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Incidence of Type 1 Diabetes in Relation to Exposure to Rotavirus Infections in Pre- and Postvaccine Birth Cohorts in Finland

Anna Parviainen, Anna But, Reijo Sund, Martti Arffman, Heli Siljander, and Mikael Knip,

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QUESTION: Is exposure to rotavirus infections associated with the incidence of type 1 diabetes in Finnish children?

CONTEXT

- Rotavirus infections have been implicated as a possible trigger of islet autoimmunity leading to type 1 diabetes.
- In Finland, commercial availability of the rotavirus vaccine since 2006 and its introduction into the national immunization program in late 2009 resulted in a great reduction in rotavirus infections.
- The incidence of type 1 diabetes among Finnish children under the age of 5 years decreased after 2010.
- Some studies have reported an association between national implementation of the rotavirus vaccine and a decrease in the incidence of type 1 diabetes in children under the age of 5 years.

METHODS

DESIGN: A nationwide register-based ecological study.

SETTING: Finland, 1995–2015 birth cohorts.

PARTICIPANTS:

The pre-vaccine (1995–2000 and 2001–2005), the partially vaccinated (2006–2009) and the post-vaccine (2010–2015) birth cohorts comprising 8,674 children diagnosed with type 1 diabetes before the age of 15 years (Diabetes in Finland [FinDM] database), and 18,154 laboratory confirmed rotavirus infections in children below the age of 5 years (National Infectious Diseases Register).

MAIN OUTCOME MEASURES:

Crude and adjusted incidence rate ratios (IRR) of type 1 diabetes.

RESULTS

In young children, both the incidence of type 1 diabetes and the exposure to rotavirus infections were significantly lower in the postvaccine birth cohorts than in the prevaccine 2001–2005 birth cohorts

- The number of children exposed to rotavirus infection confirmed by laboratory test by the age of 5 years decreased from 2,522 per 100,000 children (2.5%) to 171 per 100,000 children (0.2%).
- The incidence of type 1 diabetes in those aged below 5 years decreased from 71.5 to 54.4 per 100,000 person-years (IRR 0.79, 95% CI 0.71 to 0.86).

At the population level, a reduction of one percentage point in the proportion of rotavirus exposed children was associated with a decrease of 8% in the incidence of type 1 diabetes in those aged below 5 years (0.92, 95% CI 0.89 to 0.96).

CONCLUSION: At the population level, a decrease in exposure to rotavirus infections was associated with a decrease in the incidence of type 1 diabetes in young children.

ARTICLE HIGHLIGHTS

- **Why did we undertake this study?**
  We wished to assess the relationship between the change in rotavirus infections following the national implementation of the rotavirus vaccine in Finland and the type 1 diabetes incidence.
- **What is the specific question we wanted to answer?**
  Is the decreased exposure to rotavirus infections resulting from the inclusion of the rotavirus vaccine in the national vaccination program associated with a change in the type 1 diabetes incidence?
- **What did we find?**
  Both the incidence of type 1 diabetes and exposure to rotavirus infections decreased significantly in children <5 years of age and born after the national implementation of the rotavirus vaccine.
- **What are the implications of our finding?**
  Rotavirus vaccination may reduce the type 1 diabetes incidence in young children.

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Anna Parviainen,[1,2] Anna But,[3] Reijo Sund,[4] Martti Arffman,[5] Heli Siljander,[6] and Mikael Knip,[1,2,7]

BRIEF REPORT

OBJECTIVE

To explore the incidence of type 1 diabetes in children in relation to exposure to rotavirus infections.

RESEARCH DESIGN AND METHODS

A nationwide register-based ecological study on the 1995–2015 birth cohorts in Finland compared those born before and after the national implementation of the rotavirus vaccine in 2009.

RESULTS

When the prevaccine 2001–2005 birth cohorts were compared with the postvaccine birth cohorts, the number of children exposed to rotavirus infection by the age of 5 years decreased from 2,522 per 100,000 children (2.5%) to 171 per 100,000 children (0.2%), while the incidence of type 1 diabetes in those aged <5 years decreased from 71.5 to 54.4 per 100,000 person-years (incidence rate ratio 0.79, 95% CI 0.71–0.86).

CONCLUSIONS

At the population level, a decrease in exposure to rotavirus infections was associated with a decrease in the incidence of type 1 diabetes in young children.

Rotavirus infections may be a trigger of islet autoimmunity leading to type 1 diabetes (1–4), and some studies have reported an association between national implementation of the vaccine and a decrease in the type 1 diabetes incidence in children younger than the age of 5 (5–7). In Finland, rotavirus vaccines became commercially available in 2006 and were introduced into the Finnish vaccination program in July 2009, and the incidence of type 1 diabetes decreased after 2010 among children younger than the age of 5 compared with years 2003–2006 (8). We conducted an ecological study on the pre- and postvaccine birth cohorts in Finland to study changes in the diabetes incidence in relation to exposure to rotavirus infections.

RESEARCH DESIGN AND METHODS

Study Design and Setting

In this ecological birth cohort study, we followed the 1995–2015 birth cohorts of 1,085,137 children from birth up to the age of 5 years for exposure to rotavirus

[1]Pediatric Research Center, New Children's Hospital, Helsinki University Hospital, Helsinki, Finland
[2]Research Program for Clinical and Molecular Metabolism, Faculty of Medicine, University of Helsinki, Helsinki, Finland
[3]Biostatistics Consulting, Department of Public Health, University of Helsinki and Helsinki University Hospital, Helsinki, Finland
[4]Institute of Clinical Medicine, Faculty of Health Sciences, University of Eastern Finland, Kuopio, Finland
[5]Department of Public Health and Welfare, Finnish Institute for Health and Welfare, Helsinki, Finland
[6]Center for Military Medicine, Logistics Command, Finnish Defense Forces, Helsinki, Finland
[7]Center for Child Health Research, Tampere University Hospital, Tampere, Finland

Corresponding author: Mikael Knip, mikael.knip@helsinki.fi

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infection (laboratory-confirmed infections in the National Infectious Diseases Register [NIDR]) and maximally up to the age of 14 years for the occurrence of type 1 diabetes (Diabetes in Finland [FinDM] database). The population at risk was determined using the public population database of Statistics Finland. The number of rotavirus infections and cases of type 1 diabetes (excluding those diagnosed younger than the age of 6 months as likely representing monogenic disease) were tabulated by birth year, 1-year age-group, and sex. In addition, four birth cohort groups were formed according to the availability and coverage of the rotavirus vaccine: the prevaccine (1995–2000 and 2001–2005), partly vaccinated (2006–2009), and the postvaccine (2010–2015) birth cohorts.

Table 1—Children exposed to rotavirus infections (i.e., laboratory-confirmed infections) younger than the age of 5 years of the population at risk by birth cohort group and sex (follow-up between 1995 and 2016)

Sex	Birth cohort group	Exposed (*n*)	Population (*n*)	Exposed (%)	Exposed *n* /100,000 person-years (95% CI)
All	1995–2000	7,649	386,415	2.0	1,979 (1,936–2,024)
	2001–2005	7,261	287,851	2.5	2,522 (2,466–2,580)
	2006–2009	2,935	230,390	1.3	1,274 (1,229–1,321)
	2010–2012	309	180,481	0.2	171 (153–191)
Males	1995–2000	4,181	196,961	2.1	2,123 (2,060–2,187)
	2001–2005	4,094	147,021	2.8	2,785 (2,702–2,870)
	2006–2009	1,635	117,723	1.4	1,389 (1,324–1,457)
	2010–2012	178	92,309	0.2	193 (167–223)
Females	1995–2000	3,468	189,454	1.8	1,831 (1,771–1,892)
	2001–2005	3,167	140,830	2.3	2,249 (2,173–2,328)
	2006–2009	1,300	112,667	1.2	1,154 (1,093–1,218)
	2010–2012	131	88,172	0.2	149 (125–176)

Birth cohorts 2013–2015 were excluded from the analyses due to incompletely observed age span.

Statistical Analysis

Please see the statistical analysis section in the Supplemental Material.

RESULTS

Of 18,154 children exposed to rotavirus infection younger than the age of 5 years, 14,910 (82%) belonged to the prevaccine birth cohorts (1995–2005). The number of exposed peaked in the 2001–2005 birth cohort group and decreased in children born thereafter, reaching a nadir in the postvaccine 2010–2015 birth cohort group (Supplementary Fig.1). The number of children exposed by the age of 5 years per 100,000 children was 2,522 (2.5%) in the 2001–2005 birth cohort group and 171 (0.2%) in the 2010–2012 birth cohorts, with an absolute reduction of 2,351 per 100,000 children (95% CI 2,291–2,411) (Table 1).

A total of 8,674 individuals were diagnosed with type 1 diabetes before the age of 15 years from a total follow-up of ∼13 million person-years. In the youngest age-group (both boys and girls), the incidence followed the same trend as the exposure to rotavirus infections (i.e., peaked in the 2001–2005 birth cohort group, and decreased thereafter) (Fig. 1 and Supplementary Table 1).

Trends in the diabetes incidence coincided only partly when calculated using observed and both observed and imputed counts, due to the incompletely observed age range (Supplementary Fig. 2). We focused on the relative differences that were statistically significant and consistent in both the main and the sensitivity analyses. Compared with the 2001–2005 birth cohort group, the relative differences in the type 1 diabetes incidence (Table 2) were statistically significant and consistent in both the main and the sensitivity analyses for the following birth cohort and age-groups: for the 1995–2000 birth cohort group, the overall reduction was 5% and in the youngest age-group 21%; for the partially vaccinated 2006–2009 birth cohort group, the incidence was 11% higher among those aged 5 to 9 years; for the postvaccine 2010–2015 birth cohort group, a reduction of 21% was seen in the youngest age-group, with a corresponding absolute reduction of 17.1 cases per 100,000 person-years (95% CI 10.9–23.3).

In both main and sensitivity analyses, a reduction of 1 percentage point in the proportion of children with laboratory-confirmed rotavirus infections was associated with a 5% decrease in type 1 diabetes incidence in children aged 0.5 to 14.9 years (Table 3). Results were consistent for both main and sensitivity analyses in the youngest age-group only, where a reduction of 1 percentage point in the proportion of children with laboratory-confirmed rotavirus infections was associated with an 8% decrease in the incidence of type 1 diabetes (Table 3).

CONCLUSIONS

Our ecological study on the 1995–2015 birth cohorts in Finland found an association

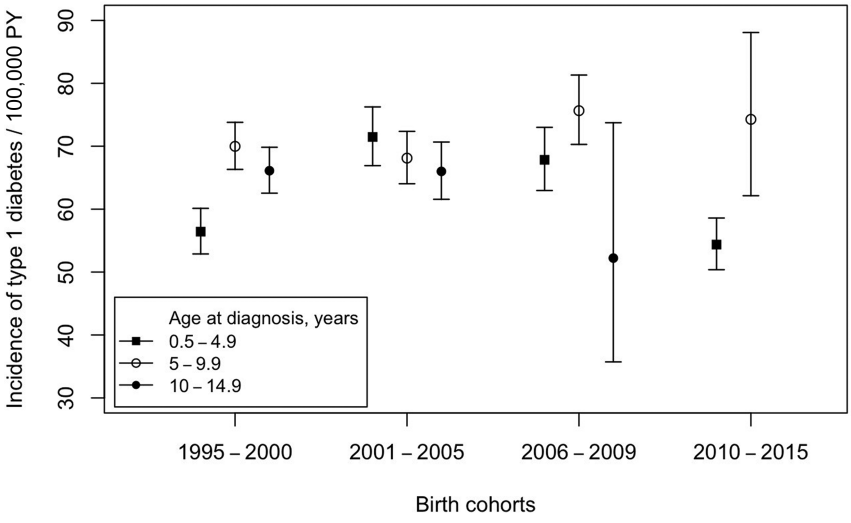

Figure 1—Age-specific incidence rates per 100,000 person-years (PY) with 95% CIs of type 1 diabetes in Finnish children and adolescents in four birth cohort groups between 1995 and 2015.

Table 2—The overall (0.5–14.9 years) and age-specific incidence rate ratios of type 1 diabetes in Finnish children and adolescents calculated for birth cohort groups 1995–2000, 2006–2009, and 2010–2015 compared with birth cohort group 2001–2005 (reference)

	Age-group							
	0.5–14.9 years		0.5–4.9 years		5.0–9.9 years		10.0–14.9 years	
Birth cohort group, analyses performed	Crude IRR (95% CI)	Adjusted* IRR (95% CI)	Crude IRR (95% CI)	Adjusted* IRR (95% CI)	Crude IRR (95% CI)	Adjusted* IRR (95% CI)	Crude IRR (95% CI)	Adjusted* IRR (95% CI)
1995–2000, main analyses	**0.94 (0.90–0.99)**	**0.95 (0.90–1.00***)**	**0.79 (0.72–0.86)**	**0.79 (0.72–0.86)**	1.03 (0.95–1.11)	1.03 (0.95–1.11)	1.00 (0.92–1.09)	1.03 (0.94–1.12)
1995–2000, sensitivity analyses	**0.94 (0.89–0.98)**	**0.94 (0.89–0.98)**	**0.79 (0.72–0.86)**	**0.79 (0.72–0.86)**	1.03 (0.95–1.11)	1.03 (0.95–1.11)	0.97 (0.90–1.05)	0.97 (0.90–1.05)
2001–2005**	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
2006–2009, main analyses	1.04 (0.97–1.10)	1.04 (0.98–1.11)	0.95 (0.86–1.05)	0.95 (0.86–1.05)	**1.11 (1.01–1.22)**	**1.11 (1.01–1.22)**	0.79 (0.56–1.13)	0.74 (0.52–1.07)
2006–2009, sensitivity analyses	**1.06 (1.00***–1.12)**	**1.06 (1.01–1.12)**	0.95 (0.86–1.05)	0.95 (0.86–1.05)	**1.11 (1.01–1.21)**	**1.11 (1.01–1.21)**	**1.11 (1.01–1.21)**	**1.10 (1.01–1.21)**
2010–2015, main analyses	**0.83 (0.77–0.90)**	**0.89 (0.82–0.97)**	**0.76 (0.69–0.84)**	**0.79 (0.71–0.87)**	1.09 (0.91–1.31)	1.08 (0.89–1.30)	Not available	Not available
2010–2015, sensitivity analyses	1.02 (0.98–1.07)	1.03 (0.98–1.08)	**0.81 (0.74–0.88)**	**0.81 (0.74–0.88)**	**1.09 (1.01–1.18)**	**1.09 (1.00***–1.18)**	**1.16 (1.07–1.26)**	**1.16 (1.07–1.26)**

In the main analyses, calculations were based on cases of type 1 diabetes diagnosed during 1995–2016 (incomplete age span for birth cohorts 2003–2016). Main analyses calculated using observed data, sensitivity analyses calculated using imputed data. Statistically significant results are marked in bold. IRR, incidence rate ratio. *Adjusted for age and sex when fitted to the whole data, for sex in the analyses stratified by age. **Observed data as a reference for main analyses, imputed data as a reference for sensitivity analyses. ***1 is not included in the CI, although it appears so due to rounding of decimals.

between changes in exposure to rotavirus infections and changes in the type 1 diabetes incidence in children younger than the age of 5. Exposure to rotavirus infections in children younger than the age of 5 years first increased to 2,552 per 100,000 children in the prevaccine 2001–2005 birth cohort group and then decreased to 171 per 100,000 children in the postvaccine 2010–2015 birth cohort group. The type 1 diabetes incidence in children aged <5 years changed in parallel and was 21% lower in the 2010–2015 birth cohorts than in the 2001–2005 cohorts. The lower incidence in the 1995–2000 birth cohort group is in line with previous observations that the increase in incidence rate was faster than ever before in the time period 2000–2005 and that the increase was fastest among those <5 years (9). At the population level, in the 1995–2015 birth cohorts, a reduction of 1 percentage point in the proportion of exposed children associated with a decrease of 8% in the incidence of type 1 diabetes in children younger than the age of 5 years.

Several studies, including a recent meta-analysis, have reached conclusions similar to the current ones; that is, that there may be an association between the introduction of a nationwide rotavirus vaccination program (and subsequent decrease in rotavirus infections) and a decrease in the type 1 diabetes incidence rate, specifically in children younger than the age of 5 years (5–7,10,11). The aforementioned meta-analysis included a number of individual-level cohort studies (12–16) that provided no support for such a protective association. Nonetheless, the

Table 3—Crude and adjusted incidence rate ratios with 95% CIs, demonstrating changes in the incidence rate of type 1 diabetes per 1 percentage point decrease in the exposure to laboratory confirmed rotavirus infections

	Age-groups							
	0.5–14.9		0.5–4.9		5.0–9.9		10.0–14.9	
Analyses performed	Crude IRR (95% CI)	Adjusted* IRR (95% CI)	Crude IRR (95% CI)	Adjusted** IRR (95% CI)	Crude IRR (95% CI)	Adjusted** IRR (95% CI)	Crude IRR (95% CI)	Adjusted** IRR (95% CI)
Main analyses	**0.88 (0.85–0.90)**	**0.95 (0.91–0.98)**	**0.83 (0.80–0.87)**	**0.92 (0.89–0.96)**	1.03 (0.97–1.09)	1.05 (0.99–1.12)	**0.65 (0.56–0.76)**	0.91 (0.74–1.11)
Sensitivity analyses	1.00 (0.98–1.02)	**0.95 (0.92–0.98)**	**0.90 (0.87–0.94)**	**0.94 (0.90–0.97)**	1.03 (1.00–1.06)	**1.04 (1.01–1.07)**	**1.06 (1.03–1.09)**	**1.08 (1.04–1.11)**

Birth cohorts 1995–2015, stratified into three age-groups. Main analyses were calculated using observed data, and sensitivity analyses were calculated using imputed data. Statistically significant results are marked in bold. IRR, incidence rate ratio. *Adjusted for age, sex, and year of diagnosis. **Adjusted for age and sex.

conclusion was that vaccinated children younger than the age of 5 had a decreased risk of type 1 diabetes (relative risk 0.84, 95% CI 0.75–0.95) (7).

The main strengths and limitations of our study relate to its design. To our knowledge, the current study is unique in its approach to this conundrum, examining the association between type 1 diabetes and the rotavirus vaccine from the point of view of changes in the magnitude of exposure to rotavirus infections. As the study is conducted at the population level in the country with the highest incidence of type 1 diabetes globally and using nationwide register data, it provides a large sample size, and the ∼13 million person-years and 8,674 cases of type 1 diabetes accumulated in our study provide statistical power sufficient even for subgroup analyses.

However, population-level studies inevitably suffer from a weaker level of evidence than individual-level studies. This study is restricted to exploring the association at the population level and cannot claim causality at the individual level, as this would represent ecological fallacy. We are unable to account for potential confounding factors, including other environmental factors changing over time. Moreover, as a population-level study, our study does not include individual-level data, such as whether laboratory-confirmed rotavirus infection and type 1 diabetes occurred within the same individual.

Comparisons of present and historical cohorts have several caveats, including potential differences in case detection or medical practices in the periods or possibility of noncomparable baseline transmission. However, as far as we are aware, no such changes in the diagnostic criteria of rotavirus infections or type 1 diabetes have been implemented during the 20-year study period. One aspect to keep in mind is that the NIDR data represent rotavirus infections with confirmed microbial etiology (i.e., the tip of the iceberg). In the current study, we assumed that the number of cases of rotavirus infections recorded in the NIDR, although incomplete, reflect the magnitude and changes in the underlying overall exposure at the population level and that the 93% reduction we observed between the pre- and postvaccine periods is in line with the changes reported in the study by Leino et al. (17), where cases were detected by ICD-10 diagnostic codes.

The incompletely observed age range is an unfortunate limitation, which can be remedied only once more time has passed since widespread rotavirus vaccination and more follow-up data are available. As an attempt to account for the uncertainty of the results due to the incompletely observed age range, we performed sensitivity analysis using imputed data and considered the associations robust only if they were consistent in both the observed and imputed data.

The current study adds to the evidence supporting the role of the rotavirus as a trigger of type 1 diabetes, and hence, the protective role of the rotavirus vaccination in young children, indicating a need for further individual-level studies with sufficient statistical power and follow-up time.

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