONCLUSIONS

Early vaccinations within the national Swedish program were not associated with CD risk. The Swedish epidemic of CD is not fully understood, and changes in the vaccination program or coverage do not contribute to the explanation. We found no epidemiologic evidence that the immunologic response to vaccinations increases CD risk. Interestingly,

a protective effect by BCG is suggested; however, the BCG-vaccinated group constitutes a risk group for tuberculosis and therefore the result should be interpreted with caution until confirmed in further studies.

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