Cumulative Incidence of Childhood-Onset IDDM Is Unaffected by Pertussis Immunization

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OBJECTIVE — To identify a possible effect of pertussis vaccination in infancy on the risk for developing human IDDM.

RESEARCH DESIGN AND METHODS — A comparison was made of the cumulative incidence of IDDM in children age 0–12 years between two birth cohorts born before pertussis vaccination and two birth cohorts born after pertussis vaccination had been excluded from the Swedish national immunization program. The Swedish Childhood Diabetes registry was used to identify cases of IDDM. Yearly nurse reports on administered vaccines were used to determine coverage for diphtheria/tetanus/pertussis (DTP) and diphtheria/tetanus (DT) vaccines. Pertussis vaccine coverage was estimated based on number of doses of vaccine made available on license.

RESULTS — No difference in cumulative incidence rate of IDDM up to the age of 12 years was found when the birth cohorts for 1978 and 1979 with high DTP vaccination coverage were compared with the cohorts of 1980 and 1981 with low pertussis vaccination coverage.

CONCLUSIONS — The comparison of the cumulative incidence of IDDM, up to the age of 12 years, in birth cohorts with high and low exposure to pertussis vaccine does not support the hypothesis that pertussis could induce autoimmunity to the β-cell that may lead to IDDM.

IDDM is caused by an autoimmune process leading to damage of pancreatic β-cells. Infections could be a triggering mechanism for an autoimmune reaction in sensitive individuals. The possibility that vaccines could have either a protective or a triggering effect in the development of IDDM has been discussed (1,2). Recently, Classen and Classen (3) suggested that vaccination starting after 2 months of age results in a increased incidence of diabetes. Whole-cell pertussis vaccine has an adjuvant effect (4) that could theoretically enhance an autoimmune reaction. Animal studies have indicated effects of pertussis vaccine on β-cell function. Furman et al. (5) found vaccines containing killed B-pertussis to cause hyperinsulinemia. There is little information from studies in humans. Hannik and Cohen (6) observed a modest rise in plasma insulin in infants 8 h after vaccination. On the basis of a case report of a 16-month-old girl who developed IDDM ~3 weeks after receiving diphtheria/tetanus/ pertussis (DTP) vaccine, Champsaur et al. (7) have suggested that DTP might have an adjuvant effect in the process leading to disease.

A research registry developed to study risk factors for IDDM covers all treatment cases in Sweden since July 1977 (8). This together with changes in the Swedish vaccination policy provided an opportunity to study the impact of pertussis vaccination on the incidence of IDDM.

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CHC, child health center; DT, diphtheria/tetanus; DTP, diphtheria/tetanus/pertussis; SBL, Swedish National Laboratories.

RESEARCH DESIGN AND METHODS

— In Sweden, immunization of children is carried out at child health centers (CHCs). All children are enrolled at CHCs at birth. DTP vaccination was introduced into the national CHC program in 1953. The vaccine was produced by the Swedish National Laboratories (SBL). Because of reports of serious adverse reactions and decreased efficacy of the vaccine, the Board of Health and Welfare decided on 20 September 1979 to terminate the general vaccination against pertussis (9). After that decision, pertussis vaccine (Wellcome, Bechenham, U.K.) was available on license from the Swedish Medical Products Agency only to be used for children at risk for severe illness following infection, e.g., children with cystic fibrosis. Unlike the DTP vaccine previously used, the diphtheria/ tetanus (DT) vaccine introduced in 1979 contained an aluminum adjuvant.

We compared the cumulative incidence of IDDM between two birth cohorts (1977 and 1978) with a high exposure to DTP vaccination and two birth cohorts (1980 and 1981) with a high exposure to DT and a low exposure to pertussis vaccination.

Cases of IDDM were identified from the Swedish Childhood Diabetes Registry. The registry is regularly validated by internal sources, and comparisons with external sources have shown the ascertainment to vary between 96 and 99% (10,11). Population data are obtained from the Statistical Yearbook of Sweden (12). Number of live births minus number of deaths during the first week of life was used.

All incident cases of childhood diabetes occurring in the age-group 0–12 years between 1 July 1977 and 31 December 1993 were identified from the registry. To determine population exposure to DPT and DT, we used data from the yearly CHC nurse reports on administered vaccinations (13). For pertussis vaccinations that were not reported by CHC nurses, exposure was estimated based on reported released doses of vaccine.

RESULTS

— The coverage for DT, given either as DPT or as DT, was high and stable

Table 1—*Vaccination coverage and number of cases of diabetes among four birth cohorts by year of birth*

Year	Births	% DPT coverage	% DT coverage	% Pertussis coverage	Cases in diabetes registry
1977	96,057	83	14	—	311
1978	93,248	83	14	—	311
1980	97,064	0	98	<2	334
1981	94,065	0	98	<2	311

Data are *n* or %. Number of births is live births minus number of deaths <7 days of age.

(96–97%). In contrast, the coverage for pertussis vaccine decreased from 83% (DPT) to <2% (monovalent pertussis vaccine) shown in Table 1. A total of 1,267 cases of IDDM were identified among the four cohorts during the 12-year follow-up period.

No difference in the cumulative incidence rate of IDDM up to the age of 12 years was found between the four birth cohorts (Fig. 1).

CONCLUSIONS — In a comparison of two birth cohorts with high exposure and two birth cohorts with low exposure to pertussis vaccine, we found no difference in the cumulative incidence of IDDM, up to the age of 12 years. In the 1977 cohort, no data are available for the age 0 to <6 months. Onset of IDDM in this age-group is extremely rare, with no case reported to the Swedish Childhood Diabetes Registry, in subsequent birth cohorts. Therefore, we find it unlikely that this lack of information had any significant effect on the results. Our findings suggest that there is no association between pertussis immunization and IDDM. We have, however, considered three alternative explanations for our results.

First, could a lack of immunogenicity explain the lack of observed difference between cohorts?

The pertussis vaccine used in Sweden was observed to have a low protective efficacy (14,15). If the immunogenicity was low, it may have been less likely to have initiated an autoimmune response leading to IDDM. The pertussis vaccine given to children in the studied cohorts was not without immunogenic activity. Krantz et al. (14) studied the cumulative incidence of pertussis among children in Gothenburg, Sweden, and estimated the pertussis vaccine efficacy for the vaccine used in 1977 to be 34% and, after changes in the production of the vaccine (16), to be 72% for the vaccine used in 1978 (14).

Second, could natural pertussis infection hide an effect of pertussis vaccine?

Since the decision to stop general pertussis vaccination, the incidence of pertussis disease among children in Sweden has been high (15). If natural pertussis infection has a similar effect on the immune system as pertussis vaccination, the difference between cohorts might have been reduced and therefore not detected.

However, if this occurred, we would expect the onset of IDDM to occur at an earlier age among children exposed to vaccine at 3 months of age, compared to children who experienced pertussis infection, which in Sweden has a peak incidence at age 2–5 years (17,18). No such difference in age at onset was observed.

Finally, could the introduction of aluminum adjuvant in DT vaccine have had an independent effect on IDDM incidence?

Besides stopping pertussis vaccination, a second change was made in the Swedish Childhood Immunization program in 1979. The new DT vaccine included an aluminum adjuvant. If aluminum adjuvant could induce a similar immune response as pertussis vaccine, the effect of less exposure to pertussis vaccine would be masked by an increase in incidence caused by the aluminum adjuvant. It seems unlikely that the effects of an unadjuvanted pertussis vaccine and aluminum adjuvanted DT vaccine would be so similar that no difference between birth cohorts would be detected. On the basis of this study alone, however, we can not exclude that possibility.

We conclude that on balance, the results of this study do not support the hypothesis that pertussis vaccine could induce autoimmunity to the β-cell that may lead to IDDM.

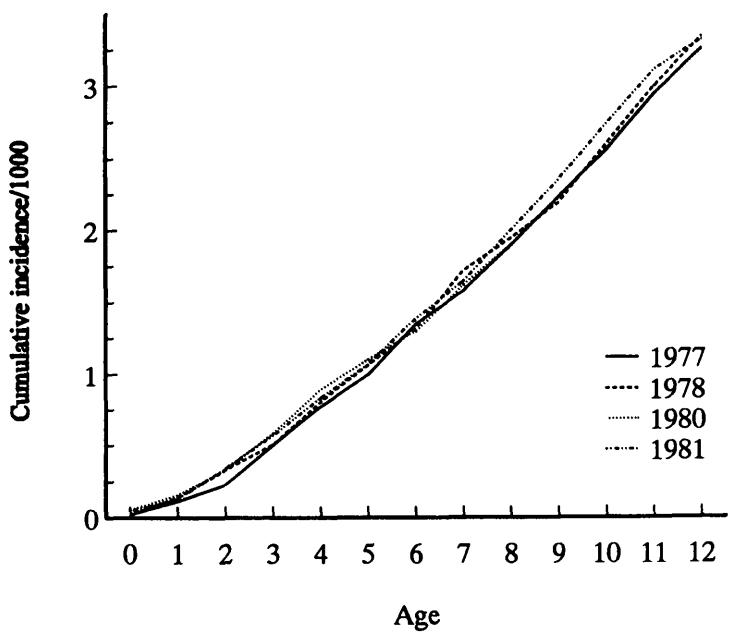

Figure 1—*No difference in the cumulative incidence rate of IDDM up to the age of 12 was found between the four birth cohorts.*

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References

1. Blom L, Nyström L, Dahlquist G: The Swedish childhood diabetes study: vaccinations and infections as risk determinants for diabetes in childhood. *Diabetologia*

34:176–181, 1991
2. Hyöty H, Hiltunen M, Reunanen A, Leinikki P, Vesikari T, Lounamaa R, Tuomilehto J, Åkerblom HK, the Childhood Diabetes in Finland Study Group: 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* 36:1303–1308, 1993
3. Classen Barthelow J, Classen DC: Vaccines modulate IDDM. *Diabetologia* 39:500–502, 1996
4. Lee JM, Olitsky PK: Simple method for enhancing development of acute disseminated encephalomyelitis in mice. *Proc Soc Exp Biol Med* 89:263–266, 1955
5. Furman BL, Wardlaw AC, Stevenson LQ: Bordetella pertussis-induced hyperinsulinemia without marked hypoglycaemia: a paradox explained. *Br J Exp Pathol* 62:504–511, 1981
6. Hannik CA, Cohen H: Changes in plasma insulin concentration and temperature of infants after pertussis vaccination. In *International Symposium on Pertussis*. Manclark CR, Hill JC, Eds. Washington, D.C., U.S. Govt. Printing Office, 1979, p. 297–299
7. Champsaur HF, Botoazzo G-B, Bertrams J, Assan R, Bach C: Virologic, immunologic and genetic factors in insulin dependent diabetes mellitus. *J Pediatr* 1:15–20, 1982
8. Dahlquist G, Blom L, Tuvemo T, Nyström L, Sandström A, Wall S: The Swedish Childhood Diabetes study: results from a nine year case register and a one year case-referent study indicating that type 1 diabetes mellitus is associated with type 2 diabetes mellitus and autoimmune disorders. *Diabetologia* 32:2–6, 1989
9. National Board of Health and Welfare: *Code of Statutes. SOSFS (M)*. Stockholm, Socialstyrelsen, 1979, p. 73
10. Nyström L, Dahlquist G, Rewers M, Wall S: The Swedish Childhood Diabetes study: an analysis of the temporal variation in diabetes incidence 1978–87. *Int J Epidemiol* 19:141–146, 1990
11. Dahlquist G, Mustonen L: Childhood onset diabetes: time trends and climatological factors. *Int J Epidemiol* 23:1239–1241, 1994
12. Statistiska Centralbyrån: *Statistical Yearbook of Sweden*. Stockholm, Statistiska Centralbyrån, 1993. p. 44
13. Romanus V, Jonsell R, Böttiger M, Alvin A, Sandzelius G: Vaccinationstatus bland Svenska förskolebarn. *Svensk Läkartidning* 82:2863–2865, 1982
14. Krantz I, Taranger J, Trollfors B: Estimating incidence of whooping cough over time: a cross-sectional recall study of four Swedish birth cohorts. *Int J Epidemiol* 18:901–905, 1989
15. Romanus V, Jonsell R, Bergquist S-O: Pertussis in Sweden after the cessation of general immunization in 1979. *Pediatr Infect Dis J* 6:364–371, 1987
16. Askelöf P, Saarikoski L, Salenstedt CR, Tiru M: Kvaliteten hos kikhostevaccin. Några parametrar som påverkar kikhostevaccinets kvalitet (Abstract). *Hygiea* 87:348, 1978
17. Isacson J, Trollfors B, Taranger J, Zackrisson G, Lagergård T: How common is whooping cough in a non vaccinating country? *Pediatr Infect Dis J* 12:284–288, 1993
18. Mark A, Granström M: Cumulative incidence of pertussis in an unvaccinated preschool cohort based on notifications, interview and serology. *Eur J Epidemiol* 7:121–126, 1991