The Childhood Vaccination Schedule and the Lack of Association With Type 1 Diabetes

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Abstract

OBJECTIVES: Safety studies assessing the association between the entire recommended childhood immunization schedule and autoimmune diseases, such as type 1 diabetes mellitus (T1DM), are lacking. To examine the association between the recommended immunization schedule and T1DM, we conducted a retrospective cohort study of children born between 2004 and 2014 in 8 US health care organizations that participate in the Vaccine Safety Datalink.

METHODS: Three measures of the immunization schedule were assessed: average days undervaccinated (ADU), cumulative antigen exposure, and cumulative aluminum exposure. T1DM

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incidence was identified by International Classification of Disease codes. Cox proportional hazards models were used to analyze associations between the 3 exposure measures and T1DM incidence. Adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs) were calculated. Models were adjusted for sex, race and ethnicity, birth year, mother's age, birth weight, gestational age, number of well-child visits, and study site.

RESULTS: In a cohort of 584 171 children, the mean ADU was 38 days, the mean cumulative antigen exposure was 263 antigens (SD = 54), and the mean cumulative aluminum exposure was 4.11 mg (SD = 0.73). There were 1132 incident cases of T1DM. ADU (aHR = 1.01; 95% CI, 0.99–1.02) and cumulative antigen exposure (aHR = 0.98; 95% CI, 0.97–1.00) were not associated with T1DM. Cumulative aluminum exposure >3.00 mg was inversely associated with T1DM (aHR = 0.77; 95% CI, 0.60–0.99).

CONCLUSIONS: The recommended schedule is not positively associated with the incidence of T1DM in children. These results support the safety of the recommended childhood immunization schedule.

Routine vaccination in the United States is one of the greatest public health achievements of the last century.[1] However, some parents have expressed concerns about the recommended immunization schedule and believe that infants receive too many vaccines over a short period of time.[2,3] Specifically, there are beliefs that vaccine antigen exposure during infancy overwhelms the immune system and that vaccine ingredients, such as aluminum, increase the risk for autoimmune diseases.[4–8] Survey and vaccination coverage data suggest that such safety concerns are prompting ~10% to 15% of parents to refuse or delay recommended vaccines for their children,[2,9–12] contributing to numerous outbreaks of vaccine-preventable diseases across the country.[13,14]

In response to these concerns, the Institute of Medicine issued a report in which researchers examined the safety of the childhood immunization schedule recommended by the Advisory Committee on Immunization Practices (ACIP).[15] The report concluded that although the available evidence suggests that the recommended schedule is safe, studies examining the cumulative long-term effects of the schedule are lacking. It further emphasized the need to conduct observational studies using existing medical record databases because clinical trials would be infeasible or unethical. In such observational studies, the report added, researchers would need to develop metrics to represent the immunization schedule as a whole and assess chronic health outcomes, such as allergies and autoimmune diseases.

We conducted an epidemiological study in which we examined associations between 3 measures of the childhood immunization schedule and the incidence of type 1 diabetes mellitus (T1DM) in children aged 2 to 14 years. The measures were the average number days undervaccinated, cumulative vaccine antigen exposure, and cumulative vaccine aluminum exposure through the first 23 months of life. T1DM was examined because it is a chronic autoimmune disease, with both genetic and environment risk factors, that is increasing in incidence and affects an estimated 27 000 children annually in the United States.[16,17] The study was conducted within the Vaccine Safety Datalink (VSD), a collaboration between the Centers for Disease Control and Prevention and 8 integrated

health care systems that uses electronic health record databases to assess the safety of childhood and adult vaccinations.[18]

METHODS

Setting and Study Cohort

We conducted a retrospective cohort study of children enrolled in 8 integrated health care organizations that participate in the VSD. The participating sites are located in California, Minnesota, Colorado, Oregon, Washington, and Wisconsin. Each site creates standardized data sets containing demographics, membership enrollment, vaccinations, and medical encounters in outpatient, inpatient, and emergency department settings. The VSD population is demographically representative of the general US population.[19] Institution review boards at each site approved the study with a waiver of Health Insurance Portability and Accountability Act and consent.

We used the VSD databases to identify children born between January 1, 2004, and December 31, 2014. Children with continuous health plan enrollment from birth through age 23 months and at least 2 well-child visits by age 12 months were included into the cohort. Children with medical contraindications to vaccination were excluded.[20] Cohort members were followed until a T1DM diagnosis, disenrollment from the health plan, or December 31, 2019.

Across the cohort, 3 different vaccine exposures were assessed: average days undervaccinated (ADU), cumulative antigen exposure, and cumulative aluminum exposure. Although previous methodologic work has demonstrated that these exposure variables are correlated, it also showed that they can be independently examined in multiple regression models.[21]

ADU is a continuous metric that quantifies adherence to the recommended immunization schedule from birth through age 23 months.[10,12] For each child, the calculation of ADU begins by taking the difference between when a vaccine dose was administered and when the dose should have been administered according to ACIP recommendations.[22] For example, the first dose of the pneumococcal conjugate vaccine is due at age 60 days but is not considered late until 92 days. For this dose, days undervaccinated would begin to accrue on day 93. The number of days undervaccinated is then summed across all doses of all vaccines to calculate the total number of days undervaccinated. The total number of days undervaccinated is then divided by the number vaccines the child should have received according the ACIP schedule, yielding ADU. For the ADU calculation, the recommended schedule comprised 7 different vaccines and 20 individual doses before 2006 and 8 vaccines and 23 doses after 2006. The calculation did not include the hepatitis A vaccine because of the long period for on-time vaccination (age 12–23 months) or the influenza vaccine because it is administered seasonally.[10,20] The total number of days undervaccinated could range from 0 (fully vaccinated and on-time) to 3834 (completely unvaccinated, 0 doses), and ADU could range from 0 to 638 days. Undervaccination can arise from refused or delayed vaccines, barriers to health care, missed or late well-child visits, or gaps in health care coverage.[2,3,9,11,14,23,24]

Cumulative antigen exposure was measured as the summed total number of immunogenic proteins and polysaccharides in each vaccine dose from birth through age 23 months. The number of antigens in recommended infant vaccines ranges from 1 to 93 per dose (Supplemental Table 2).[25,26] Children who received all recommended doses in the ACIP schedule could have been exposed to between 193 and 355 cumulative antigens.

Cumulative aluminum exposure was measured as the summed total amount of aluminum in each vaccine dose from birth through age 23 months. In the VSD data files, the administered vaccine type is linked with the vaccine manufacturer. The aluminum amount for each dose was obtained by linking the vaccine manufacturer with the vaccine package insert, which documents the maximum amount of aluminum in milligrams per dose.[27] The amount of aluminum in recommended vaccines ranges from 0 to 0.85 mg per dose (Supplemental Table 2). Children vaccinated according to the recommended schedule could have been exposed to between 1.68 and 6.00 mg of cumulative aluminum.

Type 1 Diabetes Cases

Children with incident T1DM were identified by the following *International Classification of Diseases, Ninth Revision, Clinical Modification* and *International Classification of Diseases, Tenth Revision, Clinical Modification* codes: 250.1x, 250.3x, or E10.xx. To be considered a case of T1DM, children had to have 1 of these codes in the outpatient setting; the first occurrence of the code represented the incident date. Previous work has shown that this method identifies T1DM cases with a high degree of accuracy.[28,29]

Statistical Analyses

We conducted a post hoc power analysis based on a Cox proportional hazards regression model. For the power calculation, the incidence proportion was 0.0024 for children exposed to >3.00 mg of aluminum and 0.0019 for children exposed to 3.00 mg. Based on these parameters, the study could detect a hazard ratio of 1.43 for exposure to >3.00 mg of aluminum with 90% power and an α of 0.05.

Baseline cohort characteristics were examined with descriptive statistics. Cohort data were analyzed with Cox proportional hazards regression to examine associations between the 3 different vaccine exposure measures and T1DM incidence. The exposures were modeled as time-varying continuous variables. Cumulative aluminum exposure was assessed in 1-mg increments, ADU was scaled to 25-unit increments, and cumulative antigen exposure was scaled to 10-unit increments. For ADU, 25 represents the ADU for a child missing a dose of diphtheria, tetanus-acellular, pertussis (DTaP); and 10 is the approximate number of antigens per vaccine dose by age 12 months (mean = 11.6 antigens per dose). The following risk factors for T1DM were included in the models: sex, race and ethnicity, birth year, mother's age, birth weight, and gestational age.[17,30–35] Models were also adjusted for VSD site and number of well-child visits between ages 30 days and 23 months. We examined 2-way interactions between the exposure variable and race and ethnicity, VSD site, gestational age, and birth weight. Adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs) were calculated. We conducted 2-sided statistical tests with a *P* < .05 cutoff for statistical significance.

For all models, we assessed the assumption of linearity in log hazard by plotting the cumulative martingale residuals against the continuous exposure variables and by conducting a Kolmogorov-type supremum test in which a *P* value was calculated on the basis of a sample of 1000 simulated residual patterns.[36] When a departure from linearity was indicated (*P* < .05), the continuous exposure variable was transformed into a categorical variable, and the association between the categorical variable and T1DM incidence was modeled with Cox regression. The category-specific coefficient estimates were then plotted against the midpoints of the categories to identify appropriate cut points for the transformed variable, and the adjusted Cox regression analysis was re-run with the transformed variable. The proportional hazards assumption was evaluated with Schoenfeld residuals plots, a global goodness-of-fit test, and supremum tests for each independent variable.

We conducted 2 subanalyses. Because cumulative antigen exposure is driven by the measles-mumps-rubella (MMR) and varicella live vaccines (93 total antigens), we conducted an analysis in which we compared children who were up to date on all recommended vaccines to children who received all recommended vaccines but were missing either MMR or varicella or both MMR and varicella vaccines. We also conducted a subanalysis in which we compared fully vaccinated children to children who were completely unvaccinated.

To account for missing covariate data, we conducted multiple imputation using SAS PROC MI Statement (SAS Institute, Inc, Cary, NC). The fully conditional specification discriminant function was used to impute missing categorical data, and fully conditional specification regression was used to impute missing continuous data.[37] The data were imputed 10 times.

A risk factor for diabetes that was not captured in the VSD databases was also assessed: family history of T1DM. If also associated with vaccination status, this unmeasured variable could confound the results. For example, it is possible that parents of families with a history of diabetes may be less likely to fully vaccinate their children than those without a family history of diabetes out of concern that vaccines could increase the risk of diabetes in their children. We assessed its impact on the results by conducting a probabilistic bias analysis (PBA) based on the estimated prevalence of family history of T1DM by vaccine aluminum exposure status and on the strength of association between family history of T1DM and T1DM incidence. PBA is a type of sensitivity analysis used to evaluate the magnitude and direction of bias by using Monte Carlo techniques to simulate bias parameters.[38] We began by creating an additional cohort from 2 of the VSD sites (Kaiser Permanente Colorado and Southern California Kaiser Permanente) that linked children with their parents and siblings to estimate associations between family history of T1DM and aluminum exposure status and T1DM incidence. These estimates were then used to create a prediction model in the additional cohort, which, through simulation, was extrapolated to the larger cohort of children without information on family history of T1DM. Results from this PBA were used to assess the robustness of our conclusions in the presence of unmeasured confounding bias.

Analyses were conducted with SAS, version 9.4 software (SAS Institute, Cary NC).

RESULTS

Study Cohort and Type 1 Diabetes Cases

Between January 1, 2004, and December 31, 2014, there were 663 089 children born in the VSD with continuous health plan enrollment through age 23 months. We excluded 78 918 children (12%) for the following reasons: diagnosis of neonatal diabetes mellitus or cystic fibrosis[39] ($n = 417$), medical contraindication to vaccination ($n = 6161$), receipt of a vaccine that is not in the ACIP schedule ($n = 5074$), <2 well-child visits by age 23 months ($n = 12$ 843), diagnosis of T1DM before age 12 months ($n = 27$), and no manufacturer information for administered vaccines ($n = 54$ 396) (Fig 1). Of those with a medical contraindication, the most common reasons were cancer diagnosis ($n = 1768$; 29.0%), receipt of intravenous immunoglobulin ($n = 1425$; 23.2%), and disorder involving an immune mechanism ($n = 1227$; 19.9%) (Supplemental Table 3).

In the final cohort ($n = 584$ 171), children had a mean (SD) birth weight of 3347 (572) g and were followed for a mean of 7 years (SD 3.7 years) (Table 1).

Approximately 40% of the cohort ($n = 241$ 790) was undervaccinated for at least 1 day; the mean (SD) ADU for the cohort was 38 days (106). The distribution of ADU was skewed to the right because ~60% of the cohort was up to date, with ADU = 0 (Supplemental Fig 3). One-fifth (20.2%) of the cohort was missing 1 dose of a vaccine, and 1.1% of the cohort received no vaccines (ADU = 638 days). The mean cumulative antigen exposure was 263 (SD = 54) (Supplemental Fig 4).

The mean cumulative aluminum exposure was 4.11 mg (SD = 0.73) (Supplemental Fig 5). There were 40 662 children who received more vaccine doses than recommended by the ACIP schedule and were therefore exposed to >6.00 mg of aluminum. Although cumulative aluminum exposure ranged from 0 to 9.35 mg, 90% of the cohort received between 3.32 and 4.68 mg. The distribution of baseline characteristics by percentile of vaccine exposure are presented in Supplemental Table 4.

We identified 1132 incident cases of T1DM, representing an incidence rate of 25.06 cases per 100 000 person-years. Of the children diagnosed with T1DM, 48% were girls, 52.7% non-Hispanic White, 23.7% Hispanic, 8.5% Black, and 6.3% Asian American. The mean age at diagnosis was 6.4 years (SD = 3.5) (Table 1).

Associations Between ADU, Cumulative Antigen Exposure, Cumulative Aluminum Exposure, and Type 1 Diabetes

ADU and cumulative antigen exposure were not associated with T1DM. The aHRs for these 2 associations were 1.01 (95% CI, 0.99–1.02) for every 25-unit increase in ADU and 0.98 (95% CI, 0.97–1.00) for every 10-unit increase in cumulative antigen exposure. On the basis of martingale residual plots and Kolomogorov-type supremum tests, the assumption of linearity in the log hazard did not appear to be violated for these models (Supplemental Figs 6 and 7).

Initially, cumulative aluminum exposure (per 1-mg increase) was inversely associated with T1DM (aHR = 0.89; 95% CI, 0.81–0.97). However, the martingale residual plot and Kolomogorov-type supremum test indicated a deviation from linearity (P = .007). (Supplemental Fig 8). Cumulative aluminum exposure was then transformed into a 6-level categorical variable on the basis of 1-mg increments and assessed with Cox regression (Supplemental Table 5). The plot of the category-specific parameter estimates against midpoint of the categories revealed a threshold at 3.00 mg, leading us to dichotomize cumulative aluminum exposure as 3.00 mg versus >3.00 mg (Supplemental Fig 9). In the adjusted Cox regression model, cumulative aluminum exposure >3.00 mg was inversely associated with T1DM (aHR = 0.77; 95% CI, 0.60–0.99) (Fig 2). None of the interactions between aluminum exposure and race and ethnicity, VSD site, gestational age, and birth weight were statistically significant (P > .05).

The proportional hazards assumption for all 3 models did not appear to be violated on the basis of the Schoenfeld residual plots, global goodness-of-fit tests, or supremum tests (P > .05).

We excluded 14.8% of observations because of missing data on race and ethnicity (5.8%), mother's age (8.4%), gestational age (8.9%), and birth weight (8.6%). A total 141 (12.5%) children with T1DM were missing data for 1 covariate. After imputing missing data, the aHRs for developing T1DM remained similar: 1.01 (95% CI, 0.99–1.02) for ADU, 0.98 (95% CI, 0.97–0.99) for cumulative antigen exposure, and 0.80 (0.63–1.00) for cumulative aluminum exposure.

In the first subanalysis, receiving MMR, varicella, or both MMR and varicella vaccines was not associated with T1DM (aHR = 0.98; 95% CI, 0.59–1.63). In the second subanalysis comparing fully vaccinated to completely unvaccinated children, the aHR was 0.67 (95% CI, 0.37–1.19).

Sensitivity Analysis for Unmeasured Confounding

To assess family history of T1DM, we created a cohort of 167 678 children who were matched to their parents and any older siblings, and 1811 children (1.0%) had at least 1 family member with a T1DM diagnosis (Supplemental Table 6). Families with a history of T1DM were 6.41 times as likely (95% CI, 4.11–10.00) as families without a history of T1DM to have a child in the cohort with a T1DM diagnosis. Children with a family history of T1DM were 1.26 times as likely (95% CI, 0.96–1.65) as children without a family history of T1DM to be exposed to 3.00 mg of cumulative aluminum.

Based on these parameters, the PBA for the association between cumulative aluminum exposure and T1DM yielded an aHR of 0.78 (95% CI, 0.60–1.00), adjusted for family history of T1DM.

DISCUSSION

In this multisite cohort study, we did not find evidence that adherence to the recommended childhood immunization schedule increases the risk of T1DM in children. ADU and

cumulative vaccine antigen exposure were not associated with T1DM incidence, whereas cumulative vaccine aluminum exposure >3.00 mg was associated with a reduced incidence of T1DM. This study provides additional evidence to support the safety of the overall childhood immunization schedule.

Aluminum adjuvants have been shown to induce a type 2 T helper (Th2) cell response in animals.[40] Such a response that skews the immune system toward a Th2 response could theoretically increase the risk of atopic conditions such as asthma.[41,42] However, it is generally thought that type 1 T helper cells, rather than Th2 cells, are associated with the pathogenesis leading to the destruction of islet β-cells and T1DM disease onset.[43,44] This may suggest a possible biological mechanism for how exposure to aluminum during infancy could reduce the risk of T1DM.

Studying the effects of aluminum adjuvants in an observational setting poses challenges. Aluminum is a ubiquitous exposure, representing the third most abundant element on earth, after oxygen and silicon.[40] Common sources of aluminum exposure include food, breast milk, infant formula, and antacids. It is not possible to accurately measure all possible exposures to aluminum by using electronic health record databases, which could create bias if any of the variables are associated with both vaccination status and T1DM. Moreover, a child in our cohort was exposed to, at most, 9.35 mg of aluminum from vaccines, whereas breast milk, as an example, contains ~40 mg of aluminum per L.[7] It is therefore possible that our observed negative association between vaccine aluminum exposure and T1DM can be explained by unmeasured confounding, particularly because the effect size was modest (aHR = 0.77). To verify this potential unintended benefit of vaccination, more comprehensive capture of known sources of aluminum exposure and risk factors for T1DM would be needed.

We assessed the potential for unmeasured confounding by conducting a PBA with family history of T1DM. Family history of T1DM was positively associated with both undervaccination (lower aluminum exposure) and T1DM incidence in children, which implies that incidence of T1DM in children exposed to lower amounts of aluminum was overestimated, biasing the results away from the null hypotheses (overestimating the magnitude of the negative association). Examining this variable in the PBA yielded an aHR that was similar in magnitude than the observed association (0.77 vs 0.78), thus affirming our conclusion that vaccine aluminumexposure was inverselyassociated with T1DM incidence.

This study has limitations. Although the incidence of T1DM peaks between 10 and 14 years, our longitudinal cohort of >580 000 children was followed for a mean of 7 years. Although we used 3 different metrics to assess exposure to the recommended schedule, the study was observational and susceptible to bias. A randomized clinical trial design could be used to rigorously assess the safety of the schedule, but such a study would be resource intensive and potentially unethical.

In previous research, including a case-control study conducted by the VSD, researchers did not identify an association between childhood vaccines and T1DM.[45–47] These studies,

however, were focused on individual vaccines or doses of vaccines from earlier versions of the recommended schedule that did not include either the pneumococcal conjugate, live attenuated rotavirus, hepatitis A, seasonal influenza, or recent combination vaccines (DTaP–hepatitis B–inactivated poliovirus vaccine, DTaP–inactivated poilivirus vaccine and/or *Haemophilus influenzae* type b, and MMR-varicella). In this study, we responded to an Institute of Medicine report and used 3 novel metrics to assess the association between exposure to the entire current childhood immunization schedule and incident T1DM in children.

CONCLUSIONS

In this safety study, we did not identify any concerning associations between various measures of the recommended schedule and T1DM in children. The observed negative association between cumulative vaccine aluminum exposure and T1DM was an unanticipated result and should be examined with future research. To maintain public trust in the US childhood immunization program, in future studies, researchers should also continue to examine the safety of the entire recommended immunization schedule relative to other health conditions that concern the public.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

ABBREVIATIONS

ACIP:	Advisory Committee on Immunization Practices
aHR:	adjusted hazard ratio
ADU:	average days undervaccinated
CI:	confidence interval
DTaP:	diphtheria, tetanus-acellular, pertussis
MMR:	measles-mumps-rubella
PBA:	probabilistic bias analysis
T1DM:	type 1 diabetes mellitus
Th2:	type 2 T helper
VSD:	Vaccine Safety Datalink

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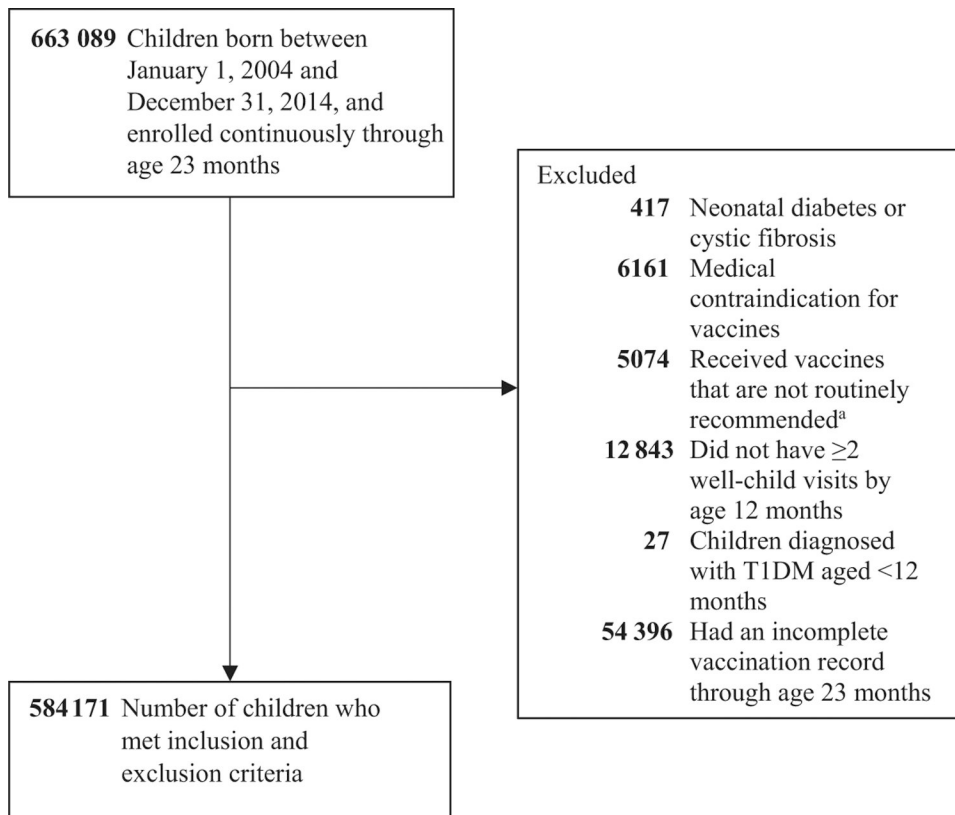
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WHAT'S KNOWN ON THIS SUBJECT:

The association between the current recommended US childhood immunization schedule and incident type 1 diabetes mellitus (T1DM) in children has not been assessed. The effect of cumulative vaccine aluminum exposure on T1DM incidence is also unknown.
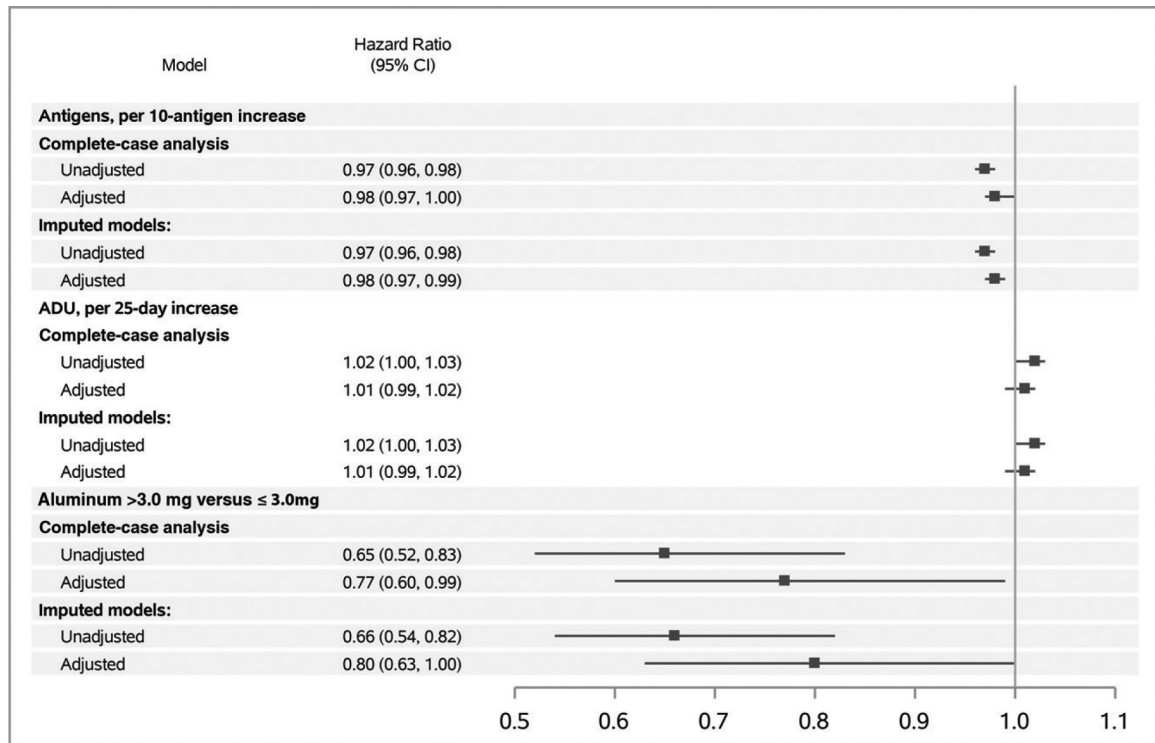
WHAT THIS STUDY ADDS:

We used 3 vaccination metrics (average days undervaccinated and cumulative aluminum and cumulative antigen exposure) to assess associations between the current childhood immunization schedule and T1DM. Results indicate that the recommended schedule does not increase the risk of T1DM.

663 089 Children born between January 1, 2004 and December 31, 2014, and enrolled continuously through age 23 months

Excluded
- 417 Neonatal diabetes or cystic fibrosis
- 6161 Medical contraindication for vaccines
- 5074 Received vaccines that are not routinely recommended[a]
- 12 843 Did not have ≥2 well-child visits by age 12 months
- 27 Children diagnosed with T1DM aged <12 months
- 54 396 Had an incomplete vaccination record through age 23 months

584 171 Number of children who met inclusion and exclusion criteria

FIGURE 1.

Cohort exclusions. [a] Children were excluded if they received nonstandard vaccines that are not in the ACIP schedule, such as experimental vaccines, Japanese encephalitis, rabies, or typhoid.

Model	Hazard Ratio (95% CI)
Antigens, per 10-antigen increase	
Complete-case analysis	
Unadjusted	0.97 (0.96, 0.98)
Adjusted	0.98 (0.97, 1.00)
Imputed models:	
Unadjusted	0.97 (0.96, 0.98)
Adjusted	0.98 (0.97, 0.99)
ADU, per 25-day increase	
Complete-case analysis	
Unadjusted	1.02 (1.00, 1.03)
Adjusted	1.01 (0.99, 1.02)
Imputed models:	
Unadjusted	1.02 (1.00, 1.03)
Adjusted	1.01 (0.99, 1.02)
Aluminum >3.0 mg versus ≤ 3.0mg	
Complete-case analysis	
Unadjusted	0.65 (0.52, 0.83)
Adjusted	0.77 (0.60, 0.99)
Imputed models:	
Unadjusted	0.66 (0.54, 0.82)
Adjusted	0.80 (0.63, 1.00)

FIGURE 2.

The risk of developing T1DM. Complete-case analysis consisted of 497 636 children, of whom 991 developed T1DM. The imputed models used all 584 171 patients and 1132 children who developed T1DM. We adjusted for sex, race and ethnicity, year and season of birth, the mother's age at birth, birth weight, gestational age, VSD site, and number of well-child visits between 30 days and 2 years of life.

TABLE 1

Patient Characteristics

Characteristic	Children (N = 584 171), n (%)	Children With T1DM (n = 1132), n (%)
Sex		
Female	284 799 (48.8)	544 (48.1)
Male	299 360 (51.2)	587 (51.9)
Unknown	12 (0.002)	1 (0.1)
Race and ethnicity		
Asian American	90 426 (15.5)	71 (6.3)
Black	38 039 (6.5)	96 (8.5)
Hispanic	157 727 (27.0)	268 (23.7)
Non-Hispanic White	253 126 (43.3)	647 (57.2)
Other	11 024 (1.9)	16 (1.4)
Unknown	33 829 (5.8)	34 (3.0)
Birth year of child		
2004–2005	92 561 (15.8)	315 (27.8)
2006–2007	106 215 (18.2)	269 (23.8)
2008–2009	113 082 (19.4)	240 (21.2)
2010–2011	108 002 (18.5)	156 (13.8)
2012–2013	109 110 (18.7)	117 (10.3)
2014	55 201 (9.4)	35 (3.1)
Season of child's birth		
Spring	146 068 (25.0)	323 (28.5)
Summer	152 737 (26.1)	295 (26.1)
Fall	147 476 (25.2)	253 (22.3)
Winter	137 890 (23.6)	261 (23.1)
Mother's age category		
14–30	189 726 (32.5)	394 (34.8)
30–34	144 999 (24.8)	377 (33.3)
35–55	197 767 (33.9)	267 (23.6)
Unknown	51 679 (8.8)	94 (8.3)
Weight at birth, mean (SD), g	3347 (572)	3414 (579)
Gestational age, mean (SD), wk	39 (2)	38.7 (1.9)
No. well-child visits between 30 d and 2 y, mean (SD)	6 (1)	5.6 (1.4)
Follow-up, y, mean (SD)	7.3 (3.7)	5.5 (3.3)
ADU, mean (SD)	38 (106)	44 (115)
Undervaccinated	241 790 (41.4)	491 (43.4)
No ACIP vaccines through age 23 mo	6308 (1.1)	15 (1.3)
Children who delayed starting vaccines	4267 (0.7)	9 (0.8)
Missing 1 vaccine series	59 733 (10.2)	136 (12.0)
Missing 1 vaccine dose	118 127 (20.2)	257 (22.7)