Risk of Vaccine Induced Diabetes in Children with a Family History of Type 1 Diabetes

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Abstract: Cohort data from Denmark in all children born from January 1, 1990 to December 31, 2000 was analyzed to assess the association between immunization and type 1 diabetes in all Danish children and in a subgroup where children had a sibling with type 1 diabetes. Pediatric vaccines were associated with a statistically significant increased risk of type 1 diabetes in 12 of 21 endpoints in the general population. The rate ratios in children who received at least one dose of a specific vaccine were also elevated in the subgroup and were statistically the same as in the general population. Three doses of the hemophilus vaccine were associated with a rate ratio of 1.23 (1.02<<RR<<1.48) and an absolute risk in the general population of three cases/100,000 per year compared to 1.58 (0.60<<RR<<4.15) and an absolute risk of 2885 cases/100,000 per year in the subgroup with a sibling with type 1 diabetes. The hemophilus immunization is associated with a cumulative attributable risk of 2.3/100 (2.3%) in the subgroup.

Keywords: Type 1 diabetes mellitus, vaccines, hemophilus, pertussis, polio.

INTRODUCTION

Data exists that supports a causal relationship between the hemophilus immunization and type 1 diabetes [1, 2]. Causation is supported by a large prospective randomized clinical trial, which demonstrated statistically significant clusters of extra cases of diabetes occurring between 36 to 48 months after immunization. Four smaller epidemiology studies as well as animal toxicity data support the findings of the clinical trial [1]. The mechanisms by which vaccines can induce IDDM have been extensively reviewed [3]. These mechanisms are not specific to the hemophilus vaccine and all vaccines have the potential to induce diabetes.

A causal relationship between the hemophilus vaccine and type 1 diabetes is further supported by a study showing hemophilus immunization is associated with autoantibodies to islet cells [4] and several independent studies showing these autoantibodies pre-date the development of diabetes by 3.2 years, which is identical to the delay between hemophilus immunization and the development of diabetes that was seen in a prospective randomized clinical trial [1]. Researchers have prospectively followed a group of 765 initially non diabetic siblings of type 1 diabetic patients in Finland [5, 6]. Diabetes manifested after a mean time of 3.2 years from the detection of anti islet cell antibodies in those that were initially negative at the beginning of the study [5]. A German study prospectively followed children from birth that were at risk for developing diabetes because of family history. Researchers screened blood at birth, nine months, two years, and five years. They found that in children who had two autoantibodies by age two, 50% developed diabetes by age five, a median onset of approximately 36 months after detection of autoantibodies [7]. Further support for causation is derived from the fact that the temporal delay of 24-48 months between immunization and the rise in the rates of diabetes is consistent with earlier papers showing a two-to-four year delay between mumps infections and increases in type 1 diabetes [8-11]. A temporal delay of 24-48 months between vaccination and the rise in rates of type 1 diabetes also has been detected with the DTP and other vaccines [2].

Several papers have looked at the relationship between vaccines and type 1 diabetes and have not found an association [12, 13]. These papers actually show the same elevated relative risk or odds ratio as seen in the clinical trial from Finland [1]. However, they are under powered and thus do not reach statistical significance. Because the risk in these "negative" studies [12, 13] is nearly identical to the findings in Finland, the data actually supports the association between vaccines and type 1 diabetes [1]. More recently, a paper from a vaccine manufacturer in Denmark examined the association between vaccines and type 1 diabetes. However, the authors presented only results that had been adjusted, and employed a novel adjuster [14]. Because of the obvious conflict of interest, and because at least one of the adjusters was novel and controversial, the data was re-analyzed. The paper also provides data on the association between vaccines and IDDM in children who have a sibling with type 1 diabetes. The data is potentially valuable because studies have not looked at the risk of vaccine induced diabetes in individuals with a family history of type 1 diabetes.

METHODS

A cohort analysis was performed in all children born in Denmark from January 1, 1990 to December 31, 2000. Children were followed for the development of type 1 diabetes through the age of 12, or until December 31, 2001. The immunization schedule of each child was extracted from a computerized registry, as was the development of diabetes. Cohorts were constructed based on which vaccines and how many doses the children received. Data was obtained from a published source [14]. The rate of diabetes was calculated for each cohort and the rate ratio was calculated by comparing the

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cohorts receiving the vaccines to a cohort that did not receive the vaccine. A separate but identical analysis was performed in the subgroup of children that had a sibling with type 1 diabetes.

STATISTICS

Statistics were performed using the program *Epi InfoTM version 6, developed by the CDC and WHO*. Taylor series 95% confidence intervals were used for calculating the rate ratio range. Chi square analysis was performed for determining P values.

RESULTS

The results (Table **1**) show that in the general population there was an elevated unadjusted rate ratio associated with many different vaccines including the hemophilus, MMR, polio, whole cell pertussis, and the combined diphtheria, tetanus inactive polio vaccine. The vaccines were associated with an statistically increased risk of type 1 diabetes in 12 of 21 endpoints in the general population. No endpoints showed that vaccines were associated with a decreased risk of diabetes. The data showed that the three doses of the hemophilus vaccine were associated with a rate ratio of 1.23 (p=0.03) after approximately eight years of follow-up. A statistically significant dosing effect was seen with the polio vaccine and a non significant trend was seen with the whole cell pertussis vaccine, the hemophilus vaccine, and the combined diphtheria, tetanus, and inactive polio vaccine.

There were only a small number of children with a family history of type 1 diabetes, and this significantly reduced the power of the study. However, 2 of 21 endpoints were statistically significant in the subgroup with siblings with type 1 diabetes. The rate ratios in children who received at least one dose of a specific vaccine in the subgroup were elevated and not statistically different from the elevated rate ratio seen in the general population, though the rate ratios in the subgroup were often numerically larger. The rate ratio associated with a single dose of the pertussis vaccine in the group with the family history of diabetes (8.26; 1.76<<RR<<38.71) exceeds the confidence interval of the same group in the general population (1.29; 0.93<<RR<<1.79), but there is a small overlap in the confidence intervals. Likewise, the rate ratio associated with three doses of the polio vaccine in the diabetic group (4.71; 1.28<<RR<<20.44) exceeds the upper limit of the confidence interval in the group in the general population (2.52; 2.06<<RR<<3.08), but the confidence intervals overlap. The subgroup with a sibling with type 1 diabetes had a numerically smaller rate ratio with the MMR vaccine (1.26; 0.51<<RR<< 3.12) compared to the whole population (1.88, 1.55<<RR<< 2.29), but the confidence intervals overlapped. In contrast, the differences in the attributable or absolute risk were quite different between those in the general population and those in the diabetic group. For example, in the group that received three doses of polio vaccine, the attributable risk in the general population was 12 cases/100,000 per year, while the attributable risk in the diabetic population was 720 cases/100,000 per year.

DISCUSSION

The results of this study are consistent with previous studies showing an association between vaccines and type 1 diabetes with relative risks ranging from 1.1 to greater than 2 depending on the vaccine and the time interval [1, 2]. The results showed vaccines were associated with an statistically increased risk of type 1 diabetes in 12 of 21 endpoints in the general population, while there were no endpoints that showed vaccines associated with a decreased risk of type 1 diabetes. The data allowed analysis of the association of immunization with type 1 diabetes in a subgroup of children with a sibling with type 1 diabetes. In general, the results show that the rate ratio was similar or slightly increased compared to the general population. However, the absolute risk is about 100 times greater in the subgroup. This fact affects the clinical decisions regarding the risk/benefit of immunization as described below.

The results significantly differ from a previous analysis by employees of a vaccine manufacturer [14] in which only the "adjusted" results were published. The previous analysis adjusted for "age, sex and calendar period" and limited the subgroup analysis to relative risk instead of comparing the absolute risk in the subgroup to the general population. The authors concluded that vaccines were not associated with an increased risk of diabetes and those with a family history of diabetes were not at an increased risk of diabetes. The differences are explained below.

The results from this paper (Table **1**) show that the three doses of the hemophilus vaccine were associated with a rate ratio of 1.23 (p=0.03) after approximately eight years of follow-up, which is nearly identical to findings that four doses of the hemophilus vaccine were associated with a relative risk of 1.26 (p=0.03) after seven years of follow-up in a clinical trial, and consistent with results from several smaller case control studies (2). In contrast, Hviid [14] found that the hemophilus vaccine, after adjustments, was associated with a rate ratio of 0.99. The fact that the vaccine manufacturer's adjusted results are not consistent with previous findings, while the unadjusted results are consistent with previous findings, strongly suggests Hviid erred by over adjusting. An analysis of Hviid's adjustment is included below.

The vaccine manufacturer [14] presented only "adjusted" data and would have the reader believe that all the statistically significant endpoints are the result of discrepancies of age, sex and "calendar period" between the vaccinated and unvaccinated groups. However, the authors do not justify their use of the adjusters nor explain precisely how they adjusted. While type 1 diabetes is more prevalent in older children [15], this would not explain the results with the hemophilus or MMR vaccine since the unvaccinated groups contain older children. There is a sex difference in the incidence of type 1 diabetes that could account for a rate ratio of 1.10 [15] if all the vaccinated children were of one sex and the un-immunized of another sex. However, since there is generally only a small sex skewing with immunization, the attributable rate ratio would be negligible, around 1.02, if there were a 20% skewing of gender in the groups. The adjustment for "calendar period (in one year intervals)" is simply unprecedented. A large study looking at all cases of IDDM in Europe showed no seasonal effect based on birth [16].

Hviid *et al*. do not explain precisely how they adjusted, but have adjusted off the rise in diabetes following the introduction of vaccines. Immunization practices change as new

Table 1.

Vaccine	All Children					Children with at Least 1 Sibling with Type 1 Diabetes				
	Person-yr Risk	No. of Cases	Unadjusted Rate 100,000 Per Year	Unadjusted Rate Rate Ratio	(95% CI)	Person-yr Risk	No. of Cases	Unadjusted Rate 100,000 Per Year	Unadjusted Rate Rate Ratio	(95% CI)
Hemophilus Influenza										
unvaccinated	1,596,918	211	13.21	1		1419	7	493	1	
1 Dose	835,833	123	14.72	1.11	(0.89<<RR<<1.39)	799	7	876	1.78	(0.63<<RR<<5.05)
2 Doses	850,946	114	13.40	1.01	(0.81<<RR<<1.27)	709	2	282	0.57	(0.12<<RR<<2.75)
3 Doses	1,436,820	233	16.22	1.23	(1.02<<RR<<1.48)	1281	10	781	1.58	(0.60<<RR<<4.15)
At least 1 dose			15.05	1.14	(0.97<<RR<<1.34)			681	1.38	(0.58<<RR<<3.28)
Diptheria, Tetanus and Inactivated Polio										
Unvaccinated	1,110,803	110	9.90	1		258	1	388	1	
1 Dose	276,557	33	11.93	1.20	(0.82<<RR<<1.78)	1092	8	733	1.89	(0.24<<RR<<15.05)
2 Doses	1,134,823	178	15.69	1.58	(1.25<<RR<<2.01)	2136	16	749	1.93	(0.26<<RR<<14.51)
3 Doses	2,198,334	360	16.38	1.65	(1.34<<RR<<2.05)	723	1	138	0.36	(0.02<<RR<<5.68)
at least one dose			15.82	1.60	(1.60<<RR<<1.96			633	1.63	(0.22<<RR<<12.0)
Diptheria, Teatanu, Acellular Pertussis and Inactivated Polio										
Unvaccinated	3,734,846	552	14.78	1		3437	21	611	1	
1 Dose	296,026	39	13.17	0.89	(0.64<<RR<<1.23)	258	4	1,550	2.54	(0.88<<RR<<7.34)
2 Doses	242,792	24	9.89	0.67	(0.44<<RR<<1.01)	167	0	0	0.00	(0.00<RR<<4.91)
3 Doses	446,854	66	14.77	1.00	(0.77<<RR<<1.29)	347	1	288	0.47	(0.06<<RR<<3.50)
at least one dose			13.09	0.89	(0.73<<RR<<1.07)			648	1.06	(0.40<<RR<<2.80)
Whole-Cell Pertussis										
Unvaccinated	995,949	109	10.94	1		721	2	277	1	
1 Dose	382,317	54	14.12	1.29	(0.93<<RR<<1.79)	349	8	2,292	8.26	(1.76<<RR<<38.71)
2 Doses	1,383,584	194	14.02	1.28	(1.01<<RR<<1.62)	1298	14	1,079	3.89	(0.89<<RR<<17.06)
3 Doses	1,958,668	324	16.54	1.51	(1.22<<RR<<1.88)	1841	2	109	0.39	(0.06<<RR<<2.78)
at least one dose			15.36	1.40	(1.14<<RR<<1.72)			688	2.48	(0.59<<RR<<10.47)
Measle Mumps Rubella										
unvaccinated	1,373,401	124	9.03	1		1053	6	570	1	
1 dose	2,934,287	499	17.01	1.88	(1.55<<RR<<2.29)	2795	20	716	1.26	(0.51<<RR<<3.12)
unknown	412,830	58	14.05			361	0	0		
Oral Polio										
Unvaccinated	1,655,931	137	8.27	1		1030	2	194	1	
1 Dose	742,807	95	12.79	1.55	(1.19<<RR<<2.01)	591	3	508	2.61	(0.44<<RR<<15.60)
2 Doses	825,780	137	16.59	2.01	(1.58<<RR<<2.54)	837	5	597	3.08	(0.60<<RR<<15.82)
3 Doses	1,496,000	312	20.86	2.52	(2.06<<RR<<3.08)	1750	16	914	4.71	(1.08<<RR<<20.44)
at least one dose			17.75	2.15	(1.78<<RR<<2.59)			755	3.89	(0.92<<RR<<16.43)

vaccines are added to the immunization schedule or old vaccines are discontinued. In a population study such as the current study, the vaccinated groups will have been born on a different year than the unvaccinated group. In the case of the hemophilus vaccine, the vaccinated group was born after the unvaccinated group. In the case of the whole cell pertussis vaccine, the unvaccinated group was born after the vaccinated group. If one adjusts for changes in the incidence of diabetes with time, one will adjust off any effect of the vaccine, since the vaccinated and control subjects are born on different years. This over adjustment explains why almost all of the vaccine manufacturer's results showed that vaccines were associated with a rate ratio close to 1.

The results (Table **1**) show that the rate ratios of immunization in children receiving at least one dose of vaccine in the subgroup of children with a sibling with diabetes is elevated and not statistically different than the elevated rate ratio seen in the general population. The rate ratio is, in fact, often numerically greater than the rate ratio seen in the general population. The power is lower in the subgroup; however, the results are clinically important because the rate ratio is significantly elevated in 12/21 endpoints in the general population and the rate ratio is the same in the subgroup.

The data shows the clinically significant higher absolute or attributable risk of vaccine associated type 1 diabetes in children with a sibling with type 1 diabetes. With three doses of the hemophilus vaccine for example, the attributable risk in the general population is 3 (16.22-13.21) cases/100,000 per year compared to 288 (781-493) cases/100,000 per year in the subgroup with siblings with type 1 diabetes is almost a 100-fold increase. Over an eight year period, the approximate length of the study, the vaccine is associated with a cumulative attributable risk of 2,304/100,000 or 2.3% chance of developing vaccine induced type 1 diabetes in the subgroup of children with a sibling with type 1 diabetes. In contrast, the hemophilus vaccine was introduced to prevent seven deaths and 7 to 26 cases of severe disability per 100,000 immunized [17]. The results from this finding indicate that a child with a sibling with type 1 diabetes may be 70 to 150 times more likely to develop diabetes from the hemophilus vaccine than to benefit from the vaccine.

The hemophilus vaccine rate ratios in the subgroup are not statistically significant except in 2/21 endpoints, which can be explained by the low power from having too few children in the subgroup. However, the rate ratios are numerically and statistically the same as in the general population, and rate ratios in population generally are statistically significant. This fact is very troubling in light of data from a clinical trial that supports a causal relationship between the hemophilus vaccine and type 1 diabetes [1, 2]. Furthermore, data from the polio vaccine shows the same large attributable risk in the same subgroup and the results with the polio vaccine are statistically significant and show a dosing effect as well.

In conclusion, the data from Denmark supports an association between pediatric immunization and the development of type 1 diabetes. The data provides an initial look at the risks of vaccine associated IDDM in children already at high risk because of a sibling with type 1 diabetes. The studies provide data that these children have an extraordinary absolute or attributable risk of immunization. Physicians and parents should consider whether to administer the vaccine. While the subgroup results were often not statistically significant, except for the polio vaccine, it would be justifiable to abstain from immunization in this subgroup at present.

DISCLAIMER

The author is president and stock holder of Classen Immunotherapies, Inc. which holds patents on methods of testing vaccines for causing autoimmunity and methods of administering vaccines to prevent vaccine induced autoimmunity.

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