Childhood Vaccinations, Vaccination Timing, and Risk of Type 1 Diabetes Mellitus

Frank DeStefano, MD*; John P. Mullooly, PhD‡; Catherine A. Okoro, MS*; Robert T. Chen, MD*; S. Michael Marcy, MD§; Joel I. Ward, MD‖; Constance M. Vadheim, PhD‖; Steve B. Black, MD¶; Henry R. Shinefield, MD¶; Robert L. Davis, MD#; Kari Bohlke, ScD#; and the Vaccine Safety Datalink Team

ABSTRACT. *Objectives.* **To evaluate suggested associations between childhood vaccinations, particularly against hepatitis B and *Haemophilus influenzae* type b, and risk of developing type 1 diabetes; and to determine whether timing of vaccination influences risk.**

Methods. **We conducted a case-control study within 4 health maintenance organizations (HMOs) that participate in the Vaccine Safety Datalink project of the Centers for Disease Control and Prevention. Study eligibility was restricted to children who met the following criteria: 1) born during 1988 through 1997; 2) HMO member since birth; 3) continuously enrolled for first 6 months of life; and 4) at least 12 months of HMO membership before diabetes incidence date (or index date for controls) unless incidence date was before 12 months of age. All 4 HMOs maintain registries of their members who have diabetes, and we used the registries to identify potential cases of diabetes. We conducted chart reviews to verify that potential cases met the World Health Organization epidemiologic case definition for type 1 diabetes mellitus (ie, a physician's diagnosis of diabetes plus treatment with daily insulin injections). We defined the incidence date of diabetes as the first date that the child received a diagnosis of diabetes. We attempted to match 3 controls to each case. Controls had the same eligibility criteria as cases and were matched to individual cases on HMO, sex, date of birth (within 7 days), and length of health plan enrollment (up to the incidence or index date). The index date for controls was defined as the incidence date of the case to which the control was matched. Chart abstraction was performed by trained chart abstractors using standardized forms. In addition to complete vaccination histories, the chart abstraction forms for both cases and controls included information on sociodemographic characteristics, selected medical conditions, history of breastfeeding, and family medical history. We used conditional logistic regression to estimate the odds ratio (OR) of diabetes associated with vaccination, with vaccine exposure defined as before the diabetes incidence date (or index date for controls).**

Results. **Two hundred fifty-two confirmed cases of diabetes and 768 matched controls met the study eligibility criteria. The OR (95% confidence interval) for the association with type 1 diabetes was 0.28 (0.07–1.06) for whole cell pertussis vaccine (predominantly in combination as diphtheria, tetanus toxoids and pertussis vaccine), 1.36 (0.70–2.63) for measles-mumps-rubella, 1.14 (0.51–2.57) for *Haemophilus influenzae* type b, 0.81 (0.52–1.27) for hepatitis B vaccine, 1.16 (0.72–1.89) for varicella vaccine, and 0.92 (0.53–1.57) for acellular pertussis-containing vaccines. Compared with children who had not received hepatitis B vaccine, the OR of diabetes was 0.51 (0.23–1.15) for children vaccinated at birth and 0.86 (0.54–1.35) for those first vaccinated against hepatitis B at 2 months of age or later. Race and ethnicity and family history of diabetes were independently associated with risk of type 1 diabetes, but adjustment for these factors did not materially alter the ORs for any of the vaccines.**

Conclusions. **In this large, population-based, case-control study, we did not find an increased risk of type 1 diabetes associated with any of the routinely recommended childhood vaccines. Our study adds to previous research by providing data on newer vaccines, including hepatitis B, acellular pertussis, and varicella vaccines. For the older vaccines, our results are generally in agreement with previous studies in not finding any increased risks. Ours is the first epidemiologic study to evaluate the possibility that timing of vaccination is related to risk of clinical diabetes in children. Our results on hepatitis B vaccine do not support the hypothesis; risk of type 1 diabetes was not different between infants vaccinated at birth and those who received their first vaccination later in life. The results of our study and the preponderance of epidemiologic evidence do not support an association between any of the recommended childhood vaccines and an increased risk of type 1 diabetes. Suggestions that diabetes risk in humans may be altered by changes in the timing of vaccinations also are unfounded. *Pediatrics* 2001;108(6). URL: http://www.pediatrics.org/cgi/content/full/108/6/e112; *hepatitis B vaccine*, Haemophilus influenzae *type b vaccine, epidemiology.***

From the *National Immunization Program, Centers for Disease Control and Prevention, Atlanta, Georgia; ‡Center for Health Research, Northwest Kaiser Permanente, Portland, Oregon; §Kaiser Foundation Hospital, Panorama City, California; ‖Center for Vaccine Research, Harbor-University of California Los Angeles Medical Center, Torrance, California; ¶Pediatric Vaccine Study Center, Northern California Kaiser Permanente, Oakland, California; #Center for Health Studies, Group Health Cooperative, Seattle, Washington.

Received for publication Jun 8, 2001; accepted Sep 4, 2001.

Address correspondence to Frank DeStefano, MD, MPH, Centers for Disease Control and Prevention, 4770 Buford Hwy NE, Mailstop F34, Atlanta, GA 30341-3724. E-mail: fdestefano@cdc.gov

ABBREVIATIONS. Hib, *Haemophilus influenzae* type b; HMO, health maintenance organization; OR, odds ratio; MMR, measles-mumps-rubella.

Type 1 diabetes (formerly known as insulin-dependent diabetes mellitus or juvenile diabetes) results from autoimmune destruction of pancreatic β-cells. Its cause is not known, although genetic and environmental factors are believed to be involved. Vaccinations are among the environmental

factors that have been studied, but most studies have not found an increased risk of type 1 diabetes associated with vaccination.[1–7] Most of the previous studies, however, were conducted before 1990 and do not provide information on many of the currently recommended childhood vaccines.

Classen and Classen[8,9] have hypothesized that certain vaccines (eg, hepatitis B, BCG), if given at birth, can decrease the risk of developing type 1 diabetes mellitus, whereas first vaccination at 2 months of life or later can increase the risk of type 1 diabetes. The few studies reported to date, however, have evaluated vaccine exposure without regard to timing. No controlled epidemiologic studies have been published concerning timing of vaccinations and diabetes risk.

Classen[8] has also hypothesized an association of *Haemophilus influenzae* type b (Hib) vaccination and diabetes. However, a 10-year follow-up study of over 100 000 Finnish children involved in a clinical trial of Hib vaccine did not find an increased risk of diabetes associated with vaccination or with number of vaccinations received.[10] The clinical trial compared children who had received 4 doses of vaccine at 3, 4, 6, and 14 to 18 months of age to children who received only 1 dose at 24 months of age. To provide a nonvaccinated comparison group, the follow-up study included data on a cohort of children born before the vaccination period. Thus, the nonvaccinated group was not concurrent with the 2 vaccinated groups.

We conducted a study in 4 large health maintenance organizations (HMOs). Our objectives were to evaluate the association between receipt of routine childhood vaccines and the risk of type 1 diabetes; to determine whether the timing of hepatitis B vaccine influences diabetes risk; and to assess associations between the schedule of Hib vaccinations and diabetes risk.

METHODS

We conducted a case-control study within 4 HMOs that participate in the Vaccine Safety Datalink project of the Centers for Disease Control and Prevention.[11] Study eligibility was restricted to children who met the following criteria: 1) born during 1988 through 1997; 2) HMO member since birth (ie, "born into the HMO"); 3) continuously enrolled for first 6 months of life; and 4) at least 12 months of HMO membership before diabetes incidence date (or index date for controls) unless incidence date was before 12 months of age.

Cases

All 4 HMOs maintain registries of their members who have diabetes, and we used the registries to identify potential cases of diabetes. In general, the registries include patients who have received a diagnosis of diabetes (*International Classification of Diseases, Ninth Revision* code 250) or filled a prescription for insulin or other glucose-lowering medication. We conducted chart reviews to verify that potential cases met the World Health Organization epidemiologic case definition for type 1 diabetes mellitus: a physician's diagnosis of diabetes plus treatment with daily insulin injections.[12] None of the cases had diabetes secondary to other conditions (eg, cystic fibrosis).

We defined the incidence date of diabetes as the first date that the child received a diagnosis of diabetes. Although the case definition required a physician's diagnosis at some time, the diagnosis for establishing the incidence date (ie, the first diabetes diagnosis) could have been made by a physician or other medical care provider (eg, physician's assistant or nurse practitioner). The diagnosis must have been a definite diagnosis of diabetes; "rule-out," "possible," or other indeterminate diagnoses were not accepted for the case definition or for establishing the incidence date.

Controls

We attempted to match 3 controls to each case. Controls had the same eligibility criteria as cases and were matched to individual cases on HMO, sex, date of birth (within 7 days), and length of health plan enrollment (up to the index date). The index date for controls was defined as the incidence date of the case to which the control was matched. Controls were selected from the HMOs' enrollment files.

Data Collection

Chart abstraction was performed by trained chart abstractors using standardized forms. In addition to complete vaccination histories, the chart abstraction forms for both cases and controls included information on sociodemographic characteristics, selected medical conditions, history of breastfeeding, and family medical history.

Analysis

We used conditional logistic regression to estimate the odds ratio (OR) of diabetes associated with vaccination. In the main analysis, relevant vaccine exposure was considered before the diabetes incidence date (or index date for controls). In the analyses of timing of hepatitis B vaccination, we categorized exposure according to age at first vaccination as follows:

- Never vaccinated (referent)
- Birth to 14 days of age
- Fifteen to 55 days of age
- ≥56 days of age

The vaccination timing hypothesis would predict that the OR should be <1.0 in the birth- to 14-day group and >1.0 in the ≥56-day group.

We also performed an analysis evaluating possible differences according to schedule of Hib vaccination, focusing on the schedules used in the Finnish Hib trial (ie, 3 doses in the first 8 months of life plus a fourth dose at 12–18 months vs only 1 dose at 21–27 months).

For each analysis, we present the results of 2 conditional logistic regression models. Model 1 is stratified by the matching variables: HMO, date of birth, sex, and length of health plan enrollment. Model 2 is also stratified by the matching variables and in addition includes covariables to adjust for race and ethnicity and family history of possible type 1 diabetes. We defined family history of possible type 1 diabetes as type 1 or unknown type of diabetes in a first-degree relative (ie, parent or sibling).

RESULTS

From the diabetes registries, we identified 318 potential cases, of which 255 met the study eligibility criteria and case definition after review of their medical records. An additional 3 cases were excluded because of missing vaccination records (2) or inconsistent data in the medical records (1). The remaining 252 cases were included in the analysis along with their 768 matched controls. The control-to-case ratio was slightly more than 3 to 1 because 1 HMO oversampled controls. A majority of cases were male, half were born during 1988 through 1990, and their ages at first diagnosis of diabetes ranged from 10 months to 10 years (Table 1). Because of matching, the controls had the same distributions as the cases for the preceding characteristics. The proportion of blacks and Hispanics were similar among cases and controls, whereas cases were less likely than controls to be Asians or Pacific Islanders and more likely to be white. Twenty-one percent of the cases had a family history of possible type 1 diabetes in a first-degree

TABLE 1. Characteristics of Cases and Controls

Characteristic	Cases (N = 252) N (%)	Controls (N = 768) N (%)
Gender		
Male	143 (56.8)	433 (56.4)
Female	109 (43.3)	335 (43.6)
Year of birth		
1988–1990	126 (50.0)	387 (50.4)
1991–1993	90 (35.7)	273 (35.6)
1994–1997	36 (14.3)	108 (14.1)
Age (incidence/index)		
10–28 mo	65 (25.8)	191 (24.9)
29–47 mo	64 (25.4)	200 (26.0)
48–72 mo	62 (24.6)	185 (24.1)
73–122 mo	61 (24.2)	192 (25.0)
Race/ethnicity		
Black	20 (7.9)	72 (9.4)
Asian/Pacific Islander	9 (3.6)	68 (8.9)
Hispanic	49 (19.4)	156 (20.3)
White	141 (56.0)	307 (40.0)
Other	7 (2.8)	35 (4.6)
Unknown	26 (10.3)	130 (16.9)
Family history of diabetes (possible type 1)	38 (21.1)	8 (4.0)
Breastfed (≥6 mo)	56 (22.2)	170 (22.1)

relative versus only 4% of controls. A similar proportion of cases and controls had been breastfed when they were 6 months or older.

The vaccination histories of cases and controls were similar (Table 2). Forty-four percent of cases versus 46% of controls had been vaccinated against hepatitis B before their incidence or index date, resulting in an OR of 0.81 with a 95% confidence interval of 0.52 to 1.27 (Model 1). Additional adjustment for race or ethnicity and family history of possible type 1 diabetes (Model 2) resulted in a small decrease in the OR to 0.73. Only 11 cases had not been vaccinated with Hib and 10 cases did not receive whole cell pertussis vaccine, resulting in less precise OR estimates for these 2 vaccines. Nonetheless, there was little evidence that either vaccine increased the risk of diabetes. In fact, the OR for whole cell pertussis vaccine suggested a decreased risk associated with this vaccine and the 95% confidence interval in the Model 2 results excluded 1.0. Vaccination with measles-mumps-rubella (MMR) vaccine was just over 90% in both cases and controls; the ORs in both models were around 1.4 with confidence intervals that overlapped 1.0. Acellular pertussis and varicella vaccines became part of the childhood immunization schedule during the later years of our study, and a minority of cases and controls had received these 2 vaccines. Neither vaccine showed an association with diabetes risk. Only 1 case and 3 controls had not received oral polio vaccine and thus we were not able to evaluate its association with diabetes.

The analysis of risk according to timing of hepatitis B vaccination indicated that the risk of diabetes was not related to timing of vaccination (Table 3). Children who were vaccinated within 14 days of birth had a risk about half of that of children who were not vaccinated (Model 1), but the confidence intervals around this estimate overlapped 1.0. The OR increased to 0.66 after adjustment for race or ethnicity and family history of type 1 diabetes (Model 2). Children who received their first hepatitis B vaccinations >14 days after birth also had lower risks than unvaccinated children, but again the 95% confidence intervals overlapped 1.0.

For hepatitis B vaccine, we also evaluated whether number of vaccine doses was related to risk of diabetes, but did not find any associations. Relative to unvaccinated children, the ORs (Model 1) were 0.63 (0.26–1.52) for children who had received 1 dose of vaccine and 0.85 (0.53–1.37) for children who had received 2 or more doses; the Model 2 results were not materially different.

For Hib vaccine, we evaluated relative risks according to different vaccination schedules. These analyses were restricted to children who were 27 months of age or older on their incidence or index date. We made this restriction because one of the schedules we compared involved receipt of a single dose of vaccine between 21 and 27 months. Using the currently recommended schedule (3 doses by 8 months of age with a fourth dose at 12–18 months of age) as the referent, the ORs were <1.0 for children who had received only 1 dose of vaccine at 21 to 27 months of age (Table 4). Only 8 cases, however, had been vaccinated according to the latter schedule and the confidence intervals were wide and overlapped 1.0. The ORs were also <1.0 for children vaccinated according to different schedules and those who were not vaccinated, but all the confidence intervals overlapped 1.0.

TABLE 2. Association Between Childhood Vaccines and Type 1 Diabetes

Vaccine	Vaccinated		OR (95% CI)	
	Cases N (%)	Controls N (%)	Model 1*	Model 2**
Hepatitis B	111 (44.0)	356 (46.4)	0.81 (0.52–1.27)	0.73 (0.45–1.19)
Hib	241 (95.6)	729 (94.9)	1.14 (0.51–2.57)	1.23 (0.53–2.89)
Pertussis (whole cell)	242 (96.0)	748 (97.4)	0.28 (0.07–1.06)	0.23 (0.06–0.93)
Pertussis (acellular)	58 (23.0)	177 (23.0)	0.92 (0.53–1.57)	1.12 (0.63–1.99)
MMR	232 (92.1)	696 (90.6)	1.36 (0.70–2.63)	1.43 (0.71–2.86)
Varicella	40 (15.9)	112 (14.6)	1.16 (0.72–1.89)	1.02 (0.61–1.72)

CI indicates confidence interval.
* Conditional logistic regression model stratified by matching variables (HMO, length of enrollment, gender, date of birth).
** As in Model 1, plus adjusted for race/ethnicity and family history of possible type 1 diabetes.

TABLE 3. Timing of Hepatitis B Vaccination and Risk of Type 1 Diabetes

Age at First Vaccination	Cases *N* (%)	Controls *N* (%)	OR (95% CI)	
			Model 1*	Model 2**
Not vaccinated	141 (56.0)	412 (53.7)	1.00 (referent)	1.00 (referent)
0–14 d	51 (20.2)	168 (21.9)	0.51 (0.23–1.15)	0.66 (0.27–1.59)
15–55 d	6 (2.4)	24 (3.1)	0.53 (0.18–1.52)	0.65 (0.21–2.0)
≥56 d	54 (21.4)	164 (21.4)	0.86 (0.54–1.35)	0.74 (0.45–1.21)

CI indicates confidence interval.
* Conditional logistic regression model stratified by matching variables (HMO, length of enrollment, gender, date of birth).
** As in Model 1, plus adjusted for race/ethnicity and family history of possible type 1 diabetes.

TABLE 4. Hib Vaccination Schedule and Risk of Type 1 Diabetes*

Schedule	Cases *N* (%)	Controls *N* (%)	OR (95% CI)	
			Model 1**	Model 2***
3 Doses by 8 mo plus 1 dose at 12–18 mo	52 (27.2)	135 (22.8)	1.00 (referent)	1.00 (referent)
1 Dose only at 21–27 mo	8 (4.2)	29 (4.9)	0.59 (0.22–1.57)	0.45 (0.15–1.30)
Other schedules	123 (64.4)	402 (67.8)	0.69 (0.41–1.16)	0.71 (0.41–1.24)
Not vaccinated	8 (4.2)	27 (4.6)	0.68 (0.26–1.81)	0.64 (0.22–1.81)

CI indicates confidence interval.
* Restricted to cases and controls ≥27 mo of age at incidence/index date.
** Conditional logistic regression model stratified by matching variables (HMO, length of enrollment, gender, date of birth).
*** As in Model 1, plus adjusted for race/ethnicity and family history of possible type 1 diabetes.

DISCUSSION

In this large, population-based, case-control study, we did not find an increased risk of type 1 diabetes associated with any of the routinely recommended childhood vaccines. Timing of hepatitis B vaccination also was not related to diabetes risk.

The possibility that vaccination may increase the risk of type 1 diabetes has been evaluated in a few epidemiologic studies. Classen[8] has provided the only evidence of a possible increased risk, but the nature of the evidence is strictly ecological, involving comparisons between countries or between different time periods in the same country. Such comparisons, however, may be influenced by many factors unrelated to vaccination, such as genetic predisposition and other environmental exposures. Moreover, similar ecological analyses conducted by other investigators have not found significant correlations between diabetes and several vaccines, including BCG, pertussis, and mumps.[2,3,5]

None of the epidemiologic studies that included control or comparison groups have found an increased risk of type 1 diabetes associated with vaccination. One of the largest and most comprehensive was a case-control study conducted in Sweden in the mid-1980s.[1] Overall, the 339 cases and 528 controls had similar vaccination histories for BCG, smallpox, pertussis, tetanus, rubella, and mumps vaccines. The only significant difference was a decreased risk of type 1 diabetes associated with measles vaccination. In a retrospective cohort study conducted in Canada, no association was found between BCG vaccine and risk of diabetes, although there was a suggestion that vaccination may have delayed the onset of diabetes.[4] A 10-year follow-up study of over 100 000 Finnish children who participated in a clinical trial of Hib vaccine also did not find an increased risk of diabetes associated with vaccination or with number of vaccinations received.[10]

Our study adds to previous research by providing data on newer vaccines, including hepatitis B, acellular pertussis, and varicella vaccines. For the older vaccines, our results are generally in agreement with previous studies in not finding any increased risks. We were not able to replicate Blom's finding that measles vaccine may decrease the risk of type 1 diabetes. All of the cases and controls in our study, however, had received MMR vaccine; thus, we could not evaluate the effect of single-antigen measles vaccine.

We also had limited ability to evaluate differences according to different Hib vaccination schedules. Only a few of the cases and controls in our study did not receive Hib vaccine or received only 1 dose at 21 to 27 months of age. Thus, our relative risk estimates for these groups were relatively unstable. The best data comparing different Hib schedules comes from the follow-up study of the Finnish clinical trial participants, and no significant differences were found in that study.[10] A remaining possible question is whether type of Hib conjugate influences risk,[13] but to address this question we would need additional data.

To our knowledge, ours is the first epidemiologic study to evaluate the possibility that timing of vaccination is related to risk of clinical diabetes in children. Classen[8,9] has suggested that certain vaccines, if given at birth, may decrease the occurrence of diabetes, whereas if initial vaccination is administered after 2 months of age, the occurrence of diabetes increases. The theory is based on results from experiments in laboratory animals, as well as comparisons of the rates of diabetes between countries with different immunization schedules. The possibil-

ity that vaccination shortly after birth may protect against the development of diabetes is supported by experiments in animal models conducted by other investigators.[7,14,15] Data in humans, however, have been lacking. Our results on hepatitis B vaccine do not support the hypothesis; risk of type 1 diabetes was not different between infants vaccinated at birth and those who received their first vaccination later in life.

Data from the Diabetes Autoimmunity Study also provides evidence against the notion that vaccination or timing of vaccination is associated with the development of type 1 diabetes.[16] This was a prospective study of 317 children who had a first-degree family member with type 1 diabetes. The children were monitored for the development of autoimmunity to pancreatic β-cells, an early precursor in the development of type 1 diabetes. No association was found between development of β-cell autoimmunity and receipt of any of a number of vaccines, including hepatitis B, Hib, polio, or diphtheria and tetanus toxoids and pertussis; nor was there an association with age at first vaccination with any of these vaccines.

Our main analyses evaluated the risk associated with ever being vaccinated. Several of our ORs were <1.0, so we further evaluated risk according to time since vaccination to investigate the possibility that vaccination of children with diabetes may have been deferred because they were in poor health before their diagnosis. If this were the case, we would have expected to see lower risks in time intervals closer to vaccination (ie, within 1 year) compared with more distant time periods (ie, >1 year). We did not see any decreased risks in the intervals closer to vaccination (data not shown); thus, it does not seem that deferral of vaccination because of poor health status influenced our results.

CONCLUSION

The results of our study and the preponderance of epidemiologic evidence do not support an association between any of the recommended childhood vaccines and an increased risk of type 1 diabetes. Suggestions that diabetes risk in humans may be altered by changes in the timing of vaccinations also are unfounded.

ACKNOWLEDGMENTS

Members of the Vaccine Safety Datalink project include (by site): Frank DeStefano, MD, MPH, Robert T. Chen, MD, MA, John Glasser, PhD, MPH, Philip H. Rhodes, PhD, Piotr Kramarz, MD, Thomas Verstraeten, MD, David Walker, MPH, and Catherine Okoro (National Immunization Program, Centers for Disease Control and Prevention, Atlanta, Georgia); Robert S. Thompson, MD, Lisa A. Jackson, MD, MPH, Robert L. Davis, MD, MPH, William E. Barlow, PhD, Kari Bohlke, ScD, Patti Benson, MPH, Barbara Carste, MPH, Jo Ann Habakangas, BA, Christi Hanson, BA, Minqi Jiang, MS, Paula Lee Poy, BA, Darren Malais, BS, Viviana Rebolledo, BS, Wendy Rogers, BA, David Rubanowice, BS, Dennis Sheeran, MS, Onchee Yu, MS, and Ann Zavitkovsky, MPH, MPA (Group Health Cooperative, Seattle, Washington); John P. Mullooly, PhD, Julie E. Maher, PhD, MS, Sheila Weinman, PhD, Lois Drew, BA, Jill Mesa, Kim Olson, Heather Houston, RN, Colleen Chun, MD, Steven Gancher, MD, John A. Pearson, MD, Jerry Slepak, MD, Alan Bauck, BS, Teresa Kimes, MS, Joseph Murphy, BA, Nadia Redmond, MSPH, Karen Riedlinger, BS, Roberleigh Schuler, MS, Carol Sullivan, and Gayle Thomas-Monk (Kaiser Permanente Northwest Region, Portland, Oregon); Steve B. Black, MD, Henry R. Shinefield, MD, Paula Ray, MPH, Edwin Lewis, MPH, Bruce H. Fireman, MA, Joan Schwalbe, Ajit De Silva, and Patti Hallam (Kaiser Permanente of Northern California, Oakland, California); Joel I. Ward, MD, Connie M. Vadheim, PhD, Hang Lee, PhD, Ken Zangwill, MD, Eileen Eriksen, MPH, Tracy Zhang, MS, Jennifer Lee, MS, Jennie Jing, MA, Nancy Goff, and Jeffrey Perlman, MD (Center for Vaccine Research Harbor-University of California Los Angeles Medical Center, Torrance, California); S. Michael Marcy, MD, and Marlene Lugg, DrPH (Southern California Kaiser Permanente, Los Angeles, California); M. Miles Braun, MD, MPH, Robert P. Wise, MD, MPH, and Robert Ball, MD, MPH (Center for Biologics Evaluation and Research, Food and Drug Administration, Rockville, Maryland); Vito Caserta, MD, MPH, and Geoffrey Evans, MD (Division of Vaccine Injury Compensation, Health Resources and Services Administration, Rockville, Maryland).

REFERENCES

1. Blom L, Nystrom L, Dahlquist G. The Swedish childhood diabetes study: vaccinations and infections as risk determinants for diabetes in childhood. *Diabetologia*. 1991;34:176–181
2. Hyoty H, Hiltunen M, Reunanen A, et al. Decline of mumps antibodies in type 1 (insulin-dependent) diabetic children and a plateau in the rising incidence of type 1 diabetes after introduction of the mumps-measles-rubella vaccine in Finland. *Diabetologia*. 1993;36:1303–1308
3. Dahlquist G, Gothefors L. The cumulative incidence of childhood diabetes mellitus in Sweden unaffected by BCG-vaccination. *Diabetologia*. 1995;38:873–874
4. Parent M, Fritschi L, Siemiatycki J, Colle E, Menzies R. Bacille Calmette-Guérin vaccination and incidence of IDDM in Montreal, Canada. *Diabetes Care*. 1997;20:767–772
5. Heijbel H, Chen RT, Dahlquist G. Cumulative incidence of childhood-onset IDDM is unaffected by pertussis immunization. *Diabetes Care*. 1997;20:173–175
6. Jefferson T, Demicheli V. No evidence that vaccines cause insulin dependent diabetes mellitus. *J Epidemiol Comm Health*. 1998;52:674–675
7. Institute for Vaccine Safety Workshop Panel. Childhood immunizations and type 1 diabetes: summary of an Institute for Vaccine Safety Workshop. *Pediatr Infect Dis J*. 1999;18:217–222
8. Classen DC, Classen JB. The timing of pediatric immunization and the risk of insulin-dependent diabetes mellitus. *Infect Dis Clin Pract*. 1997;6:449–454
9. Classen JB. The timing of immunization affects the development of diabetes in rodents. *Autoimmunity*. 1996;24:137–145
10. Karvonen M, Cepaitis Z, Tuomilehto J. Association between type 1 diabetes and *Haemophilus influenzae* type b vaccination: birth cohort study. *BMJ*. 1999;318:1169–1172
11. Chen RT, DeStefano F, Davis RL, et al. The Vaccine Safety Datalink: immunization research in health maintenance organizations in the USA. *WHO Bull*. 2000;78:186–194
12. WHO DIAMOND Project Group. The WHO Multinational Project for Childhood Diabetes. *Diabetes Care*. 1990;13:1062–1068
13. Elliman D. Vaccination and type 1 diabetes mellitus. *BMJ*. 1999;318:1159–1160
14. Singh B, Rabinovitch A. Influence of microbial agents on the development and prevention of autoimmune diabetes. *Autoimmunity*. 1993;15:209–213
15. In H, Singh B. BCG vaccination prevents insulin-dependent diabetes mellitus (IDDM) in NOD mice after disease acceleration with cyclophosphamide. *J Autoimmunity*. 1997;10:271–278
16. Graves PM, Yu L, Barriga KJ, et al. Lack of association between early childhood immunizations and β-cell autoimmunity. *Diabetes Care*. 1999;22:1694–1697

Childhood Vaccinations, Vaccination Timing, and Risk of Type 1 Diabetes Mellitus

Frank DeStefano, John P. Mullooly, Catherine A. Okoro, Robert T. Chen, S. Michael Marcy, Joel I. Ward, Constance M. Vadheim, Steve B. Black, Henry R. Shinefield, Robert L. Davis and Kari Bohlke

Pediatrics 2001;108;e112
DOI: 10.1542/peds.108.6.e112

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Childhood Vaccinations, Vaccination Timing, and Risk of Type 1 Diabetes Mellitus

Frank DeStefano, John P. Mullooly, Catherine A. Okoro, Robert T. Chen, S. Michael Marcy, Joel I. Ward, Constance M. Vadheim, Steve B. Black, Henry R. Shinefield, Robert L. Davis and Kari Bohlke

Pediatrics 2001;108;e112
DOI: 10.1542/peds.108.6.e112