Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. ICD-9 and ICD-10 Codes for Infections Not Targeted by Early Childhood Vaccines[a,b]

Description	ICD-9	ICD-10
Acute Lymphadenitis	683	L04.0-L04.9
Cellulitis and abscess	380.10, 680.0, 680.1, 680.2, 680.3, 680.4, 680.5, 680.6, 680.7, 680.8, 680.9, 681.00, 681.01, 681.02, 681.10, 681.11, 681.9, 682.0, 682.1, 682.2, 682.3, 682.4, 682.5, 682.6, 682.7, 682.8, 682.9	H60.0-H60.1 L02.0-L03.9
Certain bacterial diseases	020.0, 020.1, 020.2, 020.3, 020.4, 020.5, 020.8, 020.9, 021.0, 021.1, 021.2, 021.3, 021.8, 021.9, 022.0, 022.1, 022.2, 022.3, 022.8, 022.9, 023.0, 023.1, 023.2, 023.3, 023.8, 023.9, 024, 025, 026.0, 026.1, 026.9, 027.0, 027.1, 027.2, 027.8, 027.9, 030.0, 030.1, 030.2, 030.3, 030.8, 030.9, 031.0, 031.1, 031.2, 031.8, 031.9, 034.1, 036.1, 036.2, 036.3, 036.40, 036.41, 036.42, 036.43, 036.81, 036.82, 036.89, 036.9, 038.8, 039.0, 039.1, 039.3, 039.8, 039.9, 040.0, 040.1, 040.41, 040.42, 040.82, 040.89, 041.00, 041.11, 041.12, 041.5, 041.81, 041.89, 041.9, 078.3, 078.88, 079.88, 079.98, 088.0, 090.0, 090.1, 090.2, 090.3, 090.40, 090.41, 090.42, 090.49, 090.5, 090.6, 090.7, 090.9, 091.0, 091.1, 091.2, 091.3, 091.4, 091.50, 091.51, 091.52, 091.61, 091.62, 091.69, 091.7, 091.81, 091.82, 091.89, 092.0, 092.9, 093.0, 093.1, 093.20, 093.21, 093.22, 093.23, 093.24, 093.81, 093.82, 093.89, 093.9, 094.0, 094.1, 094.2, 094.3, 094.81, 094.82, 094.83, 094.84, 094.85, 094.86, 094.89, 094.9, 095.0, 095.1, 095.2, 095.3, 095.4, 095.5, 095.6, 095.7, 095.8, 095.9, 096, 097.0, 097.1, 097.9, 098.0, 098.11, 098.12, 098.13, 098.14, 098.15, 098.16, 098.19, 098.2, 098.31, 098.32, 098.33, 098.34, 098.35, 098.36, 098.40, 098.41, 098.42, 098.43, 098.49, 098.50, 098.51, 098.52, 098.53, 098.59,	A20.0-A32.0 A38.0-A38.9 A39.3-A39.9 A39.1 A42.2-A44.9 A48.0 A48.2-A49.9 A74.8-A74.9 A50.0-A53.9 A54.0-A54.9 A55.0-A56.9

Description	ICD-9	ICD-10
	098.6, 098.7, 098.81, 098.82, 098.83, 098.84, 098.85, 098.86, 098.89, 099.51, 099.52, 099.53, 099.54, 099.55, 099.59, 100.0, 100.81, 100.89, 100.9, 357.4, 484.5, 595.4, 614.9, 616.11, 713.5, 995.91,	
Dermatophytosis and other superficial mycoses	110, 110.1, 110.2, 110.3, 110.4, 110.5, 110.6, 110.8, 110.9, 111.0, 111.1, 111.2, 111.3, 111.8, 111.9	B35.0-B36.9
Gastrointestinal infections	001.0, 001.1, 001.9, 002.0, 002.1, 002.2, 002.3, 002.9, 003.0, 003.20, 003.21, 003.22, 003.23, 003.24, 003.29, 003.8, 003.9, 004.0, 004.1, 004.2, 004.3, 004.8, 004.9, 005.0, 005.1, 005.2, 005.4, 005.81, 005.89, 005.9, 006.0, 006.1, 006.2, 006.3, 006.4, 006.5, 006.6, 006.8, 006.9, 007.0, 007.1, 007.2, 007.3, 007.4, 007.5, 007.8, 007.9, 008.00, 008.01, 008.02, 008.03, 008.04, 008.09, 008.2, 008.41, 008.43, 008.44, 008.45, 008.49, 008.5, 008.61, 008.62, 008.63, 008.64, 008.65, 008.66, 008.67, 008.69, 008.8, 009.0, 039.2, 136.5,	A00.0-A02.0 A02.2-A09.9 A42.1
Hepatitis	070.0, 070.1, 070.20, 070.21, 070.30, 070.31, 070.32, 070.33, 070.41, 070.49, 070.51, 070.52, 070.53, 070.54, 070.59, 070.6, 070.70, 070.71, 070.9,	B15.0-B19.9
Infections in the ear	381.00, 381.02, 381.03, 381.04, 381.05, 381.06, 381.10, 381.19, 381.20, 381.29, 381.3, 381.4, 382.00, 382.01, 382.02, 382.1, 382.2, 382.3, 382.4, 382.9, 383.00, 383.01, 383.02, 383.1, 383.20, 383.21, 383.22, 383.81, 383.89,	H65.0-H67.9 H70.0-H70.9
Infections of the circulatory system	391.0, 391.1, 391.2, 391.8, 391.9, 420.90, 420.91, 420.99, 421.0, 421.9, 422.90, 422.91, 422.92, 422.93, 422.99	I00.0-I01.9 I30.0-I30.9 I33.0-I33.9 I39.8-I40.9
Infections of the eye	076.0, 076.1, 076.9, 077.0, 077.98, 372.01, 372.04, 372.06, 372.20, 372.21, 372.22, 372.39, 373.11, 373.12, 373.13, 373.2, 373.8, 373.9	A71.0-A74.0 H10.2-H10.3 H10.5-H10.8 H00.0-H01.0 H01.8-H01.9

Description	ICD-9	ICD-10
Infections of the musculoskeletal system and connective tissue	041.09, 041.10, 041.2, 041.89, 711.00, 711.01, 711.02, 711.03, 711.04, 711.05, 711.06, 711.07, 711.08, 711.09, 730.10, 730.11, 730.12, 730.13, 730.14, 730.15, 730.16, 730.17, 730.18, 730.19	M00.0-M01.9 M86.3-M86.6
Infections of the nervous system	320.9, 323.41, 323.42, 323.51, 323.52, 323.61, 323.62, 323.81, 323.82, 323.9, 324.0, 324.1, 324.9, 344.1	G04.0-G07.9
Infections of the urinary system	099.40, 597.0, 597.80, 597.81	N34.0-N34.1 N34.3
Laryngitis	032.3, 464.00, 464.01, 464.10, 464.11, 464.20, 464.21, 464.30, 464.31, 464.4, 464.50, 464.51, 476.0	A36.2 J04.0-J05.9 J37.0
Meningitis	036.0, 047.0, 047.1, 047.8, 047.9, 049.0, 049.1, 052.7, 053.0, 053.19, 054.3, 054.72, 055.0, 055.79, 072.1, 072.2, 320.0, 320.1, 320.2, 320.3, 320.7, 320.82, 320.89, 320.9, 321.1, 321.2, 321.8, 322.0, 322.1, 322.2, 322.9, 997.09	A39.0 A87.0-A87.9 B01.0-B01.1 B02.0-B02.1 B00.3-B00.4 B05.0-B05.1 B26.1-B26.2 G00.0-G03.9
Mycoses	039.4, 039.9, 112.0, 112.1, 112.2, 112.3, 112.4, 112.81, 112.82, 112.83, 112.84, 112.85, 112.89, 112.9, 114.0, 114.1, 114.2, 114.3, 114.4, 114.5, 114.9, 115.00, 115.05, 115.09, 115.10, 115.90, 116.0, 116.1, 116.2, 117.0, 117.1, 117.2, 117.3, 117.4, 117.5, 117.6, 117.7, 117.8, 117.9, 118, 321.0, 484.6, 518.6	B37.8-B49.9 B37.0-B37.6
Nasopharyngitis	032.1	A36.1
Osteomyelitis	730.00, 730.01, 730.02, 730.03, 730.04, 730.05, 730.06, 730.07, 730.08, 730.09	M86.0-M86.2
Other	032.2, 032.81, 032.82, 032.83, 032.84, 032.89, 032.9, 099.8, 099.9, 465.0, 465.8, 465.9	A36.8-A36.9 A63.8-A64.9 J06.0-J06.9
Other acute lower respiratory infections	033.0, 033.1, 033.8, 039.1, 041.00, 041.5, 041.81, 079.1, 079.2, 079.3, 079.6, 079.89, 466.0, 466.11, 466.19, 484.3, 510.0, 510.9, 511.0, 513.0, 513.1, 519.8, 530.84	A37.0-A37.9 A42.0 J20.0-J22.9 J85.0-J86.9
Other local infections of skin and	032.85, 039.0, 380.10, 380.12,	A36.3

Description	ICD-9	ICD-10
subcutaneous tissue	380.14, 380.23, 684, 686.00, 686.09, 686.8, 686.9, 690.8	L08.0-L08.9 H60.2-H60.4 H60.8-H60.9 L00.0-L01.1 L30.3
Pharyngitis	034.0, 462	J02.0-J02.9
Pneumonia	480.0, 480.1, 480.2, 480.3, 480.8, 480.9, 481, 482.0, 482.1, 482.2, 482.31, 482.32, 482.39, 482.40, 482.41, 482.42, 482.49, 482.81, 482.82, 482.83, 482.84, 482.89, 482.9, 483.0, 483.1, 483.8, 484.7, 484.8, 485, 486, 487.0, 514, 517.1	J12.0-J18.9 A48.1
Protozoal diseases, helminthiases, pediculosis, acariasis, and other infestations	084.0, 084.1, 084.2, 084.3, 084.4, 084.5, 084.6, 084.8, 084.9, 085.0, 085.1, 085.2, 085.3, 085.4, 085.5, 085.9, 086.0, 086.1, 086.2, 086.3, 086.4, 086.5, 086.9, 088.82, 088.9, 120.0, 120.1, 120.2, 120.3, 120.8, 120.9, 121.0, 121.1, 121.2, 121.3, 121.4, 121.5, 121.6, 121.8, 121.9, 122.0, 122.1, 122.2, 122.3, 122.4, 122.5, 122.6, 122.7, 122.8, 122.9, 123.0, 123.1, 123.2, 123.3, 123.4, 123.5, 123.6, 123.8, 123.9, 124, 125.0, 125.1, 125.2, 125.3, 125.5, 125.6, 125.7, 125.9, 126.0, 126.1, 126.2, 126.3, 126.8, 126.9, 127.0, 127.1, 127.2, 127.3, 127.4, 127.5, 127.6, 127.7, 127.8, 127.9, 128.0, 128.1, 128.8, 128.9, 129, 130.0, 130.1, 130.2, 130.3, 130.4, 130.5, 130.7, 130.9, 131.00, 131.01, 131.02, 131.03, 131.09, 131.8, 131.9, 132.0, 132.1, 132.2, 132.3, 132.9, 133.0, 133.8, 134.0, 134.1, 134.2, 134.8, 134.9, 136.21, 136.29, 136.3, 136.8, 136.9, 370.8, 372.15, 484.8, 581.81, 686.8	B50.0-B89.9 A59.0-A59.9
Rickettsiosis	080, 081.0, 081.1, 081.2, 081.9, 082.0, 082.1, 082.2, 082.3, 082.40, 082.41, 082.49, 082.8, 083.0, 083.1, 083.2, 083.8, 083.9	A75.0-A79.9
Sepsis	003.1, 027.0, 036.2, 038.0, 038.10, 038.11, 038.12, 038.19,	A02.1

Description	ICD-9	ICD-10
	038.2, 038.3, 038.40, 038.41, 038.42, 038.43, 038.44, 038.49, 038.8, 038.9, 112.5, 995.91	A32.7 A39.2 A40.0-A41.9 B37.7
Sinusitis	461.0, 461.3, 461.8, 473.0, 473.1, 473.2, 473.3, 473.8, 473.9	J01.0-J01.1 J01.3-J01.9 J32.0-J32.9
Spirochetal disease	087.0, 087.1, 087.9, 088.81, 101, 102.0, 102.1, 102.2, 102.3, 102.4, 102.5, 102.6, 102.7, 102.8, 102.9, 103.0, 103.1, 103.2, 103.3, 103.9, 104.8, 104.9, 528.1	A65.0-A69.9
Tonsillitis	032.0, 034.0, 463	A36.0 J03.0-J03.9
Tuberculosis	010.90, 011.30, 011.90, 012.00, 012.10, 012.20, 012.30, 012.80, 013.00, 013.10, 013.20, 013.30, 013.40, 013.50, 013.60, 013.62, 013.80, 014.00, 014.80, 015.00, 015.10, 015.20, 015.60, 015.70, 015.80, 015.90, 016.00, 016.10, 016.20, 016.30, 016.50, 016.60, 016.70, 016.90, 017.00, 017.10, 017.20, 017.30, 017.40, 017.50, 017.60, 017.70, 017.80, 017.90, 018.00, 018.80, 018.90, 363.13, 364.11, 370.31, 370.59, 379.09, 420.0, 422.0, 424.91, 425.8, 601.4, 711.45, 711.46, 711.48, 720.81, 730.88, 737.40	A15.0-A19.9
Unspecified infections	136.8, 136.9	B99.0-B99.9
Viral infections	045.10, 045.20, 045.90, 046.0, 046.11, 046.19, 046.2, 046.3, 046.71, 046.72, 046.79, 046.8, 046.9, 048, 049.8, 049.9, 050.0, 050.1, 050.9, 051.01, 051.02, 051.1, 051.2, 051.9, 052.1, 052.7, 052.8, 052.9, 053.10, 053.11, 053.12, 053.13, 053.14, 053.19, 053.20, 053.21, 053.22, 053.29, 053.71, 053.79, 053.8, 053.9, 054.0, 054.10, 054.11, 054.12, 054.13, 054.19, 054.2, 054.40, 054.41, 054.42, 054.43, 054.44, 054.49, 054.5, 054.6, 054.71, 054.73, 054.74, 054.79, 054.8, 054.9, 055.1, 055.2, 055.71, 055.79, 055.9, 056.71, 056.79, 056.9, 057.0, 057.8,	A80.0-A86.9 A88.0-A99.9 B02.2-B04.9 B08.0-B09.9 B01.2-B01.9 B00.0-B00.2 A60.0-A60.9 B00.5-B00.9 B05.2-B05.9 B06.1-B06.9 B20.0-B26.0 B26.3-B34.9 A63.0

Description	ICD-9	ICD-10
	057.9, 058.10, 058.11, 058.12, 059.00, 059.01, 059.09, 059.10, 059.11, 059.12, 059.19, 059.20, 059.21, 059.22, 059.8, 060.0, 060.1, 060.9, 061, 062.0, 062.1, 062.2, 062.3, 062.4, 062.5, 062.8, 062.9, 063.0, 063.1, 063.2, 063.8, 063.9, 064, 065.0, 065.1, 065.2, 065.3, 065.4, 065.9, 066.0, 066.1, 066.2, 066.3, 066.40, 066.41, 066.42, 066.49, 066.8, 066.9, 071, 072.0, 072.3, 072.71, 072.72, 072.79, 072.9, 074.0, 074.1, 074.20, 074.21, 074.22, 074.23, 074.3, 074.8, 075, 077.1, 077.2, 077.3, 077.4, 077.8, 077.99, 078.0, 078.11, 078.2, 078.4, 078.5, 078.6, 078.7, 078.81, 078.89, 079.0, 079.59, 079.81, 079.83, 079.89, 484.1, 573.1, 577.0, 790.8	
Viral warts	078.10, 078.12, 078.19	B07.0-B07.9

Abbreviations: ICD-9, International Classification of Diseases, 9th edition; ICD-10, International Classification of Diseases, 10th edition

[a]ICD-10 codes were obtained from Sørup et al. (Online-only Supplement reference 1), and a crosswalk tool maintained by Kaiser Permanente was used to convert these codes to their ICD-9 code equivalents.

[b]This list included some ICD codes for vaccine preventable diseases (VPDs) to be inclusive. VPDs were excluded among potential cases upon medical record review and potential controls were excluded if they had an ICD code for a VPD.

eTable 2. ICD-9 and ICD-10 Codes for Excluded Infections Targeted by Early Childhood Vaccines[a]

Description	ICD-9	ICD-10
Hepatitis	070.0, 070.1, 070.20, 070.21, 070.30, 070.31, 070.32, 070.33, 070.41, 070.49, 070.51, 070.52, 070.53, 070.54, 070.59, 070.6, 070.70, 070.71, 070.9	B15.0-B19.9
Influenza	487.x, 488.x	J11.x, J10.08, J10.1, J09.x9
Haemophilus influenzae type b	041.5	B96.3
Measles	055.x	B05.x
Mumps	072.x	B26.x
Varicella	052.x	B01.x
Pertussis	033.0, 033.1, 033.8, 033.9	A37.00, A37.1, A37.8, A37.9
Pneumococcal disease	481, 482.9, 485, 486, 320.1, 320.9, 790.7, 038.2, 038.9, 567.1, 383, 283.11, 041.2	J18.1, J15.9, J18, J18.9, G00.1, G00.9, G04.2, R78.81, A40.3, A41.9, H70.X, D59.3, B95.3
Rotavirus	008.61	A08.0
Diphtheria	032.x	A36.x
Tetanus	037.x	A35.x

Abbreviations: ICD-9, International Classification of Diseases, 9th edition; ICD-10, International Classification of Diseases, 10th edition

[a]ICD codes were not included for rubella and poliomyelitis since rubella was eliminated from the United States in 2004 (Online-only Supplement reference 2) and Americas were certified polio-free in 1994 (Online-only Supplement reference 3). For cases, medical record notes were reviewed for documentation of diseases targeted by early childhood vaccines on the same date. For controls, electronic data were used to identify inpatient or emergency department diagnoses for diseases targeted by early childhood vaccines.

eTable 3. Number of Antibody-Stimulating Protein and Polysaccharide Antigens[a] in Early Childhood Vaccines Universally Recommended by the US Advisory Committee on Immunization Practices[b]

Type of vaccine	Number of Antigens Per Dose
Hepatitis B (HepB)	1
Diphtheria-Tetanus-acellular Pertussis (DTaP)	4, 5, or 6, depending on brand
Haemophilus influenzae type b (Hib)	2
Pneumococcal	8 (against 7 types of pneumococcal bacteria)
	14 (against 13 types of pneumococcal bacteria)
Polio	15
Rotavirus	16
Measles-mumps-rubella (MMR)	24
Varicella	69
Seasonal influenza	12 (trivalent)
	14 (quadrivalent)
2009 H1N1 (Influenza A 2009 Monovalent Vaccine)	8
Hepatitis A	4
Combination Vaccines	
DTaP-HepB-Polio	21
DTaP-Hib-Polio	23
Hib-HepB	3
DTaP-Hib	6
MMR-Varicella	93

[a] The minimum estimated cumulative number of vaccine antigens a child could have received between birth and age 23 months is 0 antigens (if the child was completely unvaccinated). The number of estimated cumulative vaccine antigens in a child who is being vaccinated per the U.S. recommended immunization schedule varied throughout the time period of this study, which includes children born 2003-2012. For example, a child born in 2003 could have received 3 hepatitis B vaccines (3 x 1 antigens), 4 diphtheria-tetanus-pertussis vaccines (4 x 4 antigens), 3 *Haemophilus influenzae type b* vaccines (4 x 2 antigens), 3 pneumococcal conjugate vaccines against 7 types of pneumococcal bacteria (4 x 7 antigens), 3 polio vaccines (3 x 15 antigens), 1 measles-mumps-rubella vaccine (24 antigens) and 1 varicella vaccine (69 antigens)=193 antigens and be considered fully-vaccinated. In our study, the maximum number of cumulative vaccines antigens a child could have received between birth and age 23 months is 435: 4 hepatitis B vaccines (4 x 1 antigens), 4 diphtheria-tetanus-pertussis vaccines (4 x 6 antigens), 4 *Haemophilus influenzae type b* vaccines (4 x 2 antigens), 4 pneumococcal conjugate vaccines against 13 types of pneumococcal bacteria (4 x 14 antigens), 3 polio vaccines (3 x 15 antigens), 3 rotavirus vaccines (3 x 16 antigens), 2 Hepatitis A vaccines (2 x 4 antigens), 4 quadrivalent seasonal influenza vaccines (4 x 14 antigens), 2 measles-mumps-rubella vaccines (2 x 24 antigens), and 2 varicella vaccines (2 x 69 antigens). Per the Advisory Committee on Immunization Practices schedule, one dose of the measles-mumps-rubella and one dose of the varicella vaccine are recommended at age 12 months, and the second doses for each vaccine is recommended at ages 4 to 6 years. However, children can receive these second doses earlier, provided at least 4 weeks has elapsed since the first measles-mumps-rubella vaccine dose and 3 months has elapsed since the first varicella vaccine dose (Online-only Supplement reference 4).

[b] References for antigen amounts are Online-only Supplement references 5 and 6.

eTable 4. Common Combinations of Estimated Cumulative Vaccine Antigen Exposure From Birth Through 23 Months, by Decile of Exposure

Decile and Range of Estimated Cumulative Antigen Exposure (Number of children in decile)	**Examples of common combinations of estimated cumulative vaccine exposure (Number of children with that combination)** [a]
Decile 1: 0 – 198 antigens (n= 91)	Example 1 (n=11): 3 hepatitis B vaccines (3 x 1 antigen), 4 DTaP vaccines (4 x 5 antigens), 3 PCV7 vaccines (3 x 8 antigens), 4 Hib vaccines (4 x 2 antigens), 3 polio vaccines (3 x 15 antigens), 1 MMR vaccine (24 antigens), and 1 varicella vaccine (69 antigens) = 193 cumulative vaccine antigens Example 2 (n=8): 3 hepatitis B vaccines (3 x 1 antigen), 4 DTaP vaccines (4 x 5 antigens), 3 PCV7 vaccines (3 x 8 antigens), 3 Hib vaccines (3 x 2 antigens), 3 polio vaccines (3 x 15 antigens), 1 MMR vaccine (24 antigens), and 1 varicella vaccine (69 antigens) = 191 cumulative vaccine antigens
Decile 2: 199 – 205 antigens (n= 97)	Example 3 (n=20): 3 hepatitis B vaccines (3 x 1 antigens), 4 DTaP vaccines (4 x 5 antigens), 4 PCV7 vaccines (4 x 8 antigens), 3 Hib vaccines (3 x 2 antigens), 3 polio vaccines (3 x 15 antigens), 1 MMR vaccine (24 antigens), 1 varicella vaccine (69 antigens) = 199 cumulative vaccine antigens Example 4 (n=17): 3 hepatitis B vaccines (3 x 1 antigens), 4 DTaP vaccines (4 x 5 antigens), 4 PCV7 vaccines (4 x 8 antigens), 4 Hib vaccines (4 x 2 antigens), 3 polio vaccines (3 x 15 antigens), 1 MMR vaccine (24 antigens), 1 varicella vaccine (69 antigens), and 1 hepatitis A vaccine (4 antigens) = 205 cumulative vaccine antigens
Decile 3: 206-215 antigens (n= 100)	Example 5 (n=22): 3 hepatitis B vaccines (3 x 1 antigens), 4 DTaP vaccines (4 x 5 antigens), 4 PCV7 vaccines (4 x 8 antigens), 3 Hib vaccines (3 x 2 antigens), 3 polio vaccines (3 x 15 antigens), 1 MMR vaccine (24 antigens), 1 varicella vaccine (69 antigens), and 1 trivalent seasonal influenza vaccine (12 antigens) = 211 cumulative vaccine antigens Example 6 (n= 13) 4 hepatitis B vaccines (4 x 1 antigens), 4 DTaP vaccines (4 x 5 antigens), 4 PCV7 vaccines (4 x 8 antigens), 3 Hib vaccines (3 x 2 antigens), 3 polio vaccines (3 x 15 antigens), 1 MMR vaccine (24 antigens), 1 varicella vaccine (69 antigens), and 1 trivalent seasonal influenza vaccine (12 antigens) = 212 cumulative vaccine antigens

eTable 4, cont.

Decile and Range of Estimated Cumulative Antigen Exposure (Number of children in decile)	Examples of common combinations of cumulative vaccine exposure (Number of children with that combination)
Decile 4: 216 – 224 antigens (n= 79 children)	Example 7 (n=24): 3 hepatitis B vaccines (3 x 1 antigens), 4 DTaP vaccines (4 x 5 antigens), 4 PCV7 vaccines (4 x 8 antigens), 3 Hib vaccines (3 x 2 antigens), 3 polio vaccines (3 x 15 antigens), 1 MMR vaccine (24 antigens), 1 varicella vaccine (69 antigens), and 2 trivalent seasonal influenza vaccines (2 x 12 antigens) = 223 cumulative vaccine antigens Example 8 (n=16): 4 hepatitis B vaccines (4 x 1 antigens), 4 DTaP vaccines (4 x 5 antigens), 4 PCV7 vaccines (4 x 8 antigens), 3 Hib vaccines (3 x 2 antigens), 3 polio vaccines (3 x 15 antigens), 1 MMR vaccine (24 antigens), 1 varicella vaccine (69 antigens), 1 hepatitis A vaccine (4 antigens), and 1 trivalent seasonal influenza vaccines (12 antigens) = 216 cumulative vaccine antigens
Decile 5: 225 – 235 antigens (n= 105)	Example 9 (n=19): 3 hepatitis B vaccines (3 x 1 antigens), 4 DTaP vaccines (4 x 5 antigens), 4 PCV7 vaccines (4 x 8 antigens), 4 Hib vaccines (4 x 2 antigens), 3 polio vaccines (3 x 15 antigens), 1 MMR vaccine (24 antigens), 1 varicella vaccine (69 antigens), and 2 trivalent seasonal influenza vaccines (2 x 12 antigens) = 225 cumulative vaccine antigens Example 10 (n=15): 3 hepatitis B vaccines (3 x 1 antigens), 4 DTaP vaccines (4 x 5 antigens), 4 PCV7 vaccines (4 x 8 antigens), 4 Hib vaccines (4 x 2 antigens), 3 polio vaccines (3 x 15 antigens), 1 MMR vaccine (24 antigens), 1 varicella vaccine (69 antigens), 1 hepatitis A vaccine, and 2 trivalent seasonal influenza vaccines (2 x 12 antigens) = 229 cumulative vaccine antigens
Decile 6: 236 – 253 antigens (n= 93)	Example 11 (n=14): 4 hepatitis B vaccines (4 x 1 antigens), 4 DTaP vaccines (4 x 5 antigens), 4 PCV7 vaccines (4 x 8 antigens), 3 Hib vaccines (3 x 2 antigens), 3 polio vaccines (3 x 15 antigens), 1 MMR vaccine (24 antigens), 1 varicella vaccine (69 antigens), and 3 trivalent seasonal influenza vaccine (3 x 12 antigens) = 236 cumulative vaccine antigens Example 12 (n=11): 3 hepatitis B vaccines (3 x 1 antigens), 4 DTaP vaccines (4 x 5 antigens), 4 PCV7 vaccines (4 x 8 antigens), 4 Hib vaccines (4 x 2 antigens), 3 polio vaccines (3 x 15 antigens), 1 MMR vaccine (24 antigens), 1 varicella vaccine (69 antigens), 1 hepatitis A vaccine (4 antigens) and 3 trivalent seasonal influenza vaccine (3 x 12 antigens) = 241 cumulative vaccine antigens

eTable 4, cont.

Decile and Range of Estimated Cumulative Antigen Exposure (Number of children in decile)	Examples of common combinations of cumulative vaccine exposure (Number of children with that combination)
Decile 7: 254 – 276 antigens (n= 102)	Example 13 (n=9): 3 hepatitis B vaccines (3 x 1 antigen), 3 DTaP vaccines with 6 antigens (3 x 6 antigens), 1 DTaP vaccines with 5 antigens, 4 PCV7 vaccines (4 x 8 antigens), 4 Hib vaccines (4 x 2 antigens), 3 polio vaccines (3 x 15 antigens), 2 rotavirus vaccines (2 x 16 antigens), 1 MMR vaccine (24 antigens), 1 varicella vaccine (69 antigens), 2 hepatitis A vaccines (2 x 4 antigens), and 2 trivalent seasonal influenza vaccines (2 x 12 antigens) = 268 cumulative vaccine antigens Example 14 (n=7): 4 hepatitis B vaccines (4 x 1 antigens), 4 DTaP vaccines (4 x 5 antigens), 4 PCV7 vaccines (4 x 8 antigens), 3 Hib vaccines (3 x 2 antigens), 3 polio vaccines (3 x 15 antigens), 3 rotavirus vaccines (3 x 16 antigens), 1 MMR vaccine (24 antigens), 1 varicella vaccine (69 antigens), 1 hepatitis A vaccine (4 antigens), and 2 trivalent seasonal influenza vaccines (2 x 12 antigens) = 276 cumulative vaccine antigens
Decile 8: 277 – 292 antigens (n= 83)	Example 15 (n=5) 4 hepatitis B vaccines (4 x 1 antigen), 4 DTaP vaccines (4 x 5 antigens), 4 PCV7 vaccines (4 x 8 antigens), 4 Hib vaccines (4 x 2 antigens), 3 polio vaccines (3 x 15 antigens), 3 rotavirus vaccines (3 x 16 antigens), 1 MMR vaccine (24 antigens), 1 varicella vaccine (69 antigens), 2 hepatitis A vaccines (2 x 4 antigens), and 2 trivalent seasonal influenza vaccines (2 x 12 antigens)= 282 cumulative vaccine antigens Example 16 (n=4) 4 hepatitis B vaccines (4 x 1 antigen), 4 DTaP vaccines (4 x 5 antigens), 4 PCV13 vaccines (4 x 14 antigens), 4 Hib vaccines (4 x 2 antigens), 3 polio vaccines (3 x 15 antigens), 3 rotavirus vaccines (3 x 16 antigens), 1 MMR vaccine (24 antigens), 1 varicella vaccine (69 antigens), and 1 hepatitis A vaccine (4 antigens) = 278 cumulative vaccine antigens
Decile 9: 293 – 305 antigens (n= 94)	Example 17 (n=9) 3 hepatitis B vaccines (3 x 1 antigen), 3 DTaP vaccines with 6 antigens (3 x 6 antigens), 1 DTaP vaccines with 5 antigens, 4 PCV13 vaccines (4 x 14 antigens), 4 Hib vaccines (4 x 2 antigens), 3 polio vaccines (3 x 15 antigens), 2 rotavirus vaccines (2 x 16 antigens), 1 MMR vaccine (24 antigens), 1 varicella vaccine (69 antigens), 2 hepatitis A vaccines (2 x 4 antigens), and 3 trivalent seasonal influenza vaccines (3 x 12 antigens) = 304 cumulative vaccine antigens Example 18 (n=6) 3 hepatitis B vaccines (3 x 1 antigen), 4 DTaP vaccines with 6 antigens (4 x 6 antigens), 4 PCV13 vaccines (4 x 14 antigens), 4 Hib vaccines (4 x 2 antigens), 3 polio vaccines (3 x 15 antigens), 3 rotavirus vaccines (3 x 16 antigens), 1 MMR vaccine (24 antigens), 1 varicella vaccine (69 antigens), 1 hepatitis A vaccines (1 x 4 antigens), and 2 trivalent seasonal influenza vaccines (2 x 12) = 305 cumulative vaccine antigens

eTable 4, cont.

Decile and Range of Estimated Cumulative Antigen Exposure (Number of children in decile)	Examples of common combinations of cumulative vaccine exposure (Number of children with that combination)
Decile 10: 306 – 399 antigens (n= 100)	Example 19 (n=12) 3 hepatitis B vaccines (3 x 1 antigen), 4 DTaP vaccines with 6 antigens (4 x 6 antigens), 4 PCV13 vaccines (4 x 14 antigens), 4 Hib vaccines (4 x 2 antigens), 3 polio vaccines (3 x 15 antigens), 3 rotavirus vaccines (3 x 16 antigens), 1 MMR vaccine (24 antigens), 1 varicella vaccine (69 antigens), 1 hepatitis A vaccines (1 x 4 antigens), and 3 trivalent seasonal influenza vaccines (3 x 12) = 317 cumulative vaccine antigens Example 20 (n=10) 3 hepatitis B vaccines (3 x 1 antigen), 3 DTaP vaccines with 6 antigens (3 x 6 antigens), 1 DTaP vaccine with 5 antigens (1 x 5 antigens), 4 PCV13 vaccines (4 x 14 antigens), 4 Hib vaccines (4 x 2 antigens), 3 polio vaccines (3 x 15 antigens), 2 rotavirus vaccines (2 x 16 antigens), 1 MMR vaccine (24 antigens), 1 varicella vaccine (69 antigens), 2 hepatitis A vaccines (2 x 4 antigens), 1 trivalent seasonal influenza vaccines (1 x 12 antigens), 2 quadrivalent influenza vaccines (2 x 14 antigens) = 308 cumulative vaccine antigens

Abbreviations: DTaP, diphtheria-tetanus-acellular pertussis vaccine; PCV7, pneumococcal conjugate vaccine against 7 types of pneumococcal bacteria; PCV13, pneumococcal conjugate vaccine against 13 types of pneumococcal bacteria; Hib; *Haemophilus influenzae type b* vaccine; MMR; measles-mumps-rubella vaccine

[a] Doses of Hepatitis B, DTaP, Hib, polio, MMR and varicella vaccines may have been given individually or as part of a combination vaccine.

eTable 5. Estimated Cumulative Vaccine Antigen Amounts From Birth Through 23 Months, by Birth Year Period

Birthyear period:	**OVERALL: All birthyears combined**	**EARLY[a] 2003-2005**	**MIDDLE[a] 2006-2008**	**LATE[a] 2009-2013**
	N *Mean estimated cumulative antigens (sd)*	n (row %) *Mean estimated cumulative antigens (sd)*		
In study-eligible cohort	N=495,193 *254.6 (53.6)*	n=128,602 (26.0%) *209.9 (31.0)*	n=139,374 (28.2%) *250.8 (47.5)*	n=227,217 (45.9%) *282.2 (49.3)*
Among electronically-identified cases	N=47,061 *256.6 (50.8)*	n=11,463 (24.4%) *211.6 (28.1)*	n=14,600 (31.0%) *252.5 (45.2)*	n=20,998 (44.6%) *283.9 (45.6)*
Among cases sampled for review	N=385 *243.7 (50.2)*	n=147 (38.2%) *212.6 (25.2)*	n=118 (30.7%) *245.4 (46.2)*	n=120 (31.2%) *279.7 (52.7)*
Among confirmed cases	N=193 *240.6 (48.3)*	n=90 (46.6%) *216.4 (15.5)*	n=48 (24.9%) *242.3 (50.9)*	n=55 (28.5%) *278.7 (56.5)*

Abbreviations: sd=standard deviation

[a]We divided the study follow-up time into early, middle and late periods based on the additions of newer vaccines to the recommended U.S. Advisory Committee on Immunization Practices vaccination schedule. Early period included the expansion of the influenza vaccine recommendations (2004); middle period included the reintroduction of the rotavirus vaccine (2006) and expansion of the Hepatitis A recommendations (2006); late period included the addition of the H1N1 vaccine (2009) and pneumococcal conjugate vaccine (PCV13, 2010) (Online-only supplement references 7-11).

eTable 6. Quantitative Bias Analysis for Potential Exposure Misclassification

eTable 6a: Potential misclassification of estimated cumulative vaccine antigen exposure from birth through 23 months

		True cumulative vaccine antigen exposure	
		199 – 399 antigens	0 – 198 antigens
Observed in Vaccine Safety Datalink data	Top 90% of exposure: 199 – 399 antigens	True Positives (TP)	False Positives (FP)[b]
	Bottom 10% of exposure: 0 - 198 antigens	False Negatives (FN)[a]	True Negatives (TN)

[a]Due to children possibly receiving vaccines outside of the Vaccine Safety Datalink site, we may have exposure false negatives which would lead to imperfect exposure sensitivity: TP/(TP+FN).
[b]We assume that there are no exposure false positives. That is, if a child has immunization records indicating receipt of most or all recommended vaccines, those records are likely correct. Therefore, we assume perfect exposure specificity.

eTable 6b: Quantitative bias analysis[a] for potential exposure misclassification in estimating the association between estimated cumulative vaccine antigen exposure from birth through 23 months[b] and non-vaccine-targeted infections in inpatient and emergency department settings in ages 24 through 47 months

Non-differential exposure sensitivity	**Corrected odds ratio (95% confidence interval)**
100% - *No exposure misclassification*	1.13 (95% CI: 0.65 – 1.97)
99.0%	1.15 (95% CI: 0.62 – 2.12)
97.5%	1.18 (95% CI: 0.56 – 2.49)
95.0%	1.29 (95% CI: 0.39 – 4.23)
92.5%	1.82 (95% CI: 0.07 – 46.30)
90.0%	N/A: Exposure sensitivity levels ≤ 90% are not plausible in our data since these levels would lead to no individuals observed in the 0-198 range of vaccine antigen exposure.

[a]Using quantitative bias analysis methodology described by Lash, Fox and Fink (Online-only Supplement reference 12)

[b]In these analyses, the exposed group is children in the top 90% of exposure to estimated cumulative vaccine antigen exposure from birth through 23 months, and the reference group is children in the bottom 10% of exposure to estimated cumulative vaccine antigen exposure from birth through 23 months.

eTable 7. Association Between Estimated Vaccine Antigen Exposure and Non-Vaccine-Targeted Infections, With Exposures as Estimated Cumulative Vaccine Antigens From Birth Through 23 Months and Estimated Cumulative Vaccine Antigens From Birth Through Index Date (Primary and Secondary Analyses)[a]

Description of Analysis	Number of cases matched to ≥ 1 control	Total number of matched controls	Exposure: Estimated cumulative vaccine antigens from birth through 23 months			Exposure: Estimated cumulative vaccine antigens from birth to index date of non-vaccine-targeted infection in case		
			Mean (std), among cases	Mean (std), among controls	Matched odds ratios(mOR)[b] (95% confidence interval)	Mean (std), among cases	Mean (std), among controls	Matched odds ratio(mOR)[b] (95% confidence interval)
Primary Analysis								
Confirmed cases matched to controls without a non-vaccine-targeted infection diagnosis in an inpatient or emergency department setting.[c] Matching variables: sex, Vaccine Safety Datalink site, chronic condition status, and birthdate (± 2 weeks).	193	751	240.6 (48.3)	242.9 (51.1)	mOR – 1 unit: 0.998 (0.994 - 1.002) mOR – 30 units: 0.94 (0.84 – 1.07)	252.3 (48.1)	252.9 (52.4)	mOR– 1 unit: 0.999 (0.995 - 1.003) mOR – 30 units: 0.98 (0.86 – 1.10)
Secondary Analyses								
Same as primary analysis, but also excluding controls with non-vaccine-targeted diagnosis in an urgent care setting.[d]	174	668	239.0 (49.1)	240.3 (53.0)	mOR– 1 unit: 0.999 (0.995 – 1.003) mOR – 30 units: 0.97 (0.86 – 1.10)	250.6 (48.3)	250.2 (54.0)	mOR– 1 unit: 1.000 (0.996 – 1.004)* mOR – 30 units: 1.00 (0.89 – 1.13)*
Same as primary analysis, but also excluding controls with non-vaccine-targeted diagnosis in an urgent care setting and matching on race/ethnicity.[d,e]	145	525	242.4 (47.2)	243.4 (51.3)	mOR– 1 unit: 0.999 (0.995 – 1.004) mOR – 30 units: 0.98 (0.85 – 1.13)	253.6 (47.6)	253.2 (53.4)	mOR– 1 unit: 1.000 (0.995 – 1.004) mOR – 30 units: 0.99 (0.86 – 1.14)

eTable 7, continued

Description of Analysis	Number of cases matched to ≥ 1 control	Total number of matched controls	Exposure: Estimated cumulative vaccine antigen exposure from birth to age 23 months			Exposure: Estimated cumulative vaccine antigen exposure from birth to index date of non-vaccine-targeted infection in case		
			Mean (std), among cases	Mean (std), among controls	Matched odds ratios(mOR)[b] (95% confidence interval)	Mean (std), among cases	Mean (std), among controls	Matched odds ratios(mOR)[b] (95% confidence interval)
Confirmed cases matched to controls with an emergency department visit for an injury from 24 through 47 months.[f] Matching variables: sex, Vaccine Safety Datalink site, chronic condition status and birthdate (± 2 weeks).	168	579	241.8 (46.7)	244.2 (48.8)	mOR– 1 unit: 0.999 (0.995 – 1.004) mOR – 30 units: 0.98 (0.85 – 1.13)	253.6 (46.1)	255.0 (50.7)	mOR– 1 unit: 1.000 (0.995 – 1.004) mOR – 30 units: 0.99 (0.86 – 1.14)
Confirmed cases matched to controls with an emergency department visit for an injury from 24 through 47 months. Matching variables: sex, Vaccine Safety Datalink site, chronic condition status, birthdate (± 2 weeks), and race/ethnicity.[e,f,g]	114	339	243.7 (47.4)	245.2 (47.9)	mOR– 1 unit: 1.001 (0.994 – 1.008) mOR – 30 units: 1.03 (0.85 – 1.25)	254.8 (47.9)	255.4 (48.4)	mOR– 1 unit: 1.001 (0.995 – 1.007) mOR – 30 units: 1.03 (0.85 – 1.25)

Abbreviations: std, standard deviation; mOR – 1 unit, matched odds ratio with exposure of estimated cumulative vaccine antigen exposure unscaled ; mOR – 30 units, matched odds ratio with estimated cumulative vaccine antigen exposure scaled to 30 unit increments.

[a] For the exposure of estimated cumulative vaccine antigens from birth to index date of non-vaccine-targeted infection in case, vaccine antigens were summed from the child's birthdate through the index date of confirmed non-vaccine-targeted infection in the matched case.

[b] Cases and controls were analyzed with conditional logistic regression to estimate matched odds ratios and 95% confidence intervals. In the models, the dependent variable was case status (yes/no), and the main exposure variable was either estimated cumulative vaccine antigen exposure from birth through 23 months or estimated cumulative vaccine antigen

exposure from birth through the index date of non-vaccine-targeted infection in case. All models were adjusted for the number of outpatient visits from birth through age 23 months. For all models except for the one indicated with a *, the Hosmer-Lemeshow goodness of fit test indicated adequate model fit (p>0.05). For the model with a *, the model was run again with a log-transformation of the exposure variable of estimated cumulative vaccine antigen exposure from birth to index date of non-vaccine-targeted infection in case. In this model, the association was non-significant (OR for log-transformed predictor variable, unscaled: 1.20 [95% confidence interval: 0.69 – 2.09]), and the Hosmer-Lemeshow test indicated adequate model fit (p=0.18). For all models, Box-Tidwell tests did not indicate deviation from linearity of the logit (p>0.05 for all models).

[c] Risk set sampling was used for case-control matching. For the primary analysis, eligible controls were randomly selected from the cohort and did not have an inpatient or emergency department record of a non-vaccine-targeted infection prior to the index date. Both cases and controls were required to be continuously enrolled in the integrated health plan through the index date.

[d] Risk set sampling was used for case-control matching. For this secondary analysis, eligible controls were randomly selected from the cohort and did not have an inpatient, emergency department, or urgent care record of a non-vaccine-targeted infection from 24 through 47 months prior to the index date. Cases with an urgent care visit for a non-vaccine - targeted infection prior to their emergency department or inpatient visit for non-vaccine-targeted infection were excluded from analysis (n=19).

[e] Race/ethnicity was categorized into six mutually exclusive groups: Hispanic, any race (n=40, 20.7% of cases); White (n=97, 50.3% of cases); Black (n=9, 4.7% of cases); Asian (n=11, 5.7% of cases); Multiracial (n=10, 5.2% of cases); or Other reported race (n=1, 0.5% of cases). Race/ethnicity was missing for n=25 cases (13.0% of cases). In this analysis, n=19 cases were first excluded due to having an urgent care visit for a non-vaccine-targeted infection prior to their emergency department or inpatient visit for non-vaccine-targeted infection, and an additional n=21 cases were then excluded due to missing race. An additional n=8 cases had race/ethnicity data available, but no eligible control match, and were excluded from analysis.

[f] Risk set sampling was used for case-control matching. For this secondary analysis, controls were selected from a subset of cohort members who had an emergency department visit for an injury from 24 through 47 months. This subset of controls consisted of n=53,215 children (10.7% of the initial study cohort). Emergency department visits for injuries were identified using International Classification of Diseases (ICD), 9th addition, Clinical Modification (ICD-9-CM codes) 800.x – 999.x, excluding 960.x – 979.x. The corresponding ICD-10 codes were also identified for encounters from October through December 2015. These codes represent encounters for fractures; dislocations; sprains and strains of joins and adjacent muscles; intracranial injuries; internal injuries of thorax, abdomen and pelvis; open wounds; injury to blood vessels; late effects of injuries, poisoning, toxic effects and other external causes; superficial injuries; contusions; foreign bodies; burns; other injuries; certain traumatic complications and unspecified injuries; toxic effects of substances chiefly nonmedicinal as to source; other and unspecified effects of external causes; and complications of surgical and medical care, not elsewhere classified.

[g] In this analysis, n=25 children did not have any eligible matches from the control group regardless of the race/ethnicity matching criterion; race/ethnicity was missing for an additional n=23 cases, and an additional n=31 cases did have race/ethnicity data but did not have a match based on other matching criteria. These n=79 cases without a control match were excluded from analysis.

eTable 8. Association Between Estimated Vaccine Antigen Exposure and Non-Vaccine-Targeted Infections, With Exposures as Estimated Maximum Single-Day Vaccine Antigens From Birth Through 23 months and Estimated Maximum Single-Day Vaccine Antigens From Birth Through Index Date (Primary and Secondary Analyses)[a]

Description of Analysis	Number of cases matched to ≥ 1 control	Total number of matched controls	Exposure: Estimated maximum single day vaccine antigens from birth to age 23 months			Exposure: Estimated maximum single-day vaccine antigens from birth to index date of non-vaccine-targeted infection in case		
			Mean (std), among cases	Mean (std), among controls	Matched odds ratios(mOR)[b] (95% confidence interval)	Mean (std), among cases	Mean (std), among controls	Matched odds ratio(mOR)[b] (95% confidence interval)
Primary Analysis								
Confirmed cases matched to controls without a non-vaccine-targeted infection diagnosis in an inpatient or emergency department setting.[c] Matching variables: sex, Vaccine Safety Datalink site, chronic condition status, and birthdate (± 2 weeks).	193	751	101.0 (18.4)	100.5 (18.9)	mOR– 1 unit: 1.002 (0.993 – 1.012) mOR – 30 units: 1.07 (0.81 – 1.41)	102.1 (16.5)	100.8 (18.0)	mOR– 1 unit: 1.005 (0.995 – 1.016) mOR – 30 units: 1.17 (0.86 – 1.60)
Secondary Analyses								
Same as primary analysis, but also excluding controls with non-vaccine-targeted diagnosis in an urgent care setting.[d]	174	668	100.5 (18.9)	99.7 (19.7)	mOR – 1 unit: 1.003 (0.994 – 1.013) mOR – 30 units: 1.10 (0.83 – 1.47)	101.7 (17.0)	100.4 (18.3)	mOR – 1 unit: 1.006 (0.995 – 1.016) mOR – 30 units: 1.19 (0.87 – 1.63)
Same as primary analysis, but also excluding controls with non-vaccine-targeted diagnosis in an urgent care setting and matching on race/ethnicity.[d,e]	145	525	101.6 (17.9)	100.4 (19.4)	mOR – 1 unit: 1.006 (0.994 – 1.018) mOR – 30 units: 1.19 (0.84 – 1.69)	102.4 (16.3)	100.8 (18.4)	mOR – 1 unit: 1.008 (0.995 – 1.021) mOR – 30 units: 1.25 (0.85 – 1.84)

eTable 8, continued

Description of Analysis	Number of cases matched to ≥ 1 control	Total number of matched controls	Exposure: Maximum single day vaccine antigens from birth to age 23 months			Exposure: Maximum single day vaccine antigens from birth to index date of non-vaccine-targeted infection in case		
			Mean (std), among cases	Mean (std), among controls	Matched odds ratios(mOR)[b] (95% confidence interval)	Mean (std), among cases	Mean (std), among controls	Matched odds ratios(mOR)[b] (95% confidence interval)
Confirmed cases matched to controls with an emergency department visit for an injury from 24 through 47 months.[f] Matching variables: sex, Vaccine Safety Datalink site, chronic condition status and birthdate (± 2 weeks).	168	579	101.8 (16.8)	101.5 (18.5)	mOR – 1 unit: 1.004 (0.994 – 1.015) mOR – 30 units: 1.14 (0.83 – 1.57)	103.0 (14.5)	101.9 (17.6)	mOR – 1 unit: 1.009 (0.996 – 1.021) mOR – 30 units: 1.29 (0.89 – 1.87)
Confirmed cases matched to controls with an ED visit for an injury from 24 through 47 months. Matching variables: sex, Vaccine Safety Datalink site, chronic condition status, and birthdate (± 2 weeks), and race/ethnicity.[e,f,g]	114	339	102.0 (16.8)	101.9 (18.5)	mOR – 1 unit: 1.004 (0.990 – 1.017) mOR – 30 units: 1.12 (0.75 – 1.68)	102.7 (15.2)	102.4 (17.2)	mOR – 1 unit: 1.005 (0.990 – 1.020) mOR – 30 units: 1.15 (0.74 – 1.79)

Abbreviations: std, standard deviation; mOR – 1 unit, matched odds ratio with exposure of estimated maximum single day vaccine antigen exposure unscaled; mOR – 30 units, matched odds ratio with exposure of estimated maximum single day vaccine antigen exposure scaled to 30 unit increments.

[a] For the exposure of estimated cumulative vaccine antigens from birth to index date of non-vaccine-targeted infection in case, vaccine antigens were summed from the child's birthdate through the index date of confirmed non-vaccine-targeted infection in the matched case.

[b] Cases and controls were analyzed with conditional logistic regression to estimate matched odds ratios (mOR) and 95% confidence intervals. In the models, the dependent variable was case status (yes/no), and the main exposure variable was either estimated maximum single day vaccine antigen exposure before the child's 2nd birthday or estimated maximum single day vaccine antigen exposure from birth to index date of non-vaccine-targeted infection in case. We present these results with the exposure variables unscaled, and also with

the exposure variables scaled to 30 unit increments of vaccine antigen exposure. All models were adjusted for the number of outpatient visits from birth through age 23 months. For all models, the Hosmer-Lemeshow goodness of fit test indicated adequate model fit ($p>0.05$) and Box-Tidwell test did not indicate deviation from linearity of the logit ($p>0.05$ for all models).

[c] Risk set sampling was used for case-control matching. For the primary analysis, eligible controls were randomly selected from the cohort and did not have an inpatient or emergency department record of a non-vaccine-targeted infection prior to the index date.

[d] Risk set sampling was used for case-control matching. For this secondary analysis, eligible controls were randomly selected from the cohort and did not have an inpatient, emergency department, or urgent care record of a non-vaccine-targeted infection from 24 through 47 months prior to the index date. Cases with an urgent care visit for a non-vaccine - targeted infection prior to their emergency department or inpatient visit for non-vaccine-targeted infection were excluded from analysis (n=19).

[e] Race/ethnicity was categorized into six mutually exclusive groups: Hispanic, any race (n=40, 20.7% of cases); White (n=97, 50.3% of cases); Black (n=9, 4.7% of cases); Asian (n=11, 5.7% of cases); Multiracial (n=10, 5.2% of cases); or Other reported race (n=1, 0.5% of cases). Race/ethnicity was missing for n=25 cases (13.0% of cases). In this analysis, n=19 cases were first excluded due to having an urgent care visit for a non-vaccine-targeted infection prior to their emergency department or inpatient visit for non-vaccine-targeted infection, and an additional n=21 cases were then excluded due to missing race. An additional n=8 cases has race/ethnicity data available, but no eligible control match, and were excluded from analysis.

[f] Risk set sampling was used for case-control matching. For this secondary analysis, controls were selected from a subset of cohort members who had an emergency department visit for an injury between 24 through 47 months. This subset of controls consisted of n=53,215 children (10.7% of the initial study cohort). Emergency department visits for injuries were identified using International Classification of Diseases (ICD), 9th addition, Clinical Modification (ICD-9-CM codes) 800.x – 999.x, excluding 960.x – 979.x. The corresponding ICD-10 codes were also identified for encounters from October through December 2015. These codes represent encounters for fractures; dislocations; sprains and strains of joins and adjacent muscles; intracranial injuries; internal injuries of thorax, abdomen and pelvis; open wounds; injury to blood vessels; late effects of injuries, poisoning, toxic effects and other external causes; superficial injuries; contusions; foreign bodies; burns; other injuries; certain traumatic complications and unspecified injuries; toxic effects of substances chiefly nonmedicinal as to source; other and unspecified effects of external causes; and complications of surgical and medical care, not elsewhere classified.

[g] In this analysis, n=25 children did not have any eligible matches from the control group regardless of the race/ethnicity matching criterion; race/ethnicity was missing for an additional n=23 cases, and an additional n=31 cases did have race/ethnicity data but did not have a match based on other matching criteria. These n=79 cases without a control match were excluded from analysis.

eTable 9. Association Between Estimated Vaccine Antigen Exposure and Non-Vaccine-Targeted Infections, With Exposures as Estimated Cumulative Vaccine Antigens and Estimated Maximum Single-Day Vaccine Antigens From Birth Through 23 Months, (a) Stratified by Chronic Condition Status, (b) Stratified by Outcome Setting, (c) Excluding Children Who Did Not Receive Varicella Vaccination, and (d) Excluding Children Who Received No Vaccines From Birth Through 23 Months (Secondary Analyses)

Description of Secondary Analysis	Number of cases with ≥ 1 match to control	Total number of controls matched to a case	Exposure: Estimated cumulative vaccine antigen exposure from birth through 23 months			Exposure: Estimated maximum single-day vaccine antigens from birth through 23 months		
			Mean (std), among cases	Mean (std), among controls	Matched odds ratio[a] (95% confidence interval)	Mean (std), among cases	Mean (std), among controls	Matched odds ratio[a] (95% confidence interval)
(a) Stratified by chronic condition								
Same as primary analysis[b], but restricted only to children without a chronic condition	140	560	242.9 (46.3)	243.8 (52.6)	mOR – 1 unit: 0.999 (0.994 – 1.003) mOR – 30 units: 0.97 (0.84 – 1.11)	101.9 (17.0)	100.7 (19.2)	mOR – 1 unit: 1.003 (0.992 – 1.015) mOR – 30 units: 1.11 (0.79 – 1.55)
Same as primary analysis[b], but restricted only to children with non-complex or complex chronic conditions	53	191	234.5 (53.3)	240.5 (46.2)	mOR – 1 unit: 0.996 (0.988 – 1.004)* mOR – 30 units: 0.88 (0.69 – 1.12)*	98.7 (21.6)	99.7 (17.8)	mOR – 1 unit: 0.999 (0.982 – 1.016) mOR – 30 units: 0.97 (0.57 – 1.63)
(b) Stratified by outcome setting								
Same as primary analysis[b], but restricted to cases from the inpatient setting[c]	85	331	237.1 (53.4)	242.9 (50.7)	mOR – 1 unit: 0.997 (0.991 – 1.002) mOR – 30 units: 0.91 (0.77 – 1.07)	97.9 (21.3)	98.7 (19.2)	mOR – 1 unit: 0.999 (0.987 – 1.011) mOR – 30 units: 0.97 (0.67 – 1.40)

eTable 9, continued

Description of Secondary Analysis	Number of cases with ≥ 1 match to control	Total number of controls matched to a case	Exposure: Estimated cumulative vaccine antigen exposure from birth through 23 months			Exposure: Maximum single day vaccine antigens from birth through 23 months		
			Mean (std), among cases	Mean (std), among controls	Matched odds ratio[a] (95% confidence interval)	Mean (std), among cases	Mean (std), among controls	Matched odds ratio[a] (95% confidence interval)
Same as primary analysis[b], but restricted to cases from the emergency department setting	108	420	243.3 (44.1)	243.0 (51.4)	mOR – 1 unit: 1.000 (0.994 – 1.006) mOR – 30 units: 0.99 (0.83 – 1.18)	103.4 (15.4)	101.8 (18.5)	mOR – 1 unit: 1.006 (0.992 – 1.021) mOR – 30 units: 1.21 (0.78 – 1.89)
(c) Excluding children without varicella vaccination								
Same as primary analysis[b], but excluding children who did not receive varicella vaccine[d]	184	682	246.8 (38.4)	249.4 (41.3)	mOR – 1 unit: 0.992 (0.983 – 1.001) mOR – 30 units: 0.79 (0.60 – 1.03)	104.1 (11.4)	104.0 (11.1)	mOR – 1 unit: 1.002 (0.985 – 1.020) mOR – 30 units: 1.07 (0.63 – 1.81)
(d) Excluding completely unvaccinated children								
Same as primary analysis[b], but excluding children who did not receive any vaccines from birth through 23 months	193	749	240.6 (48.3)	243.6 (49.6)	mOR – 1 unit: 0.998 (0.993 – 1.002) mOR – 30 units: 0.93 (0.82 – 1.05)	101.0 (18.4)	100.7 (18.1)	mOR – 1 unit: 1.001 (0.992 – 1.011) mOR – 30 units: 1.04 (0.78 – 1.39)

Abbreviations: std, standard deviation; mOR – 1 unit, matched odds ratio with exposure of cumulative vaccine antigens or maximum single day vaccine antigens unscaled; mOR – 30 units, matched odds ratio with exposure of estimated cumulative vaccine antigens or maximum single day vaccine antigens exposure scaled to 30 unit increments.

[a] Cases and controls were analyzed with conditional logistic regression to estimate matched odds ratios (mOR) and 95% confidence intervals. In the models, the dependent variable was case status (yes/no), and the main exposure variable was either estimated cumulative vaccine antigen exposure or maximum single day vaccine exposure before the child's 2nd birthday. All models were adjusted for the number of outpatient visits from birth through 23 months. For all models except for the one indicated with a *, the Hosmer-Lemeshow goodness of fit test indicated adequate model fit ($p>0.05$). For the model with a *, the model was run again with a log-transformation of the exposure variable of estimated cumulative vaccine antigen exposure from birth through 23 months. In this model, the association was non-significant (OR for log-transformed exposure variable, unscaled: 0.50 [95% confidence interval: 0.14 – 1.81]), and the Hosmer-Lemeshow test indicated adequate model fit ($p=0.25$). For all models, Box-Tidwell tests did not indicate deviation from linearity of the logit ($p>0.05$ for all models).

[b] The primary analysis consisted of confirmed cases matched to controls without a non-vaccine-targeted infection diagnosis in an inpatient or emergency department setting. Matching variables were: sex, Vaccine Safety Datalink site, chronic condition status, and birthdate (± 2 weeks).

[c] This analysis including 85 inpatient patients had 80% power to detect an odds ratio (scaled to 30 unit increments) of 1.24, calculated assuming an alpha of 0.05, r-squared value of 0.20, a 1:4 case to control ratio and a standard deviation for estimated cumulative vaccine antigen exposure of 1.79. The standard deviation was calculated from the cohort prior to selecting cases and controls, and represents the standard deviation for estimated cumulative antigen exposure scaled to 30 unit increments. The power analysis was conducted using PASS 15.0.2 software (Online-only supplement references 13-15).

[d] In this analysis, matched strata (both the case and matched controls) were removed if the case had not received the varicella vaccine. In other strata, controls who had not received the varicella vaccine were also removed from the analysis.

eTable 10: Race/Ethnicity of Study-Eligible Cohort Members and of Cases and Controls From Secondary Analysis Matching on Race/Ethnicity

		Nested case-control	
	Entire Cohort	**Cases**	**Controls**
	N=495,193	**N=145**[a]	**N=525**
Race/ethnicity	**n (column %)**	**n (column %)**	**n (column %)**
Hispanic, any race	154,818 (31.3%)	39 (26.9%)	147 (28.0%)
White	171,003 (34.5%)	85 (58.6%)	310 (59.1%)
Black	23,453 (4.7%)	6 (4.1%)	14 (2.7%)
Asian	62,872 (12.7%)	8 (5.5%)	32 (6.1%)
Multiracial	11,954 (2.4%)	6 (4.1%)	21 (4.0%)
Other reported race	16,929 (3.4%)	1 (0.7%)	1 (0.2%)
Missing	54,164 (10.9%)	n/a	n/a

[a]The cases and controls presented in this table are from a secondary analysis excluding controls with a non-vaccine-targeted diagnosis in an urgent care setting and matching on race/ethnicity. For this analysis, of the n=193 cases from the primary analysis, n=19 cases were first excluded due to having an urgent care visit for a non-vaccine-targeted infection prior to their emergency department or inpatient visit for a non-vaccine-targeted infection. Then, an additional n=21 cases were excluded due to missing race. An additional n=8 cases had race/ethnicity data available, but no eligible control match. Results from this secondary analysis are shown in eTables 8 and 9.

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