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Childhood Vaccinations and the Risk of Childhood Type 1 Diabetes: Results of a Population-Based Case-Control Study

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Abstract

Aims: To investigate the association of childhood vaccinations with the risk of Type 1 diabetes in children less than 5 years of age.

Methods: During 1992-95 a nation-wide population-based case-control study was performed in Germany including 760 incident cases (71% of eligible) and 1871 controls (43% of eligible), individually matched for age, sex, and place of residence. Information on childhood vaccinations and potential confounding factors were collected by a mailed questionnaire. Data were analysed by conditional logistic regression analyses.

Results: Completed primary immunisation (≥3 doses) against pertussis, *Haemophilus influenzae* type b, poliomyelitis and diphtheria/tetanus were significantly associated with a decreased risk for Type 1 diabetes. Adjusted for potential confounders, respective odds ratios were 0.70 (0.55; 0.89), 0.63 (0.49; 0.91), 0.74 (0.55; 0.999) and 0.65 (0.46; 0.73). A measles/mumps/rubella vaccination was associated with the T1D risk only by trend (odds ratio: 0.71 (0.51-1.01), while a BCG vaccination was not associated with the T1D risk.

Conclusions: The findings of this large nation-wide population-based case-control study indicate that childhood vaccinations, in particular the *Haemophilus influenzae* type b vaccination, may be protective against the development of Type 1 diabetes.

Keywords: Case-Control Study; Childhood Vaccinations; Risk of Early-Onset Type 1 Diabetes

Introduction

During past decades, childhood vaccinations have been in debate to increase the risks of childhood Type 1 Diabetes (T1D) [1,2]. Recently, Morgan, et al. performed a meta-analysis of observational studies on the association between vaccinations and childhood T1D risk [3]. Overall, this meta-analysis provided no evidence to support an association between any of the childhood vaccinations investigated and T1D risk. Although Morgan et al. included conference proceedings in their sound literature search, the preliminary results of our large nationwide population-based case-control study in Germany on the association of childhood vaccinations with T1D risk [4] were not included in the meta-analysis. Results of our population-based case-control study on the association of atopic diseases and early infant feeding with T1D risk have been described previously [5,6]. Data of the population-based case-control study were also included in several meta-analyses (e.g. [7]). To complement the evidence from the meta-analysis, we reanalysed in detail the data of our large nationwide populations-based case-control study regarding the association of

childhood vaccinations with the risk of childhood type 1 diabetes.

Material and Methods

Details of the study design have been described previously [5,6]. In short, we performed a matched (matching by age, sex, and place of residence) population-based case-control study during 1993-1995. Case children with early-onset (<5 years) T1D during 1993-1995 were selected from a nationwide T1D register and populations-based control children were randomly selected from regional population registers. In total, 760 case families (71% of eligible) and 1871 populations-based control (43% of eligible) families participated. Data were collected from parents by self-administered questionnaires. Besides data evaluated previously [5-7], questionnaire data comprised information on routine childhood vaccinations. The number of doses administered were assessed for the following vaccinations: pertussis, Bacillus Calmette-Guérin (BCG), *Haemophilus influenzae* type b (Hib), poliomyelitis, measles, mumps, rubella, diphtheria and tetanus. Measles, Mumps and Rubella (MMR) and Diphtheria and Tetanus (DT) were assessed as combined vaccinations due to common administration during the study period. For each vaccination, we analysed the effect of a complete primary immunisation (defined according to the German Standing Committee on Vaccinations [8]) on the risk of T1D.

Descriptive analyses were performed separately for cases and controls. Crude and adjusted odds ratios were estimated using conditional logistic regression analyses. In adjusted regression analyses, family history of T1D (in parents, siblings, grandparents), socio-economic status, cow's milk consumption, duration of breastfeeding, number of siblings, mother's age at delivery of case/control child, removal during past two years, and birth weight were included as potential confounders, with confounders defined according to previous analyses [6]. For sensitivity analyses, all analyses were repeated with the assumption of no administered dose in case of missing information for specific vaccinations. Two-tailed p-values <0.05 were considered statistically significant. All analyses were performed with the statistical analysis software SAS (SAS for Windows, Release 9.4, SAS Institute Inc., Cary, NC, USA).

Results

Descriptive data and OR estimates are given in Table 1. Complete primary immunisation regarding pertussis, Hib, poliomyelitis, and DT vaccines were significantly associated with a decreased risk for T1D in unadjusted and adjusted analyses (Table 1). The MMR vaccination showed an association with the T1D risk by trend only (adjusted analysis), while the BCG vaccination was not associated with the T1D risk. All sensitivity analyses confirmed these results substantially (ESM Table 1). Associations between potential confounders and the risk of T1D (adjusted for Hib vaccination) are presented in ESM Table 2.

Vaccination	Cases	Controls	Unadjusted analysis[a]		Adjusted analysis[a,b]		
	Prevalence % (N)	Prevalence % (N)	OR (95% CI)[c]	p	Cases / Controls N / N	OR (95% CI)[c]	p
Pertussis	29.8 (671)	35.1 (1,620)	0.75 (0.59, 0.94)	0.013	671 / 1582	0.70 (0.55, 0.89)	0.004
BCG	67.3 (559)	65.9 (1,192)	1.05 (0.80, 1.37)	0.730	559 / 1166	0.96 (0.72, 1.28)	0.780
Hib	56.3 (595)	64.2 (1,386)	0.70 (0.56, 0.87)	0.002	595 / 1355	0.63 (0.49, 0.80)	<0.001
Poliomyelitis	80.4 (672)	84.1 (1,624)	0.72 (0.55, 0.95)	0.022	672 / 1585	0.74 (0.55, 0.999)	0.049
MMR	83.1 (597)	84.5 (1,377)	0.82 (0.60, 1.12)	0.210	597 / 1244	0.71 (0.51, 1.01)	0.054
DT	87.6 (672)	89.9 (1,624)	0.69 (0.51, 0.95)	0.023	672 / 1586	0.65 (0.46, 0.92)	0.013

N: total number of cases and controls included (varies dependent on matching and missing values for vaccinations and confounders)
OR: odds ratio
[a]separate regression model for each vaccination
[b]adjusted for family history T1D (parents, siblings, grandparents), socio-economic status, cow's milk consumption, duration of breastfeeding, number of siblings, mother's age at delivery, removal during past two years, birth weight
[c]complete vs. incomplete primary immunisation
Definition of complete primary immunisation according to the German Standing Committee on Vaccinations [8]:
Pertussis vaccine: 4 doses, BCG vaccine: 1 dose, Hib vaccine 3 doses, poliomyelitis vaccine: 3 doses, MMR vaccine: 1 dose, DT vaccine: 3 doses

Table 1: Vaccinations as risk factors for childhood type 1 diabetes: results from conditional logistic regression analyses.

Discussion

This large nationwide population-based case-control study provided no evidence for any of the childhood vaccinations investigated to increase the risk of T1D mellitus, in accordance with the recent meta-analysis [3]. In fact, results indicated some protective effect of vaccinations (except BCG and MMR vaccination) against the development of T1D, even after adjustment for various confounding variables. Pooled odds ratio estimates for vaccinations less than 1 indicating a lower risk were also seen in the recent meta-analysis when based on all selected studies, although effects were not significant possibly due to the large heterogeneity between studies. Restricting pooled estimates to high quality studies reduced heterogeneity between included studies but also attenuated the observed effects [3].

Associations between potential confounders and the risk of T1D (ESM Table 2) are in good accordance with previously reported findings from our case-control study [6].

Besides the strength of our large nationwide case-control study with population-based case and control children and extensive adjustment for potential confounders, our study clearly has several limitations. The study included only new T1D cases selected from a nation-wide register restricted to the age of 5 years, the study design was retrospective, the data collection was questionnaire-based, there was a considerable difference in participation among parents of cases and population-based controls (71% vs. 43%) [6], and the exact timing of immunisation [3] was not assessed and disregarded.

Therefore, the observed protective effects of immunisation may be a result of various sources of bias. Given that the participation among parents of control children was quite lower than among parents of case children, it is conceivable that health-conscious parents, who may be more likely to have their children vaccinated, are over-represented among population-based control parents compared to case parents (selection bias). This may have induced the observed protective effect of vaccinations. An under-reporting among case parents is also possible (recall bias) [3]. Another explanation could be that parents of children with T1D answer questionnaires- e.g. regarding vaccinations - more thoroughly than control parents because they are seriously concerned having a child with T1D onset and extremely motivated to contribute to the clarification of the disease cause. In particular, a greater proportion of case than control parents may have extracted their children's vaccination history from the vaccination card - although all parents were requested to do so - while more control parents may have recalled the reported vaccination history from memory and possibly over-reported vaccine administration (recall bias). Ultimately, also immune-modifying effects of vaccinations reducing T1D risk, in particular dependent on time of vaccinations [1,2], cannot completely be excluded [8].

In conclusion, this large nationwide population-based case-control study provided no evidence to support any of the routine childhood vaccinations investigated to increase the risk of T1D mellitus but indicated some protective effect. Large prospective birth cohort studies with detailed assessment of the timing of immunisation should further enlighten the impact of vaccination on T1D risk.

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Duality of Interest

The authors approve that there is no duality of interest associated with this manuscript.

Contribution Statement

JR performed the analyses and drafted the manuscript. ASP, CB, TT, KCR and GG contributed to the interpretation and discussion of the data. GG was the principle investigator of the study. All authors commented on and revised the manuscript and gave final approval to the published version of this paper. JR is the guarantor of this work.

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