Association Between Aluminum Exposure From Vaccines Before Age 24 Months and Persistent Asthma at Age 24 to 59 Months

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ABSTRACT

OBJECTIVE: To assess the association between cumulative aluminum exposure from vaccines before age 24 months and persistent asthma at age 24 to 59 months.

METHODS: A retrospective cohort study was conducted in the Vaccine Safety Datalink (VSD). Vaccination histories were used to calculate cumulative vaccine-associated aluminum in milligrams (mg). The persistent asthma definition required one inpatient or 2 outpatient asthma encounters, and ≥2 long-term asthma control medication dispenses. Cox proportional hazard models were used to evaluate the association between aluminum exposure and asthma incidence, stratified by eczema presence/absence. Adjusted hazard ratios (aHR) and 95% confidence intervals (CI) per 1 mg increase in aluminum exposure were calculated, adjusted for birth month/year, sex, race/ethnicity, VSD site, prematurity, medical complexity, food allergy, severe bronchiolitis, and health care utilization.

RESULTS: The cohort comprised 326,991 children, among whom 14,337 (4.4%) had eczema. For children with and without eczema, the mean (standard deviation [SD]) vaccine-associated aluminum exposure was 4.07 mg (SD 0.60) and 3.98 mg (SD 0.72), respectively. Among children with and without eczema, 6.0% and 2.1%, respectively, developed persistent asthma. Among children with eczema, vaccine-associated aluminum was positively associated with persistent asthma (aHR 1.26 per 1 mg increase in aluminum, 95% CI 1.07, 1.49); a positive association was also detected among children without eczema (aHR 1.19, 95% CI 1.14, 1.25).

CONCLUSION: In a large observational study, a positive association was found between vaccine-related aluminum exposure and persistent asthma. While recognizing the small effect sizes identified and the potential for residual confounding, additional investigation of this hypothesis appears warranted.

KEYWORDS: aluminum; asthma; immunization; vaccine safety; vaccine schedule

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WHAT'S NEW

In a large observational study, a positive association was found between vaccine-related aluminum exposure and persistent asthma. While recognizing the small effect sizes identified and the potential for unmeasured confounding, additional investigation of this hypothesis appears warranted.

WHILE THE SAFETY[1] and effectiveness[2] of the childhood immunization schedule are supported by extensive scientific evidence, and vaccination coverage among US children remains high relative to historical benchmarks, maintaining high coverage requires preserving public confidence in vaccine safety.[3] In the United States and globally, parents have expressed concern about the safety of the immunization schedule,[4] including regarding the safety of repeated exposure to nonantigen vaccine components such as aluminum. A small but increasing number of parents have refused, delayed, or spread out vaccination[5]; this practice increases risk of vaccine-preventable diseases[6] and vaccine-associated febrile seizures[7] without yielding any scientifically proven safety advantage.

Aluminum is integral to many vaccines, enhancing immunogenicity and effectiveness.[8] Aluminum adjuvants have a well-established safety profile,[9] and are used in many vaccines given in early childhood.[10] However, data from animal studies suggest the theoretical possibility that aluminum adjuvants could influence allergy risk through inducing a T helper 2 cell (Th2)-biased immune response.[11,12] In allergic asthma, common in children,[13] Th2 lymphocytes mediate airway inflammation and hyper-responsiveness.[14] Childhood asthma is a clinical diagnosis, made based upon recurrent episodes of symptomatic airflow obstruction, responsiveness to therapies (eg, inhaled corticosteroids and short-acting beta$_2$-agonists), and exclusion of other causes.[15]

The Institute of Medicine, in response to public concern about the safety of the childhood immunization schedule, endorsed studying the risk of chronic conditions such as asthma following vaccination, while acknowledging methodologic challenges with doing so.[16] The Vaccine Safety Datalink (VSD) is a long-standing research network established to conduct postlicensure observational studies of vaccine safety.[17] Preparatory to the current study, we evaluated the completeness of VSD immunization data,[18] the availability of vaccine-associated aluminum data,[10] and the feasibility of studying the safety of the schedule.[19] Our study objective was to examine the association between cumulative vaccine-associated aluminum exposure before age 24 months and persistent asthma incidence at age 24 through 59 months.

METHODS

STUDY SETTING

This retrospective cohort study was conducted in seven medical care organizations (referred to as "sites") participating in the VSD.[17] VSD sites are located in Minnesota, Wisconsin, Washington, Oregon, California, and Colorado, and the VSD population of ~12 million is similar to the US population with respect to demographic and socioeconomic characteristics.[20] The VSD utilizes standardized electronic health record (EHR)-derived data on insurance enrollment, demographic characteristics, medical encounters from all settings, vaccination, and prescribed medications.[17]

STUDY POPULATION

The study cohort consisted of all children born from January 1, 2008 through December 31, 2014 receiving care at a VSD site; observation time continued through December 31, 2017. For study inclusion, children were required to have continuous health insurance enrollment at a VSD site from age 42 days through age 23 months. Children were excluded if they had a medical contraindication to one or more vaccines (eg, immunodeficiency, immunosuppression, or receipt of intravenous immunoglobulin) as identified by encounter diagnosis codes. Children were excluded if they were not using a VSD site for preventive care, defined as having less than 2 well-child visits between birth through age 11 months or zero well-child visits between age 12 through 23 months. Also excluded were children who received vaccines not routinely recommended before age 24 months, and children with missing vaccine manufacturer data (for vaccines for which aluminum content varied by manufacturer). Finally, children were excluded if they received a diagnosis of asthma in any setting prior to age 24 months.

VACCINE-ASSOCIATED ALUMINUM EXPOSURE

Detailed vaccination histories were extracted from EHR data.[17] Five VSD sites had bidirectional interoperability with state immunization information systems[21]; using this process a small number of additional vaccines (<3%) were identified and included. Based on published methods, we used vaccine package inserts, material from the Institute for Vaccine Safety, and the Immunofacts textbook to identify the aluminum content in each licensed vaccine.[10] As shown in Supplementary Table 1, aluminum content differed by vaccine type and manufacturer. For each child, vaccination histories were linked with aluminum content information to calculate the cumulative amount of aluminum adjuvant received from vaccines from birth through age 23 months.

PRIMARY OUTCOME DEFINITION

The primary study outcome was persistent asthma diagnosed at age 24 through 59 months, defined as 1) 1 inpatient or 2 outpatient/emergency encounters with diagnosis codes for asthma; and 2) at least 2 long-term asthma control medication dispensing events.[15] The rationale for selecting persistent asthma as the primary outcome included: it represents a more severe form of asthma[15]; it is more likely than intermittent asthma to come to clinical attention; this case definition may have higher specificity than definitions which include milder asthma[22]; and persistent asthma prevalence is high enough (3.8% among children <5 years of age)[23] to study with adequate statistical power. Because it is difficult to clinically distinguish asthma from transient viral-induced wheezing in infants,[15] and to avoid overlapping exposure and risk windows, we excluded children with any asthma diagnosis in inpatient, emergency department, or outpatient settings before age 24 months.

COVARIATE DEFINITIONS

Several asthma risk factors were included as potential confounding variables. Prematurity was defined as moderately preterm (32 through 36 completed weeks gestation) or very preterm (<32 completed weeks).[24] The definition of food allergies required ≥2 food allergy diagnosis codes

(Supplementary Table 2) on separate days and at least one prescription for an epinephrine autoinjector. Severe bronchiolitis, possibly associated with subsequent asthma, was defined as inpatient admission for a nonbacterial acute lower respiratory infection (Supplementary Table 2) before age 12 months. Breast-feeding, found to reduce asthma risk in some but not all studies,[25] was also examined as a covariate; however, breast-feeding data were limited to 4 VSD sites which, beginning in late 2013, required EHR documentation of infant feeding. Based on prior work,[25] breast-feeding at 6 months was defined as exclusive, some, or none.

Statistical Analyses

All analyses were stratified by eczema status, based on the following considerations: 1) eczema, an early manifestation of atopy, is strongly associated with asthma risk; and 2) any effect of vaccine-associated aluminum on asthma risk might be modified by underlying allergy predisposition. Eczema was defined as ≥2 eczema diagnosis codes (Supplementary Table 2) on separate days between birth through age 11 months, and at least one prescription for a topical steroid or topical calcineurin inhibitor.

Cox proportional hazard regression models were used to test the association between cumulative vaccine-associated aluminum received birth through age 23 months and persistent asthma diagnosed at age 24 through 59 months. Aluminum was represented on a continuous scale in milligrams (mg). Days at risk was defined as the time from second birthday to the date of the following censoring events: meeting the case definition, disenrolling from a VSD site, reaching age 60 months, or study end on December 31, 2017. Models were adjusted for sex, birth month/year, race/ethnicity, VSD site (treated as a fixed effect), medical complexity (defined using the Pediatric Medical Complexity Algorithm[26]), prematurity, food allergy, severe bronchiolitis, and 2 measures of health care utilization (number of emergency department visits, and number of outpatient visits after excluding well-child and emergency department visits). In fully adjusted models, we tested for the interaction between aluminum and VSD site.

Kaplan-Meier survival curves were plotted by 1 mg increments of aluminum exposure to assess asthma incidence by age after 24 months. We assessed the functional form of vaccine-associated aluminum as a continuous variable by examining martingale residuals with a Kolmogorov-type supremum test.[27] In this context, a departure from linearity is indicated by a value of $P < .05$. The proportional hazards assumption was evaluated with martingale residual plots, Schoenfeld residual plots, global goodness-of-fit tests, and supremum tests from the Cox models. Additionally, we plotted graphically and calculated numerically the adjusted log hazard ratio for cumulative vaccine-associated aluminum in 1 mg categories, with estimates and 95% confidence intervals (CI) plotted. To assess the effect of individual covariates on the exposure-outcome association, we conducted a stepwise regression, using all covariates in the main model, recalculating the adjusted hazard ratio with the sequential addition of each covariate.

We conducted several secondary analyses. We conducted an analysis eliminating children with cumulative aluminum values at the extremes (<1 mg or ≥5 mg aluminum) while treating aluminum as continuous between 1 and 5 mg. We conducted an analysis treating cumulative aluminum as dichotomous, comparing exposure ≤3.00 mg to >3.00 mg, as has been done previously.[28] Because health care utilization may differ between fully vaccinated and under-vaccinated children (who may be under-vaccinated due to vaccination barriers or parental choice), we conducted an analysis restricted to fully vaccinated children. In a separate analysis, breast-feeding data were included as a covariate among children for whom breast-feeding data were available. Because of the acknowledged challenge in diagnosing asthma in young children,[15] we conducted a secondary analysis with the outcome of interest defined as persistent asthma at age 36 through 59 months. All covariates used in main analyses were included in secondary analyses.

Another secondary analysis explored an alternative exposure definition, maximum single-day vaccine-associated aluminum.[10] For each child in the cohort, the total aluminum from all vaccines received on a given day was summed. This amount in mg was divided by the child's weight in kilograms (kg) on the same day. For the small number of children who did not have a same-day weight, the child's weight was imputed if at least 2 weights were available from within 90 days of the vaccination date, using exponentially weighted moving average techniques. Cox models stratified by eczema status and adjusted for covariates were used to test the association with persistent asthma.

Finally, we examined all-cause injuries as a negative control outcome.[29,30] While the relevant encounter diagnosis codes for injuries (Supplementary Table 2) were closely modeled on prior studies,[31] codes for poisonings (such as from medications, vaccines, drugs, and alcohol) were excluded from the outcome definition. A case was defined as the first occurrence of an all-cause injury at 24 through 59 months of age in emergency department or inpatient settings.[31] One VSD site, representing 4.6% of the overall cohort, did not contribute to the negative control outcome, due to unavailability of some emergency department data; otherwise the cohort was identical to the primary outcome analyses. Retaining the covariates from the primary analyses, Cox models were used to examine the relationship between vaccine-associated aluminum and all-cause injuries.

Power analyses were conducted assuming an alpha of .05, r-squared value of 0.2, and standard deviation (SD) of aluminum exposure of 0.80 mg. The r-squared value represents the association between aluminum exposure and other measured covariates. Assuming a sample size of 14,000 children with eczema and an asthma prevalence of 5% among these children,[13] the minimum detectable adjusted hazard ratio would be 1.13. Assuming a sample size of 186,000 children without eczema and an asthma prevalence of 1% among these children,[13] the minimum detectable adjusted hazard ratio would be 1.08.

RESEARCH ETHICS

The human subjects review board at each participating site approved the study, and informed consent was not required.

RESULTS

As illustrated in eFigure 1, from an initial population of 398,191 children, 15,036 (3.8%) did not meet inclusion criteria, 30,976 (7.8%) had vaccine-related exclusions, and 25,188 (6.3%) were excluded due to asthma diagnosed prior to age 24 months. The final study cohort comprised 326,991 children, among whom 14,337 (4.4%) were diagnosed with eczema before age 12 months.

The demographic and clinical characteristics of the study cohort are presented in Table 1. As shown, a greater proportion of the cohort with eczema was male and non-Hispanic Black or Asian race/ethnicity compared to the cohort without eczema. The median age at a censoring event (ie, the length of follow-up since birth) was 60.0 months (interquartile range [IQR] 43.0, 60.0) for the eczema cohort and 60.0 months (IQR 43.0, 60.0) for the no eczema cohort.

The distribution of cumulative vaccine-associated aluminum received by the study cohort through age 23 months, stratified by eczema status, is presented in Figure 1. The variability in cumulative aluminum was due to either under-vaccination (ie, missing vaccine doses) or the type of vaccine product received (Supplementary Table 1). For children with eczema, the mean and median cumulative vaccine-associated aluminum were 4.07 mg (SD 0.60), and 4.18 mg (IQR 3.97, 4.43), respectively. For children without eczema, the mean and median were 3.98 mg (SD 0.72) and 4.18 mg (IQR 3.93, 4.43), respectively.

Among 14,337 children in the cohort with eczema, 859 (6.0%) met the study definition of persistent asthma; the mean age when children met the case definition was 44.2 months (SD 8.7). Among 312,654 children without eczema, 6687 (2.1%) met the study definition of persistent asthma; the mean age when these children met the case definition was 44.9 months (SD 8.7).

Table 1. Demographic and Clinical Characteristics of the Study Cohort, Stratified by Eczema Status, Vaccine Safety Datalink

Characteristic	Diagnosed With Eczema*	Not Diagnosed With Eczema	*P* Value
Total in cohort, n	14,337	312,654	
Child's sex, n (%)			<.001
Female	5726 (39.9)	157,233 (50.3)	
Male	8611 (60.1)	155,421 (49.7)	
Birth year, n (%)			.069
2008	1989 (13.9)	43,656 (14.0)	
2009	2036 (14.2)	44,476 (14.2)	
2010	2075 (14.5)	44,742 (14.3)	
2011	2174 (15.2)	44,714 (14.3)	
2012	2077 (14.5)	45,205 (14.5)	
2013	1999 (13.9)	44,888 (14.4)	
2014	1987 (13.9)	44,973 (14.4)	
Child's race and ethnicity, n (%)			<.001
Non-Hispanic White	3326 (23.2)	135,081 (43.2)	
Non-Hispanic Black	1492 (10.4)	15,855 (5.1)	
Non-Hispanic Asian	5017 (35.0)	43,100 (13.8)	
Hispanic	2884 (20.1)	85,010 (27.2)	
Other race and ethnicity	879 (6.1)	13,577 (4.3)	
Missing race and ethnicity	739 (5.2)	20,031 (6.4)	
Prematurity, n (%)			<.001
Term (37 weeks EGA or later)	13,518 (94.3)	289,935 (92.7)	
Moderately preterm (32–36 weeks EGA)	773 (5.4)	20,692 (6.6)	
Very preterm (<32 weeks EGA)	46 (0.3)	2027 (0.6)	
Medical complexity based on PMCA, n (%)			<.001
No complex or chronic conditions	12,000 (83.7)	272,106 (87.0)	
Non-complex chronic condition	1711 (11.9)	29,367 (9.4)	
Complex chronic condition	626 (4.4)	11,181 (3.6)	
Diagnosed with food allergy, n (%)	816 (5.7)	1457 (0.5)	<.001
Early-life severe bronchiolitis, n (%)	104 (0.7)	2267 (0.7)	.997
Health care utilization through age 23 mos.			
No. of outpatient visits (non-well, non-ED), mean (SD)	12.6 (9.1)	9.8 (7.8)	<.001
No. of outpatient visits (non-well, non-ED), median (IQR)	11.0 (7.0, 16.0)	8.0 (5.0, 12.0)	<.001
No. of ED visits, mean (SD)	0.8 (1.3)	0.6 (1.0)	<.001
No. of ED visits, median (IQR)	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)	<.001

ED indicates emergency department; EGA, estimated gestational age; IQR, interquartile range; PMCA, Pediatric Medical Complexity Algorithm (asthma diagnoses removed); SD, standard deviation; no., number; and mos., months.

*Eczema diagnosed prior to 12 months of age.

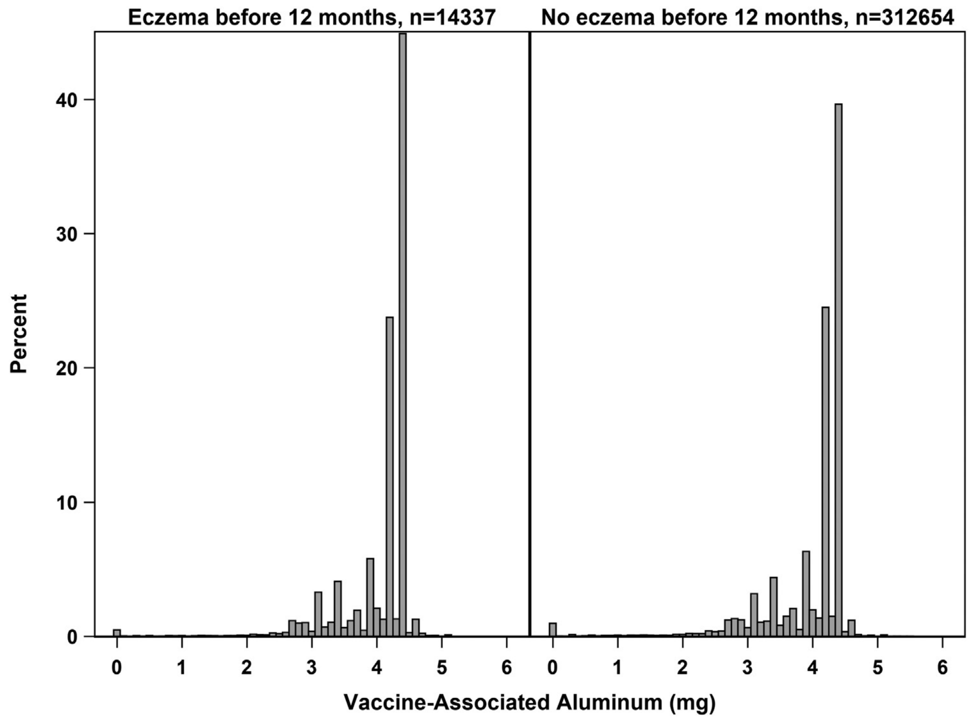

Figure 1. *Distribution of cumulative vaccine-associated aluminum received birth through 23 months of age, stratified by eczema status, Vaccine Safety Datalink.*

The crude incidence rate of persistent asthma at 24 through 59 months of age by quantity of cumulative vaccine-associated aluminum is shown in Figure 2: as illustrated, the incidence rate appeared to increase with increasing levels of aluminum exposure in the eczema and no eczema cohorts. Results of Cox proportional hazards models are presented in Table 2. Among children with eczema after adjustment for covariates, cumulative vaccine-associated aluminum was positively associated with persistent asthma (adjusted hazard ratio [aHR] 1.26 per 1 mg increase in aluminum, 95% CI 1.07, 1.49). Other covariates which remained significant in the adjusted model included male sex, non-Hispanic Black race/ethnicity, food allergies, and both measures of health care

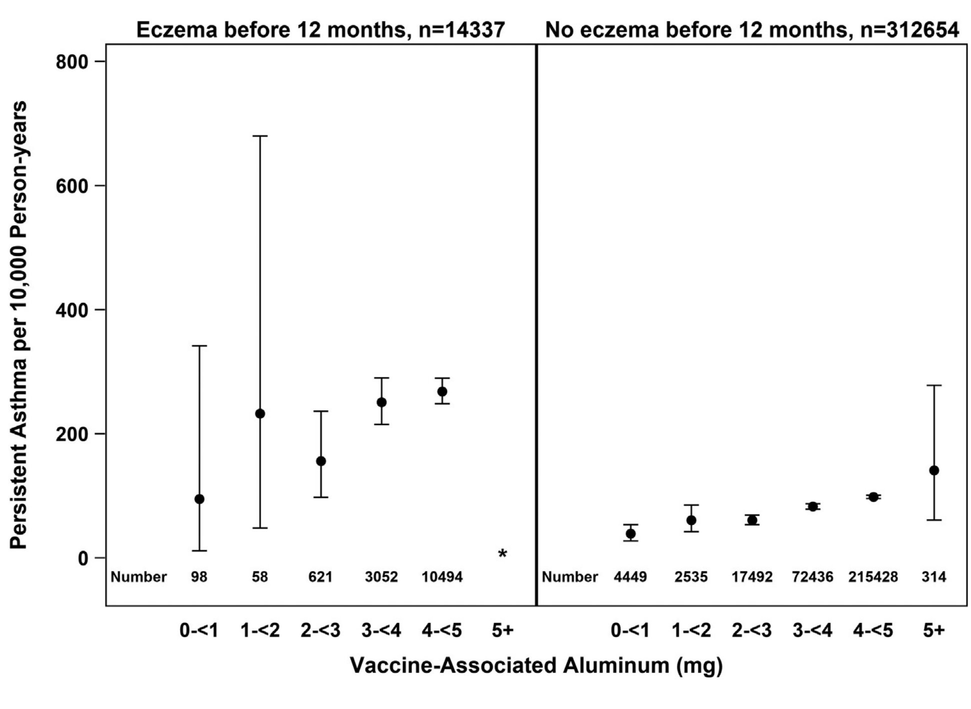

Figure 2. *Crude incidence rate of persistent asthma at 24 through 59 months of age by quantity of vaccine-associated aluminum in milligrams (mg), stratified by eczema status, Vaccine Safety Datalink.*

Table 2. The Association Between Cumulative Vaccine-Associated Aluminum Exposure Between Birth and Age 23 Months and Persistent Asthma Diagnosed Between 24 and 59 Months of Age, With Separate Models for the Eczema and No Eczema Cohorts, Vaccine Safety Datalink

	Adjusted Hazard Ratio* (95% CI) for Persistent Asthma	
Variable	Eczema† (n = 14,337)	No eczema (n = 312,654)
Vaccine-associated aluminum (per mg)	1.26 (1.07, 1.49)	1.19 (1.14, 1.25)
Child's sex		
Female	1 [Reference]	1 [Reference]
Male	1.30 (1.13, 1.50)	1.40 (1.33, 1.47)
Child's race and ethnicity		
Non-Hispanic White	1 [Reference]	1 [Reference]
Non-Hispanic Black	1.37 (1.07, 1.76)	1.81 (1.65, 1.99)
Non-Hispanic Asian	0.93 (0.77, 1.13)	1.09 (1.01, 1.18)
Hispanic	1.00 (0.81, 1.24)	1.18 (1.11, 1.26)
Other race and ethnicity	1.33 (1.00, 1.78)	1.15 (1.02, 1.29)
Missing race and ethnicity	0.82 (0.55, 1.21)	1.04 (0.92, 1.17)
Prematurity		
Term (37 weeks EGA or later)	1 [Reference]	1 [Reference]
Moderately pre-term (32–36 weeks EGA)	1.32 (1.02, 1.72)	1.34 (1.24, 1.46)
Very pre-term (<32 weeks EGA)	1.88 (0.82, 4.30)	1.68 (1.39, 2.03)
Medical complexity based upon PMCA		
No complex or chronic conditions	1 [Reference]	1 [Reference]
Non-complex chronic condition	0.96 (0.78, 1.18)	1.05 (0.97, 1.13)
Complex chronic condition	0.62 (0.44, 0.88)	0.67 (0.59, 0.77)
Diagnosed with food allergy	2.40 (1.97, 2.93)	4.32 (3.66, 5.10)
Early-life severe bronchiolitis	1.70 (0.95, 3.04)	1.40 (1.16, 1.71)
Health care utilization through age 23 mos.		
No. of outpatient visits (non-well, non-ED)	1.02 (1.02, 1.03)	1.03 (1.03, 1.03)
No. of ED visits	1.17 (1.12, 1.21)	1.16 (1.14, 1.18)

CI indicates confidence interval; ED, emergency department; EGA, estimated gestational age at the time of delivery; mg, milligram; SD, standard deviation; PMCA, Pediatric Medical Complexity Algorithm (asthma diagnoses removed); no., number; and mos., months.
*Adjusted for birth month and year, VSD site, and all covariates listed in table.
†Eczema diagnosed prior to 12 months of age.

utilization. In a separate model among children without eczema (Table 2), cumulative vaccine-associated aluminum was also positively associated with persistent asthma (aHR 1.19 per 1 mg increase in aluminum, 95% CI 1.14, 1.25). In the fully adjusted models, there was no significant interaction between cumulative aluminum and VSD site in the eczema (P = .14) and no eczema (P = .17) cohorts.

The crude (ie, unadjusted) relationship between level of aluminum exposure and asthma risk was relatively consistent over time since age 24 months, as illustrated in Kaplan-Meier survival curves (Supplementary Figs. 2 and 3). The functional form of vaccine-associated aluminum as a continuous variable did not appear to violate assumptions of linearity in the log hazard based on plotting martingale residuals (Supplementary Figs. 4 and 5) with a nonsignificant Kolomogorov-type supremum test (P = .506 for eczema cohort; P = .112 for no eczema cohort). The adjusted log hazard and corresponding 95% CIs were examined graphically (Supplementary Figs. 6 and 7) to assess for linearity. The functional form of aluminum was also examined by calculating the unadjusted and adjusted hazard ratios for each 1 mg increment of cumulative vaccine-associated aluminum in the eczema and no eczema cohorts (Supplementary Table 3); as shown, the aluminum-asthma relationship appeared close to linear, although with more variability for the eczema cohort than for the no eczema cohort. The assumption of proportionality of the hazard did not appear to be violated, based on martingale residuals (described above), the Kolmogorov supremum tests (described above), Schoenfeld residuals (Supplementary Figs. 8 and 9), and global goodness-of-fit tests from Schoenfeld plots (P = .923 for the eczema cohort; P = .472 for no eczema cohort). Finally, the effect of covariates on the aluminum-asthma relationship was examined in a stepwise manner; as shown in Supplementary Tables 4 and 5, the hazard ratio values remained consistent with the addition of each covariate.

Results of secondary analyses are presented in Table 3. There was a significant positive association between vaccine-associated aluminum and persistent asthma when aluminum was treated as a dichotomous (>3.00 mg vs ≤3.00 mg) exposure. A separate analysis was conducted among the fully vaccinated, with 9477 (66.1%) of the eczema and 188,593 (60.3%) of the no eczema cohorts fully vaccinated; in adjusted models restricted to fully vaccinated (Table 3), the association between vaccine-associated aluminum and persistent asthma was not significant for the eczema cohort but remained significant for the no eczema cohort. Breast-feeding data were available for 1913 (13.3%) of the eczema cohort and 42,909 (13.7%) of the no eczema cohort; in these smaller cohorts, vaccine-associated aluminum was not significantly associated with persistent asthma in unadjusted (P = .51 for eczema cohort, P = .06 for no eczema cohort) and adjusted (Table 3) models, although the hazard ratios

Table 3. Results for Primary Analyses, Secondary Analyses, and Negative Control Outcome, With Separate Models for the Eczema and No Eczema Cohorts, Vaccine Safety Datalink

	Eczema		No Eczema	
Model	Sample Size, n	Adjusted Hazard Ratio (95% CI) for Persistent Asthma	Sample Size, n	Adjusted Hazard Ratio (95% CI) for Persistent Asthma
Primary analyses (also shown in Table 2)	14,337	1.26 (1.07, 1.49)	312,654	1.19 (1.14, 1.25)
Secondary analyses				
Aluminum exposure as dichotomous (>3.00 mg vs ≤3.00 mg)*	14,337	1.61 (1.04, 2.48)	312,654	1.36 (1.21, 1.53)
Excluding those with aluminum exposure at the extremes (<1 mg or ≥5 mg)*,†	14,225	1.27 (1.05, 1.53)	307,891	1.18 (1.11, 1.26)
Limited to those fully vaccinated with no delays*,†	9477	1.08 (0.82, 1.43)	188,593	1.12 (1.01, 1.24)
Limited to those with breast-feeding data available†,‡	1913	1.38 (0.53, 3.60)	42,909	1.26 (0.99, 1.61)
Outcome defined as persistent asthma at 36–59 mos.*,†	12,967	1.22 (1.01, 1.47)	280,205	1.15 (1.09, 1.22)
Negative control outcome				
Outcome defined as all-cause injury at 24–59 mos.†,§	13,804	1.03 (0.94, 1.14)	298,276	1.01 (0.99, 1.03)

ED indicates emergency department; CI, confidence interval; mos., months; and VSD, Vaccine Safety Datalink.

*Adjusted for birth month and year, VSD site, sex, race/ethnicity, prematurity, medical complexity, food allergy, early-life severe bronchiolitis, utilization (outpatient, ED).

†Vaccine-associated aluminum treated as continuous linear exposure variable.

‡Adjusted for breast-feeding at 6 months (exclusive, some, or none), birth month and year, VSD site, sex, race/ethnicity, prematurity, medical complexity, food allergy, early-life severe bronchiolitis, utilization (outpatient, ED).

§Adjusted for birth month and year, VSD site, sex, race/ethnicity, prematurity, medical complexity, food allergy, early-life severe bronchiolitis, utilization (outpatient, ED, inpatient).

were similar in size and directionality to the primary analyses. A positive association was also observed when the outcome of interest was defined as persistent asthma at age 36 through 59 months. The negative control outcome is also presented in Table 3; no association was found between vaccine-associated aluminum and all-cause injuries among children with or without eczema.

The maximum single-day vaccine-associated aluminum was calculated in mg aluminum per same-day kg body weight. For 94.6% of the cohort, the maximum single-day aluminum occurred at a 2-month vaccination visit (ie, between 42 and 92 days of life). For the eczema cohort, the mean and median maximum single-day aluminum were 0.175 mg/kg (SD 0.035) and 0.176 mg/kg (IQR 0.157, 0.194), respectively; mean and median for the no eczema cohort were 0.175 mg/kg (SD 0.042) and 0.177 mg/kg (IQR 0.156, 0.196), respectively. After adjustment for covariates, no association between maximum single-day aluminum and persistent asthma was detected for the eczema cohort (aHR 1.00, 95% CI 0.89, 1.22). A positive association was detected for the no eczema cohort (aHR 1.06, 95% CI 1.03, 1.10); the adjusted hazard ratio was scaled for a 0.05 mg/kg increase in maximum single-day aluminum.

Discussion

This investigation was undertaken to address parents' vaccine safety concerns,[4] and in response to an Institute of Medicine call for studies of the safety of the immunization schedule,[16] including an explicit recommendation to research the safety of repeated exposure to immunogenic adjuvants.[16] In a retrospective cohort study of more than 325,000 children born between 2008 and 2014 and followed through 2017, we found a positive association between cumulative vaccine-associated aluminum before age 24 months and persistent asthma at age 24 through 59 months among children with and without eczema. When vaccine-associated aluminum was examined as an acute exposure (eg, maximum single-day), a small positive association was found for children without eczema. In secondary analyses with more restrictive inclusion criteria and correspondingly smaller sample size, positive associations were observed in some but not all analyses. Data on dietary aluminum intake were unavailable.

While many studies have demonstrated the effectiveness and safety of aluminum adjuvants,[9,32] they are biologically complex: desired and undesired effects may depend on aluminum type, dose, route of exposure, concomitant antigen, host characteristics, and other factors.[32] It is theoretically possible that exposure to aluminum through vaccination could produce an immune profile biased toward Th2 and away from T helper 1 cell (Th1) immune responses.[11,12] This hypothesis is a speculative one, because it is based on limited data from animal studies[11,12] and has not to our knowledge been investigated in humans. A Th2-biased immune response could, again in theory, increase risk of allergic diseases such as asthma, while decreasing risk of autoimmune diseases, such as type 1 diabetes mellitus (T1DM), which are thought to be Th1-mediated.[33] In a recent study, also conducted in the VSD using similar methods, we found a small but statistically significant reduction in T1DM incidence among children exposed to higher levels of vaccine-associated aluminum.[28] It is notable that the direction of effect (ie, reduced incidence of T1DM)[28] was in the direction hypothesized based on the current understanding of T helper cell response to aluminum adjuvants.[11,12]

Aluminum adjuvants are used in vaccines precisely because they can generate an acute immunologic response with long-lasting effect. Additionally, experimental animal models of asthma can be produced using aluminum adjuvants, with acute and chronic phenotypes developed.[34] For example, mice develop asthma-like allergic airway inflammation when given a protein (chicken ovalbumin) and aluminum adjuvant via peritoneal injection, followed by subsequent airway exposure to ovalbumin.[34] Given the many differences between experimentally produced asthma in animals and naturally occurring asthma in humans, there are limits to how much can be extrapolated. However, it appears biologically plausible that the intended effect of aluminum adjuvants (ie, enhanced immunogenicity against vaccine-preventable diseases) is not the only biologic effect of parenteral administration of aluminum adjuvants in early childhood.

Although surveillance methods have changed over time, asthma prevalence in US children appeared to steadily increase during the 1980s and 1990s; since 2001, prevalence has shown little to no increase.[23,35,36] There are many environmental and genetic risk factors for asthma,[15] and any contribution from vaccine-associated aluminum has not been proven or supported through replication. However, because most aluminum-containing vaccines were added to the routine schedule prior to 2001 (eg, diphtheria, tetanus, and acellular pertussis; hepatitis B; some formulations of *Haemophilus influenzae* type b [Hib]; and pneumococcal conjugate vaccines), observed national trends in asthma prevalence during childhood are not incongruous with the effect estimates observed here.

Using observational data to study the long-term health effects of aluminum adjuvants poses many challenges.[16,19] One particularly salient challenge is the fact that other sources of aluminum exposure, such as through diet, are not captured and cannot be estimated using EHR data. Because aluminum is present in infant formula, breast milk, and food, all infants are exposed to some amount of dietary aluminum.[37] However, a recent report concluded that "little to none of ingested aluminum appears to be absorbed" through the gastrointestinal tract,[37] and we are unaware of any studies demonstrating an immunologic response to ingested aluminum in humans. Clearly, more research is needed on the human health effects of aluminum,[37,38] including immunologic effects of injected and ingested aluminum, supplemented when feasible with biomarkers of aluminum exposure.[39] If future research continues to demonstrate that aluminum ingested through a normal infant diet is minimally absorbed and has negligible immunologic effect, the absence of dietary aluminum data in the present study would not appear to invalidate the current findings.

While not directly examining vaccine-associated aluminum exposure, several other studies provide additional context. In a VSD study of children born during 1991 through 1997, a positive association was found between receipt of Hib and hepatitis B vaccines and asthma risk, although the relative risks were small (1.18 for Hib, 1.20 for hepatitis B), and were partially accounted for by underlying health care utilization.[40] In German children at increased risk of atopy born in 1990, asthma risk was lower among children receiving more vaccine doses.[41] Other studies found that early childhood vaccination was not associated with increased asthma risk, but these studies were limited by self-report of vaccination and/or asthma status, exposure to vaccines not currently used, and small sample size.[42,43]

While negative control outcomes are useful to detect threats to the validity of observational studies,[29,30] the interpretation of negative control outcomes can be complex. An ideal negative control outcome is one which shares the potential biases of the primary outcome but cannot plausibly be related to the exposure.[29,30] Here, vaccine-associated aluminum cannot reasonably associate with future injuries in children. However, the outcomes of all-cause injuries and persistent asthma could share biases, as both outcomes may be subject to parents' health-related habits, health seeking behaviors, and overall access to care. The finding of a null negative control outcome in the current study suggests that the primary study finding is not due to potential sources of bias shared with the negative control outcome. It does not mean, however, that other forms of bias cannot be present.

The current study should be interpreted in the context of important limitations. First, misclassification of vaccine-associated aluminum exposure was possible; this could have occurred, for example, if a hepatitis B vaccine dose given at a birth hospital was not captured within VSD data. If missing exposure data were nondifferential with respect to outcome status, such misclassification would have biased toward a null finding. Second, all forms of aluminum adjuvants, including aluminum hydroxide and aluminum phosphate, were combined into a single measure of exposure, but it is possible that different chemical forms of aluminum have different biologic effects.[32] Third, while a stringent definition for persistent asthma was chosen,[22] case misclassification could have occurred. Childhood asthma is a clinical diagnosis,[15] and it is possible some cases had conditions other than asthma. It is also possible that true cases were missed, such as if children with asthma did not present for care, or children with persistent asthma symptoms were not started on long-term asthma control medications.[15] Children with mild intermittent or exercise-induced asthma were also not included in the case definition. Fourth, as with any observational study, unmeasured confounding could have influenced study results. Breast-feeding data were available for a fraction of the cohort, and data on family history of atopy and second-hand smoke exposure were unavailable. Measures of socioeconomic status such as maternal education and annual household income were also unavailable. It is difficult to predict whether these factors could have resulted in bias toward or away from the null hypothesis.

Considering the small effect size observed and the limitations described above, particularly related to unmeasured confounding, these findings do not constitute strong evidence for questioning the safety of aluminum in vaccines.[9] However, additional examination of this hypothesis appears warranted. Studies in other large databases, including in several European countries, may be able to address this question, and differences between European and US immunization schedules could provide helpful variability in aluminum adjuvant exposure. Studies in the VSD and elsewhere could examine allergic diseases other than asthma. Additionally, sophisticated assays of immunologic response following vaccination have recently been developed.[44] These techniques could be used to better characterize the immunologic response, including patterns of Th1/Th2 response, of vaccinated infants in the United States and provide additional evidence for or against the biologic plausibility of the association found in the current study.

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SUPPLEMENTARY DATA

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