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Rotavirus and Type 1 Diabetes—is there a connection? A synthesis of the evidence

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Abstract

Though the etiology of type 1 diabetes (T1D) is not well understood, it is believed to comprise both genetic and environmental factors. Viruses are the most well studied environmental trigger, and there is a small but growing body of research on the potential influence of rotavirus on T1D. Rotavirus infections were initially identified as possible triggers of T1D given similarities between viral peptide sequences and T1D autoantigen peptide sequences. Further, rotavirus infection has been shown to modify T1D risk in T1D-prone mice. However, research into associations of rotavirus infections with T1D development in humans have yielded mixed findings and suggested interactions with age and diet. As global availability of rotavirus vaccines increases, recent studies have assessed whether rotavirus vaccination modifies T1D development, finding null or protective associations. Overall, evidence to-date suggests a possible triggering relationship between some wild-type rotavirus infections and T1D, but the potential effect of rotavirus vaccination remains unclear.

SUMMARY:

Rotavirus infection and vaccination have been proposed as potential modifiers of type 1 diabetes (T1D) risk. Available evidence suggests a possible triggering relationship between some wild-type rotavirus infections and T1D, but does not clearly support any effect of rotavirus vaccination.

Keywords

Rotavirus; Rotavirus vaccine; Immunizations; Type 1 Diabetes; Pediatric gastroenteritis

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CONFLICTS OF INTEREST

No authors have any potential conflicts of interest to disclose.

Introduction

Type 1 diabetes (T1D) is an autoimmune disease in which the body destroys pancreatic beta cells that are necessary for insulin production. T1D is usually diagnosed during childhood, and recent evidence suggests that its incidence in this group may be increasing [1, 2]. However, the etiology of T1D is poorly understood. While multiple genes have been identified as playing a role in the development of T1D, environmental exposures may be necessary for progression to clinical disease [1]. Proposed environmental triggers include infections, timing of complementary food introduction, events during gestation, maternal factors, and postnatal growth [3].

Most research on infectious triggers of T1D has focused on viral pathogens such as enteroviruses, rotavirus, herpesviruses, and others [3–5]. Although the exact proposed and studied mechanisms differ by virus, hypotheses include molecular mimicry (viruses that contain sequences similar to proteins in the body), infection-induced changes to the gut mucosa, direct pancreatic infection, and other interactions between the developing immune system and the timing of infection [1, 3, 4, 6]. Although enteroviruses have been studied in most detail, there is also a small body of research on the potential effects of rotavirus infection (or rotavirus vaccination) on development of T1D. This review summarizes the evidence to date regarding the potential association of rotavirus with T1D.

Initial Observations: Molecular Mimicry as a Mechanism?

One of the earliest suggestions that rotavirus may be associated with T1D development came from the work of Honeyman et al. in identifying similarities between peptide sequences of rotavirus proteins and islet antigen-2 (IA-2), an autoantigen associated with T1D [7]. When comparing short peptide sequences of 9 amino acids, Honeyman et al. noted that IA-2 had 56% identity (defined as the percentage of amino acids in identical positions over a defined sequence) and 100% similarity (defined as the percentage of amino acids with matching ability to bind to T-cell receptor contact residues) with the VP7 protein of a human G3P[8] rotavirus strain. Based on these findings, Honeyman et al. hypothesized that rotavirus may trigger T1D through the mechanism of molecular mimicry—i.e., in susceptible individuals, T cells activated against rotavirus may become cross-reactive against islet proteins due to epitope sequence similarities. In this same work, Honeyman et al. also confirmed sequence similarities between rotavirus and the autoantigen glutamic acid decarboxylase 65 (GAD65), as first noted by Jones and Crosby [8]. Honeyman et al. later reported cross-reactivity of T cells generated to rotavirus VP7 peptide with IA-2, and vice versa [9].

Findings from Mouse Models

Mouse models have provided an additional means of investigating the possible relationship of rotavirus infection to T1D. The most commonly employed mouse model is the Non-Obese Diabetic (NOD) mouse, in which the development of clinical diabetes is modifiable by environmental factors and follows a prodromal period of insulinitis [10].

Acceleration of clinical diabetes in the NOD mouse depends on the timing and strain of rotavirus infection

The effect of rotavirus infection on diabetes development in NOD mice is modified by the age of infection: inoculation of infant NOD mice with rotavirus has been shown to delay or even prevent the development of clinical diabetes [11], whereas inoculation of older NOD mice with established insulinitis has been shown to accelerate progression to diabetes [12]. This accelerating effect appears to be strain-specific, occurring with inoculations of rhesus rotavirus (RRV), as well as a reassortant human-RRV strain, but not with porcine rotavirus CRW-8 [13, 14]. Increased antibody response has also been associated with diabetes acceleration [12, 13].

Potential mechanisms associated with disease acceleration

Several mechanisms have been proposed by which rotavirus infection may precipitate T1D: direct pancreatic infection (leading to beta cell damage), molecular mimicry (in which rotavirus proteins bearing similar sequences to autoantigens activate autoreactive T cells), and bystander activation (in which preexisting autoreactive T cells are independently activated during an immune response against rotavirus) [10].

Although RRV can directly infect NOD mouse islet cells in vitro [15], pancreatic infection by RRV has only been seen in infant NOD mice, and has not been demonstrated to extend to the islet cells in vivo [11, 12]. RRV infection of weanling non diabetes-prone mice has been associated with a temporary decrease in pancreas size as well as transient hyperglycemia, and is apparently dependent on expression of toll-like receptor 3 (TLR3) [16]; however, this effect has not been studied in NOD mice, and no immediate hyperglycemia was observed in rotavirus-infected infant NOD mice [11].

Several other studies have attempted to investigate the NOD mouse immune response to rotavirus in more detail, to provide better understanding of the possibility of molecular mimicry, bystander activation, or other mechanisms. Although sequence similarity has been observed between RRV and islet-specific glucose 6-phosphatase catalytic subunit-related protein, an autoantigen associated with diabetes development in NOD mice, no evidence of molecular mimicry was found upon investigation [17].

It seems likely that the age-based differences in the diabetogenic effect of RRV infection on NOD mice are related to differences in the immune response. In infant mice, RRV results in intestinal as well as extra-intestinal infection, with viral replication demonstrated in the mesenteric lymph nodes (MLN) and thymus [18]. Thymus infection has been associated with changes in T cell development in NOD mice; specifically, infant NOD mice inoculated with RRV displayed an increased ratio of regulatory T cells, which promote self-tolerance, to T effector cells, which act to defend the body against perceived threats [18]. When these same mice were subjected to a strong stimulus as adults, they displayed reduced T cell response, suggesting persistent alterations in immune function [18].

The immune response to RRV inoculation of adult NOD mice has also been investigated [14, 17, 19]. In adult NOD mice, RRV infection induces minimal intestinal inflammation, but RRV can be detected in the pancreatic lymph nodes (PLN) and MLN [14, 17]. Increased

expression of pro-inflammatory cytokines has been noted in the PLN, MLN, and spleen of adult NOD mice following inoculation with RRV [14, 17]. In contrast, infectious CRW-8, a porcine rotavirus, does not appear to spread to the PLN or MLN, and significant increases in pro-inflammatory cytokines were not seen in these regions following inoculation of weanling NOD mice [17]. In adult NOD mice, Major Histocompatibility Complex molecule (MHC) expression has been associated with RRV infection [14]. Further, increased B cell MHC I expression in the PLN and MLN was seen in the first week following infection with RRV, but not with CRW-8 (which does not accelerate diabetes development), suggesting that B cell MHC I expression may be related to diabetes acceleration in this mouse model [17]. Ex vivo, infection of mouse splenocytes by RRV, inactivated RRV, or CRW-8 induced B cell activation in a dose-dependent manner, with higher levels of activation in splenocytes from NOD mice as compared to non-diabetes-prone mice; however, this activation was dependent on the activity of rotavirus VP7, toll-like receptor (TLR) 7, and type 1 interferon (IFN), and the presence of CD11c+ dendritic cells (DC) [20]. Further investigation of DC activation in rotavirus-infected NOD mice showed that plasmacytoid DCs (pDCs), which produce type 1 IFN after activation, were activated by RRV but not CRW-8, and that RRV infection transiently increased the ratio of pDCs to conventional DCs (cDCs) [19]. Non-diabetes-prone mice infected with RRV appeared more resistant to these effects, and showed lower infection of the PLN and MLN [19]. RRV also induced type 1 IFN signaling in the MLN and PLN of infected NOD mice, but not non-diabetes-prone mice [19]. Even in the absence of type 1 IFN signaling, B cell activation in the PLN and MLN still occurred, albeit delayed [19]. However, type 1 IFN signaling was necessary for RRV to accelerate diabetes onset in NOD mice [19]. The role of type 1 IFN signaling in rotavirus--induced diabetogenesis was further assessed in relation to melanoma differentiation-associated factor 5 (MDA5), which is encoded by the IFIH1 gene (associated with T1D risk) [21]. Experiments showed that MDA5 was important to limiting murine infection with a human rotavirus isolate, especially in the pancreas, and that this activity occurred both dependently and independently of IFN [21].

Taken together, this body of evidence suggests that rotavirus-induced diabetes acceleration in NOD mice is strongly related to the immune response to the infection, specifically the activation of pDCs and B cells in the lymph nodes, as well as B cell MHC I expression and the activity of IFN and other pro-inflammatory cytokines. Further, preexisting diabetic pathology (insulinitis, and the existence of autoreactive cells) appears necessary for acceleration of disease progression.

Epidemiologic Evidence in Humans: Rotavirus and T1D

Longitudinal studies to examine correlations between rotavirus and T1D-associated antibodies

The possibility of molecular mimicry between rotavirus and T1D-associated autoantigens guided specific research questions within large cohorts designed to elucidate T1D etiology. The two cohorts in which this potential association has been studied in most detail are the BabyDiab cohort in Australia, and the Type 1 Diabetes Prediction and Prevention project (DIPP) in Finland [22, 23]. In both cohorts, infants at high risk of T1D are enrolled from

birth and followed longitudinally, with regular serum samples taken and assayed for T1D-associated autoantibodies (antibodies to IA-2, antibodies to GAD, and insulin antibodies [IIA]).

Researchers attempted to compare the timing of autoantibody seroconversion to the timing of rotavirus seroconversion in such cohorts, but findings were inconsistent (Table 1). Honeyman et al. studied the relationship between the appearance of autoantibodies and that of rotavirus antibodies among 24 children from the BabyDiab cohort who had developed clinical T1D or in whom autoantibodies had been detected at least twice during follow-up. Rotavirus infection, defined as an increase in rotavirus antibodies of ≥40% between consecutive time points (equivalent to an increase of ≥2 interassay coefficients of variation [CV] in this study), was found to be significantly associated with the appearance of autoantibodies in the 24 children during that same time period [22]. However, when a similar analysis was conducted by Blomqvist et al. of 29 cases from the DIPP cohort, no significant association was found in the appearance of rotavirus and autoantibody seroconversion [23]. A matched case-control analysis also demonstrated no significant differences in the occurrence of rotavirus infections during the time periods when cases developed autoantibodies [23]. Blomqvist's research group later updated this analysis with a larger population from DIPP, comprising 43 children with incident T1D, 36 children with at least 2 T1D-associated autoantibodies, and 104 children without any autoantibodies (controls) [24]. In this study, they again found no significant association between the presence of rotavirus antibodies and the presence of T1D-associated autoantibodies [24]. Cellular responsiveness to rotavirus was also not associated with T1D-associated antibodies. Production of interleukin-4 (IL-4) in response to stimulation with purified rotavirus was stronger in children with autoantibodies as compared to controls, but no significant difference was seen between children with clinical T1D and controls [24].

These discrepant findings may be attributable to population differences (both in host genetic background as well as circulating virus genotype) or to methodological differences. For instance, Honeyman et al. used human rotavirus in their EIA, and defined rotavirus infection by an increase in IgA or IgG, whereas the first Blomqvist et al. study used an indirect EIA method based on the Nebraska Calf Diarrhea Virus, and defined rotavirus infection by a 2-fold absorbance increase in IgG [22, 23]. Associations in Honeyman et al. appeared primarily driven by IgA, which was not measured by Blomqvist et al. It is also possible that evidence of rotavirus infection in the Blomqvist study population could have been masked by high levels of maternally transferred IgG early in life, which might have contributed to the null results seen. However, in the subsequent analysis of the DIPP cohort, which again showed a null association, both IgA and IgG were measured [24], suggesting additional factors at play. Definitions of separate rotavirus infection were also not consistent across populations: whereas Honeyman et al. interpreted consecutive increases in rotavirus antibody titers as additional infections, Blomqvist et al. considered such situations as part of the same initial infection. Thus, rotavirus infections may have been more sensitively detected in Honeyman's study, but more specifically detected in Blomqvist et al.'s research.

Cross-sectional studies of association between T1D and rotavirus

Outside the BabyDiab and DIPP cohorts, several other studies have assessed the potential relationship between T1D and rotavirus infection. Ataei-Pirkooh et al. conducted a case-control study of children ≤14 years of age attending the Children's Medical Center in Tehran, with cases defined by incident T1D diagnosis and controls recruited from children who presented to the hospital but did not have any diabetes-related history [25]. Although anti-rotavirus antibodies were significantly higher in cases as compared to controls, and rotavirus antibodies were significantly correlated with islet autoantibodies, the analysis was not adjusted for age, a potentially important confounder [25]. In a sex-, age-, geographical-, and time-matched case-control study, Bian et al. screened serum from 42 U.S.-based cases with new-onset T1D and 42 healthy controls (verified to be autoantibody-negative) [26]. Multiplex viral protein arrays were used to test for IgA and IgG reactivity to viral proteins from 23 viruses, including rotavirus and 6 others that had been previously associated with T1D; reactivity to the auto-antigen IA-2 was also tested [26]. Only responses to IA-2 and Epstein-Barr Virus (EBV) were significantly higher in cases as compared to controls [26]. Shulman et al. tested maternal sera and cord blood samples from healthy deliveries in Israel during the winter viral season [27]. Antibodies to rotavirus and the T1D autoantigen GAD65 were found to co-occur in some maternal and cord blood samples, while in other samples, only cord blood was antibody positive, suggesting the possibility of an independent fetal antibody response. However, the cross-sectional study design precludes any conclusions about whether these antibodies had any effect on clinical development of T1D [27].

Potential interactions with age or feeding

Makela et al. later analyzed a larger subset of children from the DIPP study to assess correlations among antibodies to enteric viruses (including rotavirus) and antibodies to bovine and human insulin [28]. Of 238 children available for analysis, 211 had information on rotavirus antibodies, 61 developed at least one autoantibody, and 46 developed at least 2 autoantibodies [28]. Rotavirus infections (as well as enterovirus and adenovirus infections) before the age of 6 months were found to be significantly associated with human and bovine insulin-binding antibodies, whereas infections occurring later in infancy were not found to be significantly associated with insulin-binding antibodies; this association appeared to be stronger in children receiving cow-milk-based formula before the age of 3 months [28]. Insulin-binding antibodies were significantly associated with development of autoantibodies as well as development of clinical T1D [28]. These interactions were further studied in another, larger case-control study drawn from the ongoing DIPP study cohort [29]. Rotavirus antibodies, respiratory syncytial virus antibodies, bovine insulin-binding antibodies, and autoantibodies were analyzed among 107 autoantibody-positive cases and 446 controls. As previously documented by this research group, rotavirus infection before the age of 6 months was associated with development of T1D-associated autoantibodies with an indication that this association was strongest in those infants exposed to cow's milk formula before the age of 3 months [29].

Other studies

Zhao et al. selected a subset of the DIPP cohort for a case-control study of the intestinal virome [30]. Eleven children who had developed autoimmunity were matched to 11 controls, and sequential stool samples were analyzed for each group [30]. No significant difference was found in rotavirus prevalence or abundance when comparing stool samples from cases (before seroconversion) and controls [30].

Could Rotavirus Vaccination Influence T1D Development in Humans?

The possible association of rotavirus infection and T1D raises the question of whether rotavirus vaccination might have an effect on T1D. This question was first investigated by Vaarala et al. using a population-based cohort study of >120,000 Finnish children [31]. National Vaccination Register data was used to classify children born in 2009 – 2010 as vaccinated (at least one dose) or unvaccinated against rotavirus, and information on T1D diagnosis was linked from the National Care register for 2009 – 2014. The authors found an adjusted relative risk of 0.91 (95% confidence interval [CI]: 0.69 – 1.20) for the effect of rotavirus vaccination on T1D, suggesting that rotavirus vaccination does not significantly alter the risk of T1D in the first 4 – 6 years of life [31]. A study with a longer follow-up time was conducted by Hemming-Harlo et al., who re-contacted the participants of the original RotaTeq trial in Finland to determine T1D status [32]. The prevalence of T1D at the time of survey (11 – 14 years after the trial) was not significantly different among vaccine and placebo recipients who responded, again suggesting no relationship between rotavirus vaccination and T1D [32].

These null cohort findings are in contrast to two articles published in 2019—an ecological analysis of the Australian population and a cohort analysis of U.S. children based on insurance records [33, 34]. Perrett et al. conducted an interrupted time-series analysis of T1D incidence in Australia before and after rotavirus vaccine introduction, finding a decrease of 15% in T1D incidence among children 0 – 4 after vaccine introduction as compared to before vaccine introduction [33]. The authors found no evidence of an effect on incidence in older age groups [33]. Rogers et al. analyzed insurance claims to compare the incidence of T1D among vaccinated U.S. children to the incidence among unvaccinated children (two reference groups comprising those born after and those born before vaccine introduction) [34]. In this analysis, they found a 33% (95% CI: 17 – 46%) reduction in T1D incidence comparing fully rotavirus vaccinated to unvaccinated children [34]. Rogers et al. also noted a stronger effect of RotaTeq, a pentavalent vaccine, as compared to Rotarix, a monovalent vaccine [34].

More recently, two additional U.S.-based cohort studies have presented null findings. Analysis by Burke et al. utilizing a different insurance claims database found no significant difference in adjusted T1D incidence in vaccinated as compared to unvaccinated children, when following children from 12 months up to 12 years of age; several sensitivity analyses were performed to assess the possibility of exposure misclassification, but reached the same conclusion [35]. Similarly, a study by Glanz et al. also found no significant association between rotavirus vaccination and T1D incidence when utilizing information from the Vaccine Safety Datalink, a U.S.-based research network that creates and analyzes

standardized datasets from the electronic health records of seven integrated health care organizations [36]. Glanz et al. also conducted an analysis stratified by rotavirus vaccine product; this analysis showed null results.

Differences in the results obtained by Rogers et al. as compared to the other retrospective cohorts may stem from differences in the populations included in each database, but are also likely attributable to differences in the assumptions, inclusion criteria, and methods. Burke et al. required continuous enrollment since birth, and Glanz et al. required continuous enrollment from 6 weeks of age (prior to when rotavirus vaccines are given), whereas Rogers et al. required only that infants be enrolled prior to 12 months of age. Stringent restrictions on continuous enrollment may help to mitigate misclassification of exposure or outcome, a key concern for insurance claims analysis. It is also possible that differences in findings between the U.S., Australian, and Finnish populations could be related to population variations in genetic background or other factors. Further data are necessary to better understand the potential relationship between rotavirus vaccination and T1D, and whether there may be important effect modifiers.

Conclusions

Despite a small but growing body of literature on the possible relationship between rotavirus infection (wild-type or vaccine) and T1D, the exact mechanisms, modifiers, and magnitude of the potential association are not yet well defined. Evidence from mouse models suggests that some rotavirus infection exacerbates existing murine T1D pathology via molecular mimicry or bystander activation—mechanisms that have also been suggested for the effect of other viral infections on T1D and other autoimmune conditions [6]. However, the extent to which these mechanisms apply to human rotavirus infection and T1D is unknown. Further, although potential interactions of rotavirus infection with age have been noted in NOD mice, these interactions have not been well explored in humans. Findings from the DIPP study suggest that the effect of rotavirus infection on T1D may be modified by infant diet, but this hypothesis has not been further tested in other populations. Similar interactions have been suggested for the effect of viral infections on celiac disease, another autoimmune condition [37]; though more research is needed, these interactions may be especially relevant to rotavirus given that infections typically happen at a young age that may coincide with the transition from breast milk to solid foods.

In the current era of widespread rotavirus vaccination (and lower incidence of natural infection), the question of whether rotavirus vaccination has an effect on T1D becomes more relevant. However, the rarity of T1D as well as its long latent period make this a challenging research question to address—especially since current rotavirus vaccines have been licensed only since 2006, with high and rapid uptake in many countries. Existing findings have led to mixed conclusions, further highlighting the need for additional research with diverse methods, data sources, and populations. However, although there is no clear evidence of a protective effect of rotavirus vaccination on T1D, neither has there been evidence supporting an increased risk of T1D following rotavirus vaccination. Overall, the body of literature reviewed supports the continuation of universal rotavirus vaccination programs.

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Table 1:

Evidence in Humans: Wild-type Rotavirus Infection

Study	Design	Location	Study Population	Main Findings
Honeyman et al., 2000	Matched case-control; case-only analysis	Australia (BabyDiab cohort)	24 autoantibody-positive cases; 17 matched autoantibody-negative controls	• Incidence of rotavirus infection not significantly different between cases and controls • Timing of rotavirus seroconversion and autoantibody seroconversion significantly positively associated among cases
Blomqvist et al., 2002	Matched case-control; case-only analysis	Finland (DIPP cohort)	29 autoantibody-positive cases; 67 matched autoantibody-negative controls	• Incidence of rotavirus infection not significantly different between cases and controls • Timing of rotavirus seroconversion and autoantibody seroconversion not significantly associated among cases
Makela et al., 2006	Case-control	Finland (DIPP cohort)	79 cases with either clinical T1D or ≥2 autoantibodies; 104 autoantibody-negative controls	• Antibody positivity to rotavirus similar in both groups of cases as in controls • T cell responses to rotavirus antigen not significantly different between cases and controls • Cytokine responses to stimulation with purified rotavirus also largely similar among groups
Makela et al., 2006	Cohort	Finland (DIPP cohort)	238 children followed from birth	• Children with a rotavirus infection before 6 months of age later had higher insulin-binding antibody levels vs. children of similar age who had not been infected with rotavirus before 6 months – Effect strongest in children exposed to cows' milk-based formula at < 3 months of age • Levels of human or bovine insulin-binding antibodies significantly positively associated with autoantibodies
Lempainen at al., 2012	Matched case-control	Finland (DIPP cohort)	107 autoantibody-positive cases; 446 matched autoantibody-negative controls	• Children with a rotavirus infection before 6 months of age later had higher insulin-binding antibody levels vs. children of similar age who had not been infected with rotavirus before 6 months • Among children exposed to cows' milk before 3 months of age, rotavirus infection before 6 months significantly positively associated with emergence of autoantibodies
Shulman et al., 2014	Cross-sectional	Israel	107 healthy mothers delivering in the winter viral season and with matched maternal and cord sera	• Antibodies to rotavirus and GAD65 co-occurred in some maternal and cord blood samples, but in other samples, only cord blood was antibody positive
Bian et al., 2016	Matched case-control	United States	42 cases with incident T1D; 42 matched autoantibody-negative controls	• No significant difference in rotavirus IgA or IgG comparing cases to controls
Zhao et al., 2017	Matched case-control	Finland (DIPP cohort)	11 autoantibody-positive cases; 11 matched autoantibody-negative controls	• No significant difference in the prevalence or relative abundance of rotavirus in pre-seroconversion stools of cases vs. stools from matched controls

Study	Design	Location	Study Population	Main Findings
Ataei-Pirkooh et al., 2019	Case-control	Iran	80 cases with incident T1D; 80 non-diabetic controls	• Levels of rotavirus IgG significantly positively associated with age, autoantibodies, and case status in crude analyses

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Table 2:

Evidence in Humans: Rotavirus Vaccines

Study	Design	Location	Study Population	Main Findings
Vaarala et al., 2017	Cohort	Finland	94,437 children vaccinated against rotavirus; 27,213 children not vaccinated against rotavirus; all from 2009 – 2010 birth cohort	• Vaccination against rotavirus not significantly associated with T1D incidence in the first 4 – 6 years following vaccination (Risk Ratio [RR] for full-series vs. no vaccination: 0.91; 95% Confidence Interval [CI]: 0.69 – 1.20)
Hemming-Harlo et al., 2019	Cohort	Finland (REST trial population)	3184 children who had received the study vaccine in the original trial; 2580 children who had received the placebo vaccine	• Vaccination against rotavirus not significantly associated with prevalence of T1D when assessed 12 – 14 years following vaccination (Prevalence 0.97% in placebo group and 1.04% in vaccine group; p = 0.81)
Perrett et al., 2019	Ecological	Australia	16,159 cases of incident T1D among 66,055,000 person-years of observation in children <14, 2000 – 2015	• Significant decrease in T1D incidence among children 0 – 4 when comparing post-rotavirus-vaccine years to pre-rotavirus-vaccine years (Rate Ratio [IRR]: 0.85; 95% CI: 0.75 – 0.97)
Rogers et al., 2019	Cohort	United States	540,317 fully rotavirus vaccinated children; 140,646 partially rotavirus vaccinated children; 246,600 children unvaccinated against rotavirus; 546,972 children born before rotavirus vaccine introduction (historical comparator); all with private health insurance	• T1D incidence significantly lower in vaccinated children vs. concurrent and historical unvaccinated groups (Hazard Ratio [HR] for full-series vs. no vaccination concurrent comparators: 0.67; 95% CI: 0.54 – 0.83)
Burke et al., 2020	Cohort	United States	1,035,198 fully rotavirus vaccinated children; 210,057 partially rotavirus vaccinated children; 318,285 children unvaccinated against rotavirus; all with employer-sponsored commercial health insurance.	• Vaccination against rotavirus not significantly associated with T1D incidence in children followed up to 12 years of age (HR for full-series vs. no vaccination: 1.09; 95% CI: 0.87 – 1.36)
Glanz et al., 2020	Cohort	United States	360,169 fully rotavirus vaccinated children; 15,765 partially rotavirus vaccinated children; 11,003 children unvaccinated against rotavirus; all enrolled in a health plan participating in the Vaccine Safety Datalink project	• Vaccination against rotavirus not significantly associated with T1D incidence in children followed up to 11 years of age (HR: 1.03; 95% CI: 0.62 – 1.72)