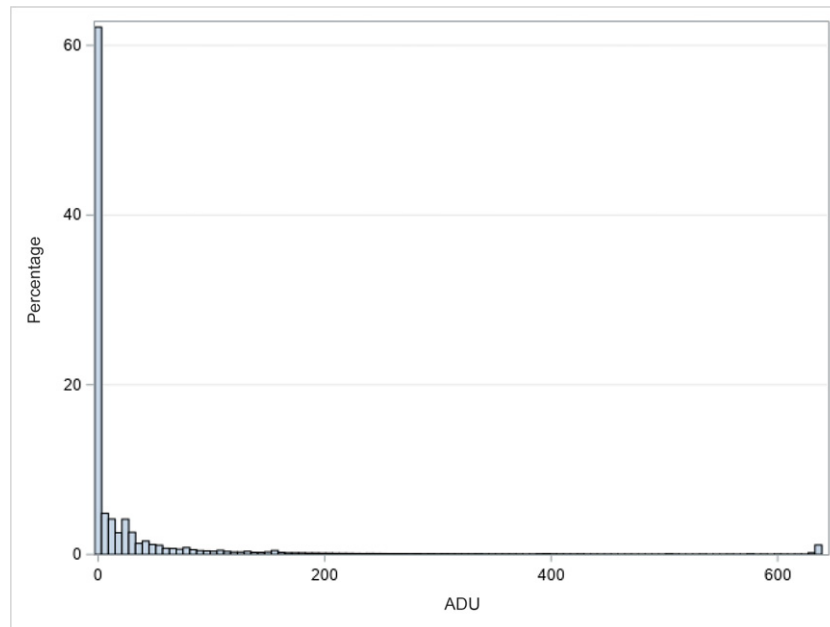
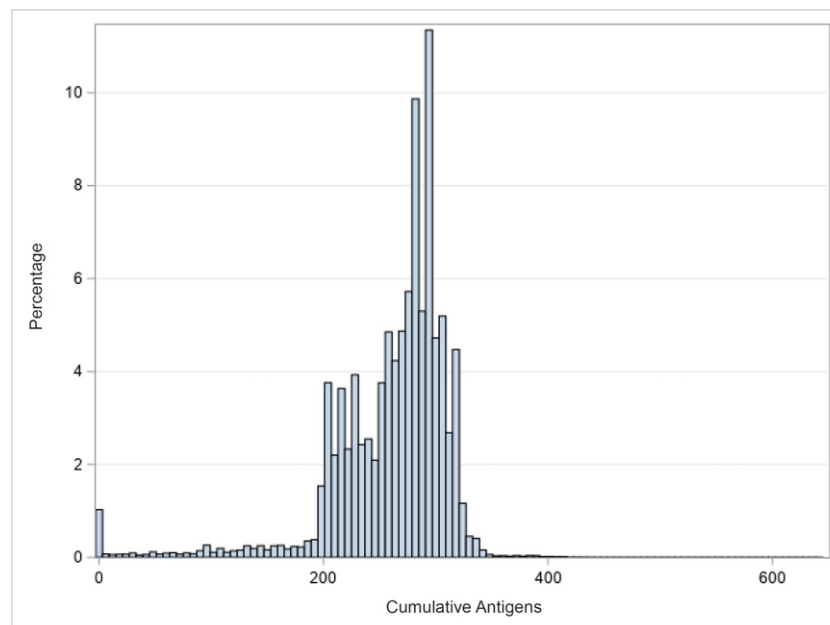


Supplemental Materials



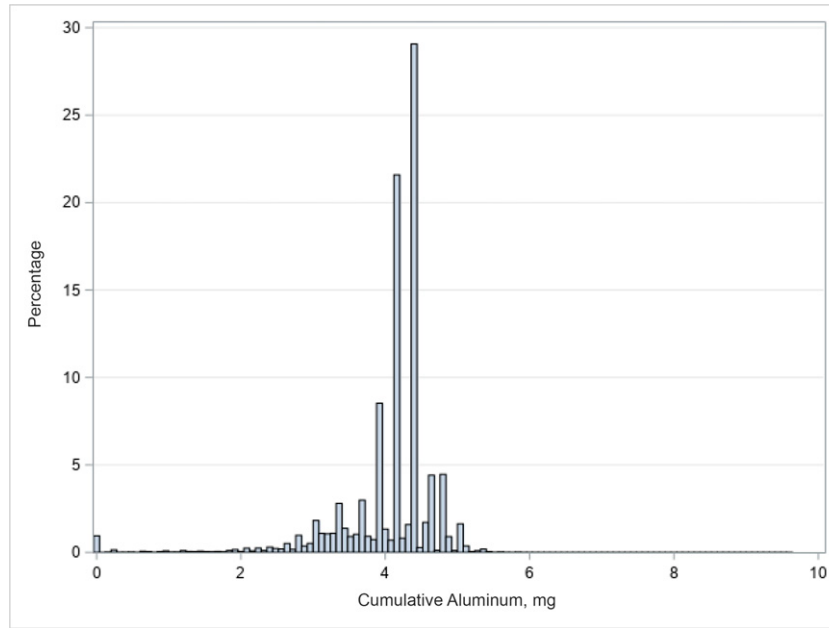
SUPPLEMENTAL FIGURE 3

Distribution of ADU through 23 months of age.



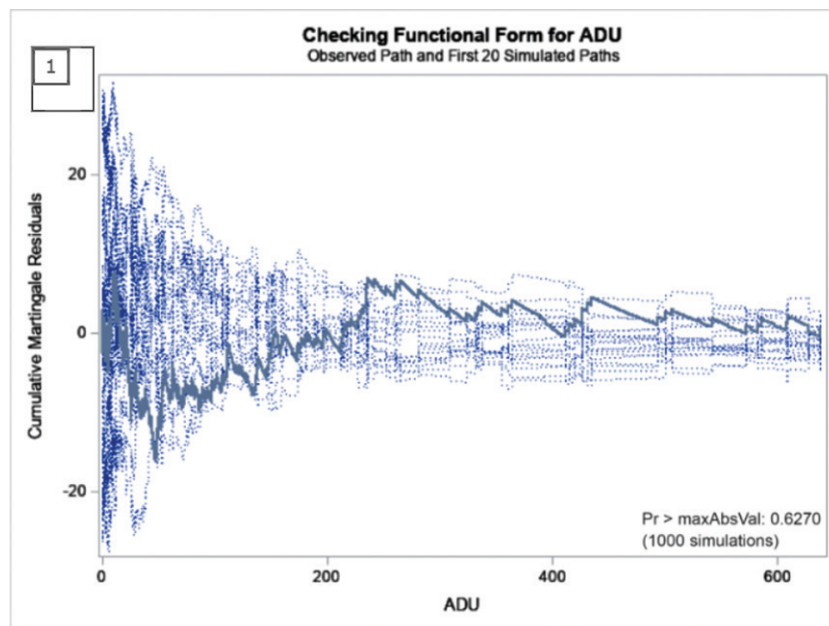
SUPPLEMENTAL FIGURE 4

Distribution of cumulative antigens through 23 months of age.



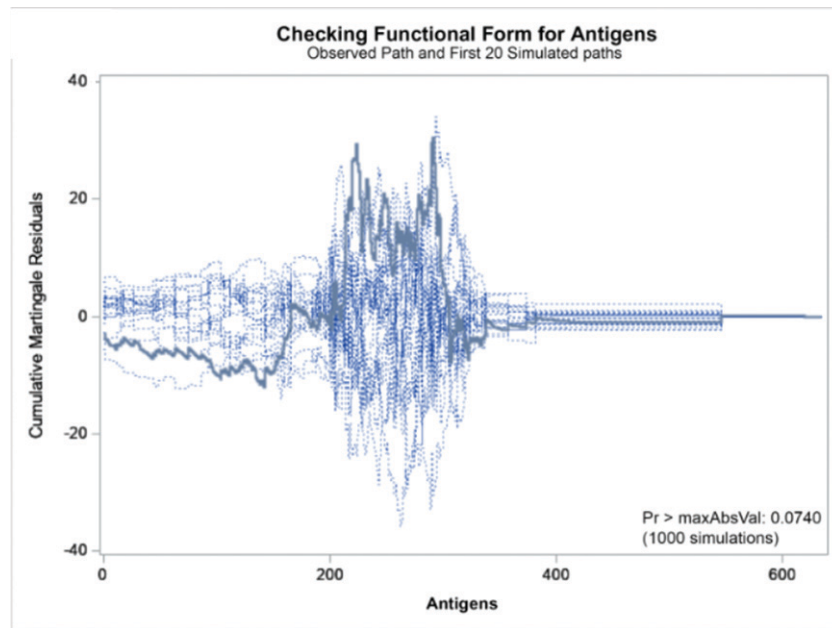
SUPPLEMENTAL FIGURE 5

Distribution of cumulative aluminum through 23 months of age.



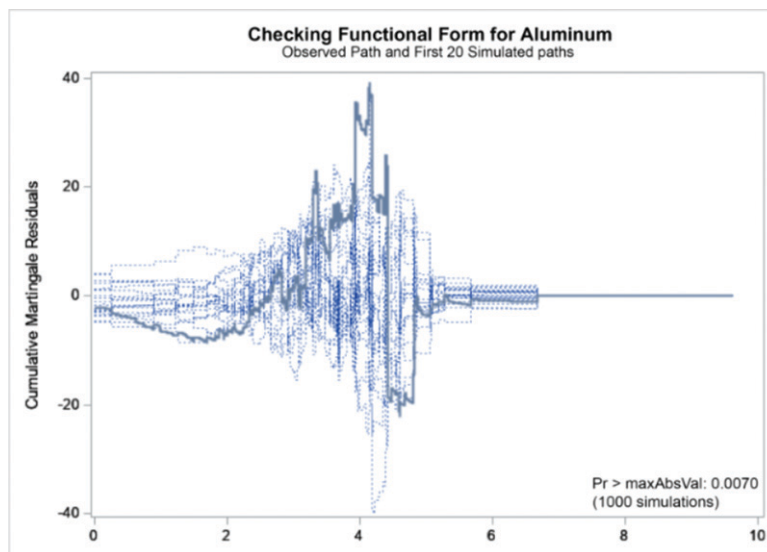
SUPPLEMENTAL FIGURE 6

Assessment of the functional form for ADU martingale residuals with Kolomogorov-type supremum tests does not indicate there is a violation in the functional form ($P = .63$).



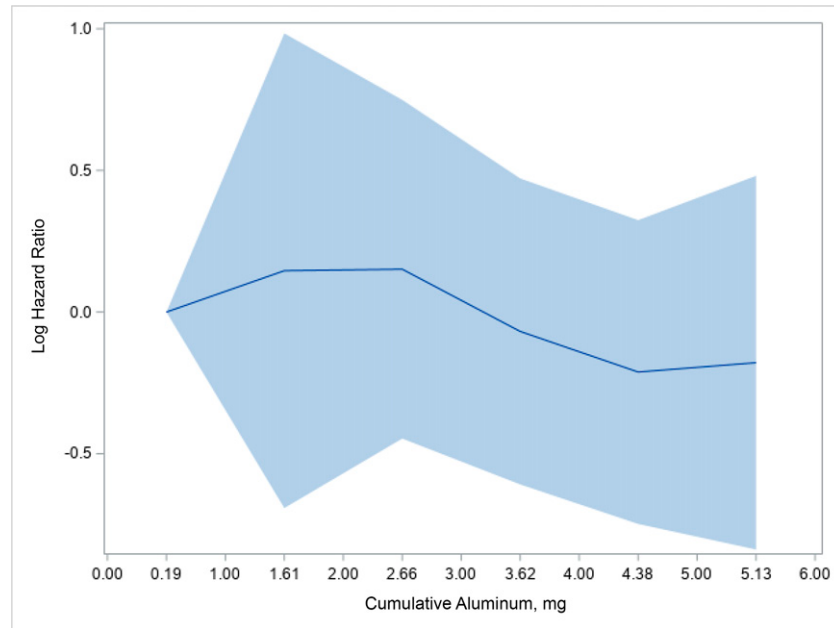
SUPPLEMENTAL FIGURE 7

Assessment of the functional form for cumulative antigen exposure martingale residuals with Kolomogorov-type supremum tests does not indicate there is a violation in the functional form ($P = .07$).



SUPPLEMENTAL FIGURE 8

Assessment of the functional form for cumulative aluminum exposure martingale residuals with Kolomogorov-type supremum tests indicate there is a violation in the functional form ($P = .007$).



SUPPLEMENTAL FIGURE 9

Cumulative aluminum analyzed in 1-mg groups; estimates and 95% CIs plotted at the midpoint for each category.

SUPPLEMENTAL TABLE 2 Number of Antigens and Aluminum Per Dose Found in Vaccines for the ACIP Schedule Through 23 Months of Age

Vaccine	No. Recommended Doses Through Age 23 mo ^a	Trade Name	No. Doses Administered in the Cohort During the Study Period ^b	Maximum Amount of Aluminum per Dose (mg) ^c	No. Antigens per Dose ^c
HepB	3	Engerix-B	362 275	0.250	1
		Recombivax	48 914	0.250	1
		Hep B, dialysis	82	0.500	1
		Unknown HepB brand	155 268	0.250	1
DTaP	4	Infanrix	541 999	0.625	5
		Tripedia	38 143	0.170	4
		Daptacel	7238	0.330	6
		Generic	692	0.250	2
Hib	3 or 4	ACTHIB (4-dose series)	1 594 976	0.000	2
		PedvaxHIB (3-dose series)	270 688	0.225	2
		Hiberix (4-dose series)	65 996	0.000	2
Pneumococcal	4	Prevnar 7	1 164 228	0.125	8
		Prevnar 13	1 108 384	0.125	14
		Pneumovax 23 ^d	1380	0.000	23
Polio	3	IPOL	63039	0.000	15
Rotavirus	2 or 3	Rotateq (3-dose series)	767 051	0.000	16
		Rotarix (2-dose series)	328 691	0.000	11
MMR	1	M-M-R II	456 249	0.000	24
		Attenuvax	316	0.000	10
		Meruvax II	226	0.000	5
		Mumps	194	0.000	9
		Measles/rubella	8	0.000	15
		Rubella/mumps	6	0.000	14
Varicella	1	Varivax	445 426	0.000	69
Hepatitis A	2	Havrix	643 020	0.250	4
		Vaqta	150 757	0.225	4
Seasonal influenza	4	Quadrivalent formulations	99 025	0.000	14
		Trivalent formulations	43 722	0.000	12
		Unknown formulation	806 751	0.000	13
		2009 H1N1 (Influenza A vaccine)	67 211	0.000	8
Combination vaccines	See above for individual vaccine components				
DTaP-HepB-Polio		Pediarix	1 502 974	0.850	21
DTaP-Hib-Polio		Pentacel	171 343	0.330	23
Hib-HepB		Comvax	19 017	0.225	3
DTaP-Hib		TriHIBit	3114	0.170	3
MMR-varicella		ProQuad	109 188	0.000	93
Meningococcal-Hib		MenHibrix	217	0.000	7
DTaP-Polio		Kinrix	338	0.600	20
		Quadracel	1	0.330	21

HepB, hepatitis B; Hib, *H influenzae* type.^a Number of recommended doses, as recommended by the ACIP.^b Number of observed doses of each vaccine administered within our study population across the study period.^c The amount of aluminum and antigens obtained from vaccine package inserts and published literature.^{8,25,27}^d One dose of Pneumovax 23 is indicated for children >24 months of age; however, some children in the VSD did receive this vaccine before 24 months of age.

SUPPLEMENTAL TABLE 3 Children Excluded from the Study Because of a Possible Contraindication to Vaccination

Contraindication Description	Children (<i>n</i> = 6161), <i>n</i> (%)
Cancer	1786 (29.0)
Received intravenous immunoglobulin	1425 (23.2)
Disorders involving the immune mechanism	1227 (19.9)
History of intussusception	872 (14.2)
Patient was immunocompromised or has an allergy to a vaccine or vaccine component	704 (11.4)
Guillain-Barré syndrome	65 (1.1)
HIV	45 (0.7)
Hematopoietic stem cell transplant	37 (0.6)

We excluded 6161 of 663 089 (0.9%) children because of a possible contraindication to vaccination.

SUPPLEMENTAL TABLE 4 Patient Characteristics by ADU and Cumulative Antigen and Cumulative Aluminum Exposure

	ADU ^a			Antigens ^b				Aluminum ^c			
	0	1–25	≥26	0–239	240–279	280–294	≥295	0–3.93	3.94–4.35	4.35–4.43	≥4.44
	342 381 (58.6)	95 775 (16.4)	146 015 (25)	156 528 (26.8)	163 625 (28)	139 827 (23.9)	124 191 (21.3)	175 286 (30)	154 500 (26.4)	169 915 (29.1)	84 470 (14.5)
Sex, <i>n</i> (%)											
Female	167 637 (49)	46 871 (48.9)	70 291 (48.1)	75 638 (48.3)	80 451 (49.2)	68 162 (48.7)	60 548 (48.8)	85 306 (48.7)	75 431 (48.8)	82 710 (48.7)	41 352 (49)
Male	174 735 (51)	48 903 (51.1)	75 722 (51.9)	80 884 (51.7)	83 171 (50.8)	71 664 (51.3)	63 641 (51.2)	89 973 (51.3)	79 067 (51.2)	87 204 (51.3)	43 116 (51)
Unknown	9 (0.0)	1 (0.0)	2 (0.0)	6 (0.0)	3 (0.0)	1 (0.0)	2 (0.0)	7 (0.0)	2 (0.0)	1 (0.0)	2 (0.0)
Race and ethnicity, <i>n</i> (%)											
Asian American	59 266 (17.3)	14 622 (15.3)	16 538 (11.3)	18 244 (11.7)	22 771 (13.9)	26 553 (19)	22 858 (18.4)	21 698 (12.4)	24 522 (15.9)	34 040 (20)	10 166 (12)
Black	19 411 (5.7)	6941 (7.2)	11 687 (8)	11 024 (7)	12 647 (7.7)	7745 (5.5)	6623 (5.3)	11 919 (6.8)	9727 (6.3)	10 009 (5.9)	6384 (7.6)
Hispanic	94 841 (27.7)	26 422 (27.6)	36 464 (25)	36 773 (23.5)	47 649 (29.1)	39 606 (28.3)	33 699 (27.1)	36 152 (20.6)	42 672 (27.6)	54 697 (32.2)	24 206 (28.7)
Non-Hispanic White	145 280 (42.4)	40 403 (42.2)	67 443 (46.2)	75 225 (48.1)	68 158 (41.7)	56 421 (40.4)	53 322 (42.9)	89 328 (51)	65 672 (42.5)	60 933 (35.9)	37 193 (44)
Other	6325 (1.8)	1916 (2.0)	2783 (1.9)	3820 (2.4)	2813 (1.7)	2217 (1.6)	2174 (1.8)	3352 (1.9)	2702 (1.7)	3046 (1.8)	1924 (2.3)
Unknown	17 258 (5.0)	5471 (5.7)	11 100 (7.6)	11 442 (7.3)	9587 (5.9)	7285 (5.2)	5515 (4.4)	12 837 (7.3)	9205 (6.0)	7190 (4.2)	4597 (5.4)
Birth year of child, <i>n</i> (%)											
2004–2005	57 631 (16.8)	15 361 (16.0)	19 569 (13.4)	85 445 (54.6)	6416 (3.9)	131 (0.1)	569 (0.5)	39 203 (22.4)	16 273 (10.5)	4533 (2.7)	32 552 (38.5)
2006–2007	56 050 (16.4)	17 835 (18.6)	32 330 (22.1)	37 660 (24.1)	50 292 (30.7)	15 619 (11.2)	2644 (2.1)	25 950 (14.8)	28 372 (18.4)	15 777 (9.3)	36 116 (42.8)
2008–2009	57 802 (16.9)	20 251 (21.1)	35 029 (24.0)	13 559 (8.7)	40 628 (24.8)	25 619 (18.3)	33 276 (26.8)	43 363 (24.7)	41 242 (26.7)	22 289 (13.1)	6188 (7.3)
2010–2011	63 627 (18.6)	18 213 (19.0)	26 162 (17.9)	8110 (5.2)	17 664 (10.8)	28 659 (20.5)	53 569 (43.1)	33 125 (18.9)	28 795 (18.6)	43 992 (25.9)	2090 (2.5)
2012–2013	69 734 (20.4)	16 753 (17.5)	22 623 (15.5)	7944 (5.1)	32 905 (20.1)	50 148 (35.9)	18 113 (14.6)	23 307 (13.3)	27 291 (17.7)	53 898 (31.7)	4614 (5.5)
2014	37 537 (11.0)	7362 (7.7)	10 302 (7.1)	3810 (2.4)	15 720 (9.6)	19 651 (14.1)	16 020 (12.9)	10 338 (5.9)	12 527 (8.1)	29 426 (17.3)	2910 (3.4)
Season of child's birth, <i>n</i> (%)											
Spring	87 058 (25.4)	23 624 (24.7)	35 386 (24.2)	40 560 (25.9)	33 397 (20.4)	35 207 (25.2)	36 904 (29.7)	45 670 (26.1)	38 645 (25.0)	40 270 (23.7)	21 483 (25.4)
Summer	88 470 (25.8)	25 767 (26.9)	38 500 (26.4)	41 933 (26.8)	44 350 (27.1)	36 863 (26.4)	29 591 (23.8)	45 345 (25.9)	39 846 (25.8)	45 120 (26.6)	22 426 (26.5)
Fall	85 881 (25.1)	23 642 (24.7)	37 953 (26.0)	36 808 (23.5)	49 433 (30.2)	35 965 (25.7)	25 270 (20.3)	42 427 (24.2)	39 158 (25.3)	45 343 (26.7)	20 548 (24.3)
Winter	80 972 (23.6)	22 742 (23.7)	34 176 (23.4)	37 227 (23.8)	36 445 (22.3)	31 792 (22.7)	32 426 (26.1)	41 844 (23.9)	36 851 (23.9)	39 182 (23.1)	20 013 (23.7)
Mother's age category, <i>n</i> (%)											
14–30	113 022 (33.0)	32 894 (34.3)	51 851 (35.5)	58 118 (37.1)	58 345 (35.7)	42 555 (30.4)	38 749 (31.2)	60 664 (34.6)	49 544 (32.1)	54 528 (32.1)	33 031 (39.1)
30–34	115 251 (33.7)	30 770 (32.1)	43 705 (29.9)	47 054 (30.1)	51 614 (31.5)	48 409 (34.6)	42 649 (34.3)	53 683 (30.6)	49 176 (31.8)	61 149 (36.0)	25 718 (30.4)
35–55	86 054 (25.1)	23 792 (24.8)	35 153 (24.1)	36 961 (23.6)	38 076 (23.3)	37 438 (26.8)	32 524 (26.2)	41 389 (23.6)	38 552 (25)	45 775 (26.9)	19 283 (22.8)
Unknown	28 054 (8.2)	8319 (8.7)	15 306 (10.5)	14 395 (9.2)	15 590 (9.5)	11 425 (8.2)	10 269 (8.3)	19 550 (11.2)	17 228 (11.2)	8463 (5.0)	6438 (7.6)
Weight at birth, mean (SD), g	3340 (557)	3357 (564)	3357 (610)	3384 (573)	3350 (580)	3331 (565)	3314 (564)	3374 (579)	3336 (588)	3333 (550)	3339 (571)
Gestational age, mean (SD), wk	39 (2)	39 (2)	39 (2)	39 (2)	39 (2)	39 (2)	39 (2)	39 (2)	39 (2)	39 (2)	39 (2)

SUPPLEMENTAL TABLE 4 Continued

	ADU ^a			Antigens ^b				Aluminum ^c			
	0	1–25	≥26	0–239	240–279	280–294	≥295	0–3.93	3.94–4.35	4.35–4.43	≥4.44
	342 381	95 775	146 015	156 528	163 625	139 827	124 191	175 286	154 500	169 915	84 470
	(58.6)	(16.4)	(25)	(26.8)	(28)	(23.9)	(21.3)	(30)	(26.4)	(29.1)	(14.5)
No. well-child visits between 30 d and 2 y, mean (SD)	6 (1)	6 (1)	5 (2)	5 (1)	6 (1)	6 (1)	6 (1)	6 (2)	6 (1)	6 (1)	5 (1)
Follow-up, median (IQR), y	7 (5–10)	7 (4–10)	7 (4–10)	8 (4–13)	7 (4–11)	6 (5–8)	7 (5–9)	7 (4–10)	7 (5–10)	6 (5–8)	10 (4–13)
ADU, mean (SD)	0 (0)	10 (7)	147 (170)	105 (179)	24 (50)	9 (24)	6 (20)	97 (172)	19 (44)	8 (23)	12 (30)
Undervaccinated, <i>n</i> (%)	0 (0.0)	95 775 (100)	146 015 (100)	91 493 (58.5)	77 197 (47.2)	41 218 (29.5)	31 882 (25.7)	102 615 (58.5)	63 700 (41.2)	48 676 (28.6)	26 799 (31.7)
No ACIP vaccines through age 23 mo, <i>n</i> (%)	0 (0.0)	0 (0.0)	6308 (4.3)	6308 (4.0)	0 (0.0)	0 (0.0)	0 (0.0)	6304 (3.6)	3 (0.0)	0 (0.0)	1 (0.0)
Children who delayed starting vaccines, <i>n</i> (%)	0 (0.0)	0 (0.0)	4267 (2.9)	3651 (2.3)	518 (0.3)	64 (0.0)	34 (0.0)	3633 (2.1)	507 (0.3)	12 (0.0)	115 (0.1)
Missing ≥1 vaccine series, <i>n</i> (%)	0 (0.0)	0 (0.0)	59 733 (40.9)	46 844 (29.9)	10 267 (6.3)	1651 (1.2)	971 (0.8)	41 537 (23.7)	9763 (6.3)	4850 (2.9)	3583 (4.2)
Missing ≥1 vaccine dose, <i>n</i> (%)	9 (0.0) ^d	5002 (5.2)	113 116 (77.5)	64 689 (41.3)	36 306 (22.2)	9912 (7.1)	7220 (5.8)	69 741 (39.8)	25 251 (16.3)	13 225 (7.8)	9910 (11.7)

IQR, interquartile range.

^a ADU, average days undervaccinated by age 24 months. The median (IQR) was 0 (0–24.65), therefore this exposure was evaluated at 0%–50%, 51%–75% and 76%–100%.^b Antigens, cumulative antigens through 23 months of age. The median (IQR) was 279 (239–294).^c Aluminum, cumulative aluminum through 23 months of age. The median (IQR) was 4.35 (3.93–4.43).^d There were 9 children born in the first quarter of 2004 with an ADU = 0 and were missing pneumococcal doses, but were not counted in the ADU counts. There was a pneumococcal vaccine shortage during this time, and thus the 3rd and 4th dose delays were not counted in the ADU.¹⁰

SUPPLEMENTAL TABLE 5 Cumulative Aluminum Analyzed in 1-mg Incremental Categories

Group	<i>n</i> (%)	Cases	IR per 100 000 Person-Years	Unadjusted	Unadjusted Complete Case	Adjusted
0.0–1.0 mg	8339 (1.43)	19	(33.63)	1.00 (1.00–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.00)
1.0–2.0 mg	4576 (0.78)	11	(35.66)	1.06 (0.50–2.22)	1.14 (0.50–2.65)	1.16 (0.50–2.67)
2.0–3.0 mg	24 078 (4.12)	60	(36.08)	1.06 (0.63–1.78)	1.11 (0.62–2.01)	1.16 (0.64–2.12)
3.0–4.0 mg	147 972 (25.33)	357	(30.10)	0.85 (0.53–1.34)	0.88 (0.51–1.50)	0.93 (0.54–1.60)
4.0–5.0 mg	384 860 (65.88)	657	(22.25)	0.64 (0.40–1.01)	0.65 (0.38–1.11)	0.81 (0.47–1.38)
>5.00 mg	14 346 (2.46)	28	(22.61)	0.62 (0.35–1.12)	0.70 (0.37–1.33)	0.84 (0.43–1.62)

IR, incidence rate.

SUPPLEMENTAL TABLE 6 Family History of T1DM

Aluminum	T1DM Status of Child	Children, <i>n</i>	Children Matched to Parents, <i>n</i>	Parent and/or Older Sibling Has T1DM, <i>n</i>	Neither Parent nor an Older Sibling Has T1DM, ^a <i>n</i>
≤3.0 mg	With	17	11	3	8
	Without	6585	4141	53	4088
>3.0 mg	With	445	313	18	295
	Without	248 741	163 213	1737	161 476
Total ^b	With	462	324	21	303
	Without	255 326	167 354	1790	165 564

^a Neither parent has T1DM, and the child either does not have an older sibling or the older sibling does not have T1DM.^b Two of the 8 VSD sites contributed data to this subanalysis.