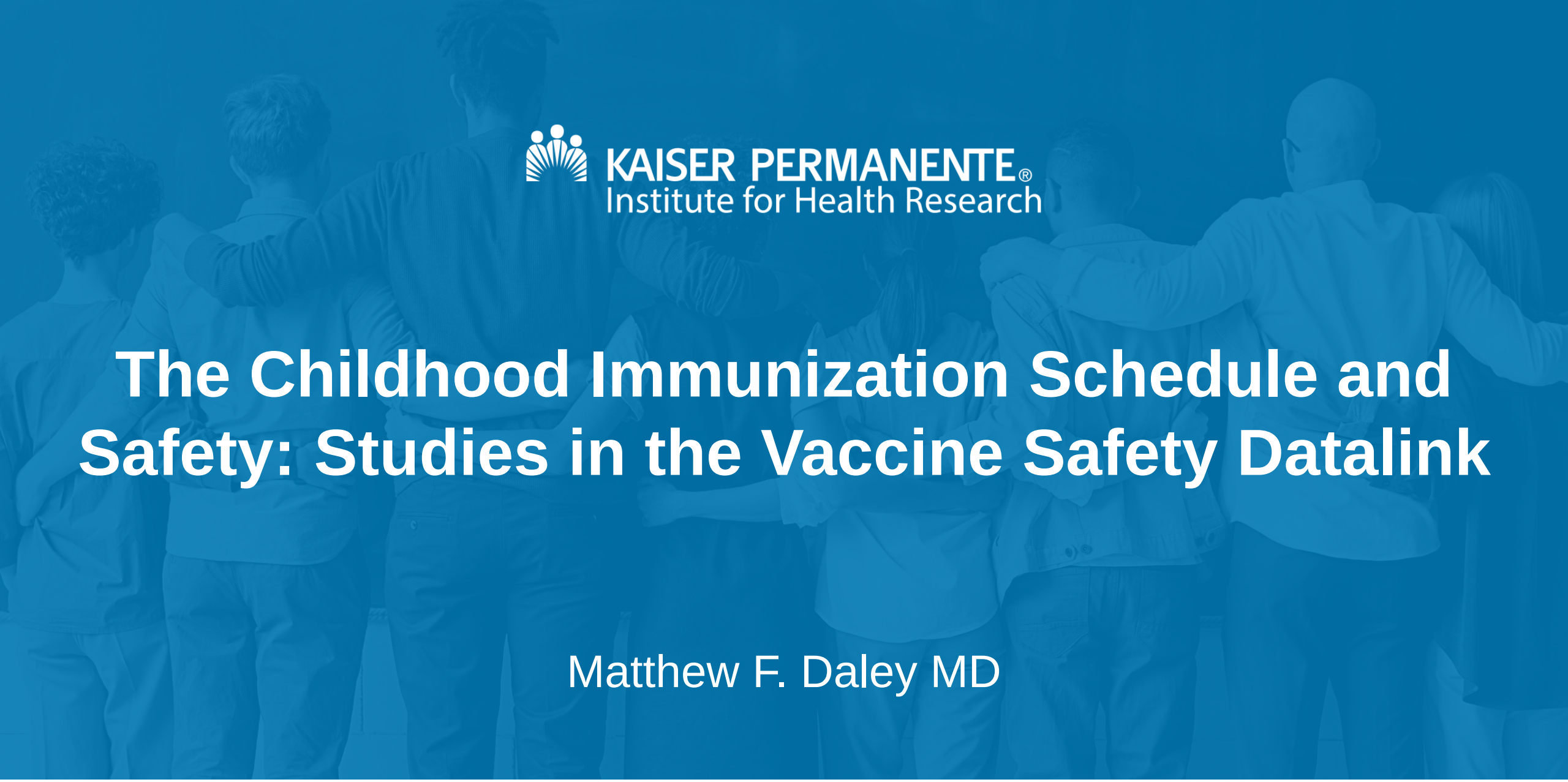

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The Childhood Immunization Schedule and Safety: Studies in the Vaccine Safety Datalink

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Advisory Committee on Immunization Practices, June 23, 2023

Disclaimers

- No conflicts of interest to disclose
- The findings in this presentation are those of the speaker and do not necessarily represent the official position of the Centers for Disease Control and Prevention

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Outline

- 2013 Institute of Medicine* (IOM) Report
- Feasibility work in Vaccine Safety Datalink (VSD)
- Three published VSD studies
  - Antigens and non-targeted infections
  - Schedule and type 1 diabetes (T1DM)
  - Aluminum and asthma
- Future investigations
- Schedule and safety: broader context

*Now referred to as The National Academies of Sciences, Engineering, and Medicine (NASEM)

IOM: The Childhood Immunization Schedule and Safety

- Subtitle: Stakeholder Concerns, Scientific Evidence, and Future Studies
- Existing evidence supported safety of schedule "as a whole"
- Evidence gaps: each new vaccine added to existing schedule; safety studies usually of acute adverse events; long-term health outcomes less well studied
- Committee conclusions:
  - Randomized clinical trials not suitable approach to address research questions about schedule for ethical reasons
  - Observational studies needed in existing surveillance systems (including in VSD)
  - Methods for such studies complex; feasibility work needed
  - Develop metrics for exposure to schedule
  - Focus on long-term outcomes: allergic, autoimmune, neurologic

Ref: Institute of Medicine, National Academies Press, 2013. DOI: 10.17226/13563.

White Paper on Studying Schedule in VSD: Feasibility, Study Design, Outcomes

- VSD: collaboration between CDC and integrated healthcare organizations, conducts vaccine safety surveillance and research
- White Paper objectives:
  - Exposure: define measures of vaccination schedule which could be evaluated, with focus on first 24 months of life
  - Outcomes: identify plausible adverse events, with emphasis on long-term adverse events
  - Key design considerations, analytic approaches
- Potential outcomes prioritized based on feasibility, public health significance, and public concern

Ref: Glanz JM et al, Vaccine. 2016;34 Suppl 1:A1-A29.

White Paper, Additional Conclusions

- High priority outcomes included: allergic disorders (e.g., asthma), autoimmune disease (e.g.,T1DM), neurologic (e.g., epilepsy)
- Some public concerns may have limited biologic plausibility
- Attention to bias, unmeasured confounding
  - Misclassification bias: survey parents of under-vaccinated children
  - Use negative control outcomes (example: injuries)
  - Control for differences in health care utilization
- Plan for a long and complex process; any initial positive associations will need studies to refute or replicate initial findings

Ref: 1) Glanz JM et al, Vaccine. 2016;34 Suppl 1:A1-A29. 2) Daley MF et al, Vaccine. 2017;35(15):1873-1878. 3) Daley MF et al, Acad Pediatr. 2018;18:754-762.

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VSD Study: Antigens and Non-Targeted Infections

- Public concern: early childhood immunization “overloads” immune system
- Design: Matched case-control
- Exposures: cumulative vaccine antigen exposure, estimated by summing number of antigens in each vaccine dose birth through age 23 months
- Outcomes:
  - Non-vaccine-targeted infections in emergency department and inpatient settings from 24 through 47 months of age
  - Manual medical record review validation of sample of outcomes
- Matching: age, sex, presence of chronic disease

Ref: Glanz MF et al, JAMA. 2018;319(9):906-913.

Results: Antigens and Non-Targeted Infections

- Among children with versus without non-vaccine-targeted infections from 24 through 47 months of age, matched odds ratio for cumulative vaccine antigen exposure not significant:
  - Matched odds ratio, 0.94; 95% CI, 0.84 to 1.07
- Secondary analyses: consistent with primary findings
- Conclusions:
  - No association between number of antigens young children receive through vaccines and likelihood of ED or inpatient encounters for infections
  - No evidence schedule “overwhelms” immune system

Ref: Glanz MF et al, JAMA. 2018;319(9):906-913.

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VSD Study: Schedule and Type 1 Diabetes

- Public concern: vaccine antigens and ingredients (including aluminum, used as adjuvant) interfere with immune function, increase risk of autoimmune disease
- Design: retrospective cohort
- Exposures:
  - Cumulative vaccine antigen
  - Cumulative vaccine aluminum
  - Average days under-vaccinated
- Outcome: T1DM, identified using diagnosis codes
- Follow up: Mean length of follow up >5 years
- Analyses adjusted for sex, race and ethnicity, maternal age, birth weight, gestational age, utilization (number of well-child visits)

Ref: Glanz MF et al, Pediatrics. 2021;148(6):e2021051910.

Results: Schedule and Type 1 Diabetes

- Main analyses, three different exposures:
  - Cumulative vaccine antigen non-significant: adjusted hazard ratio 0.98; 95% CI, 0.97–1.00
  - Cumulative vaccine aluminum inversely associated: adjusted hazard ratio 0.77; 95% CI, 0.60–0.99
  - Average days under-vaccinated non-significant: adjusted hazard ratio 1.01; 95% CI, 0.99–1.02
- Sensitivity analyses, factoring in family history T1DM: similar to primary results
- Conclusions:
  - Vaccine schedule not associated with increased risk of T1DM
  - Decreased risk at higher vaccine aluminum exposure: modest effect size; more study needed to refute or replicate this finding

Ref: Glanz MF et al, Pediatrics. 2021;148(6):e2021051910.

VSD Study: Aluminum and Asthma

- Public concern: vaccine ingredients (specifically aluminum, used as adjuvant) increase risk of allergic disorders including asthma
- Biologic plausibility: based on animal data, aluminum in vaccines could “skew” toward T-helper cell 2 (Th2) response; Th2 cells play role in allergic asthma
- Design: retrospective cohort
- Exposure: cumulative vaccine aluminum received birth through 23 months of age
- Outcome: persistent asthma at 24 through 59 months of age
  - One inpatient or two outpatient diagnoses of asthma PLUS
  - One or more prescriptions for a long-term asthma control medication
- All analyses done separately for children with and without eczema

Ref: 1) Baylor NW et al, Vaccine. 2002;20 Suppl 3:S18-23. 2) Goullé JP et al, Med Mal Infect. 2020;50:16-21. 3) Hogenesch H. Front Immunol. 2012;3:406. 4) Sastry M et al, PLoS One. 2017;12:e0186854. 5) Alessandrini F et al, Front Immunol. 2020;11:575936. 6) Daley MF et al, Acad Pediatr. 2023 Jan-Feb;23(1):37-46.

Results: Aluminum and Asthma Study

- N=14337 with eczema: 6.0% developed persistent asthma
- N=312654 without eczema: 2.1% developed persistent asthma
- Median vaccine-associated aluminum:
  - Eczema cohort=4.18 mg
  - No eczema cohort=4.18 mg

Ref: Daley MF et al, Acad Pediatr. 2023 Jan-Feb;23(1):37-46.

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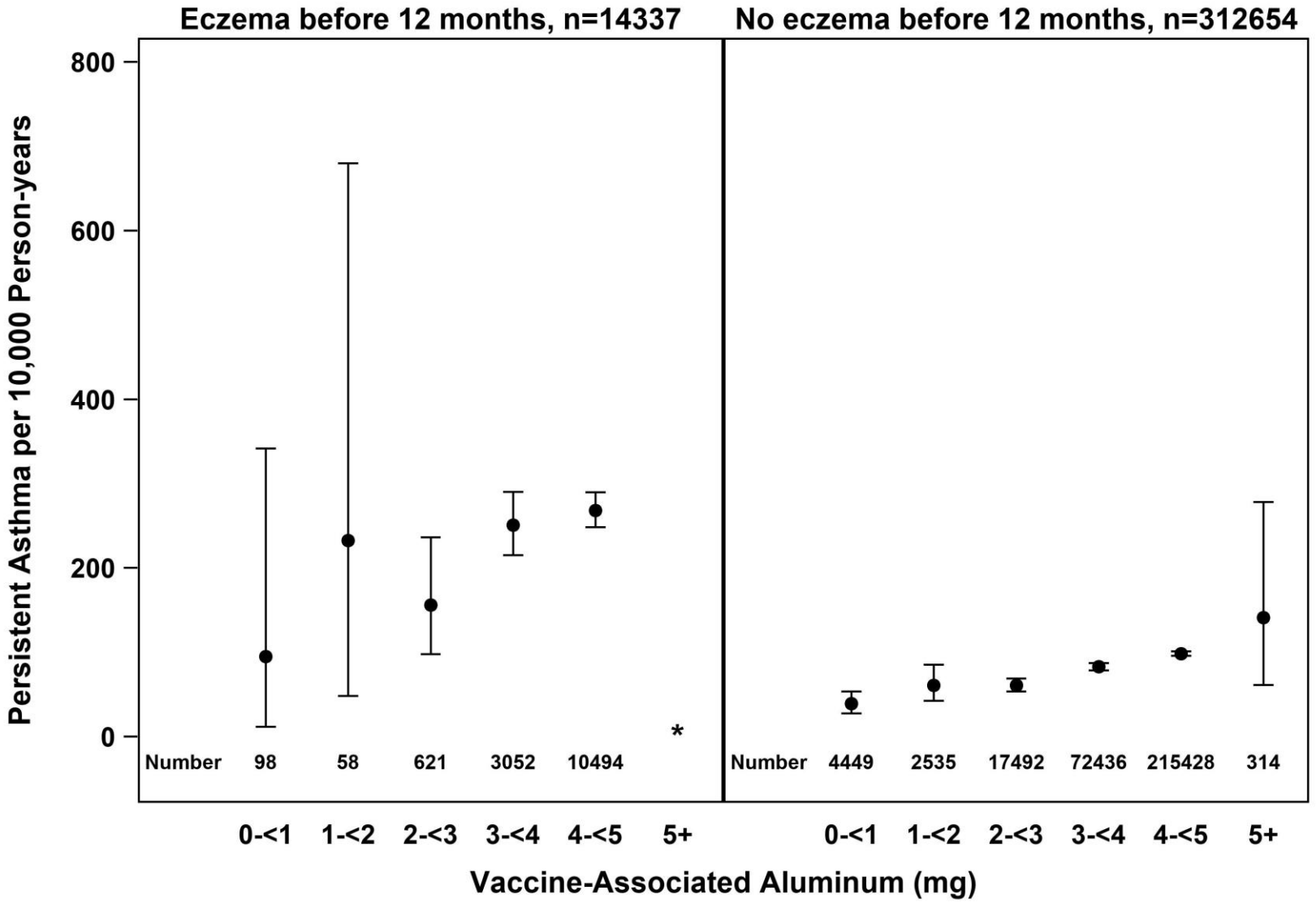
Crude Incidence Rate of Asthma by Quantity of Vaccine-Associated Aluminum



* Sample size n=14, not sufficient to estimate incidence rate and confidence intervals

Ref: Daley MF et al, Acad Pediatr. 2023 Jan-Feb;23(1):37-46.

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Association between Cumulative Vaccine-Associated Aluminum and Persistent Asthma

Variable	Adjusted hazard ratio (95% CI), eczema cohort (n=14337)	Adjusted hazard ratio (95% CI), no eczema cohort (n=312654)
Vaccine-associated aluminum (per mg)	1.26 (1.07, 1.49)	1.19 (1.14, 1.25)
Child's sex		
Female	1 [Ref]	1 [Ref]
Male	1.30 (1.13, 1.50)	1.40 (1.33, 1.47)
Prematurity (EGA)		
Term (≥37 weeks)	1 [Ref]	1 [Ref]
Moderately preterm (32-36 weeks)	1.32 (1.02, 1.72)	1.34 (1.24, 1.46)
Very preterm (<32 weeks)	1.88 (0.82, 4.30)	1.68 (1.39, 2.03)
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)

Notes: Cox proportional hazards analyses; separate models for eczema and no eczema cohorts; other covariates included number of outpatient visits; number of ED visits; child's race/ethnicity; medical complexity; VSD site; birth month and year. EGA, estimated gestational age.

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Aluminum and Asthma Study: Secondary Analyses

Variable	Sample size, eczema cohort	Adjusted hazard ratio (95% CI), eczema cohort (n=14337)	Sample size, no eczema cohort	Adjusted hazard ratio (95% CI), no eczema cohort (n=312654)
Primary analyses (previously shown)	14337	1.26 (1.07, 1.49)	312654	1.19 (1.14, 1.25)
Dichotomous aluminum (>3.00 mg vs ≤3.00 mg)	14337	1.61 (1.04, 2.48)	312654	1.36 (1.21, 1.53)
Excluding aluminum extremes (<1 mg or ≥5 mg)	14225	1.27 (1.05, 1.53)	307891	1.18 (1.11, 1.26)
Fully vaccinated	9477	1.08 (0.82, 1.43)	188593	1.12 (1.01, 1.24)
Adjusted for breast-feeding (limited data)	1913	1.38 (0.53, 3.60)	42909	1.26 (0.99, 1.61)
Persistent asthma at 36-59 months	12967	1.22 (1.01, 1.47)	280205	1.15 (1.09, 1.22)
Negative control: all-cause injury (ED, inpatient) at 24-59 months	13804	1.03 (0.94, 1.14)	298276	1.01 (0.99, 1.03)

Notes: Cox proportional hazards analyses; separate models for eczema and no eczema cohorts; other covariates included number of outpatient visits; number of ED visits; child's race/ethnicity; medical complexity; VSD site; birth month and year

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Interpretation: Aluminum and Asthma Study

- Small positive association between cumulative vaccine-associated aluminum before 24 months and persistent asthma 24-59 months
- Positive finding for children with and without eczema
- Secondary analyses: positive associations in some but not all analyses
- Study strengths: deliberate process; extensive feedback; large sample; VSD with high data quality; sophisticated analyses
- Study limitations: no data on dietary/environmental aluminum exposure (although little to none of ingested aluminum absorbed per recent AAP report); no data on social determinants of health; unmeasured confounding; antigen effects
- The first step of a multi-step research process

Ref: 1) Daley MF et al, Acad Pediatr. 2023 Jan-Feb;23(1):37-46. 2) Corkins MR, AAP Committee on Nutrition. Pediatrics. 2019;144:e20193148.

Asthma Prevalence among Children <18 years of Age: United States, 1980–2020

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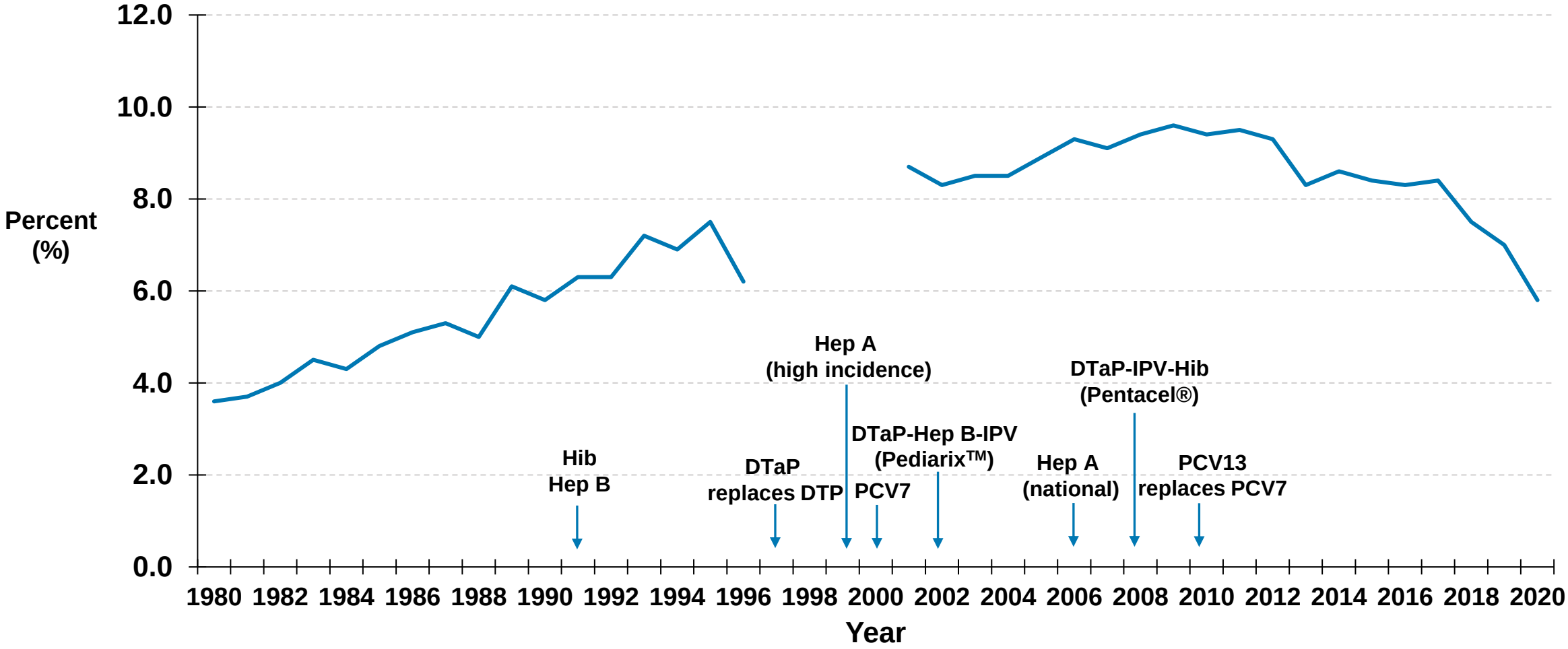

Ref: The data from 1980-1996 and 2001-2020 are from National Health Interview Survey (NHIS): 1) 1980–1996 data are from Akinbami LJ, Schoendorf KC, Parker J. Am J Epidemiolol. 2003. 2) 2001–2020 data are from https://www.cdc.gov/asthma/nhis/default.htm

Further Investigations, Vaccine Aluminum and Risk of Asthma

- Denmark national databases (Dr. Anders Hviid presentation at ACIP)
- New study in VSD:
  - Cohort: larger cohort, longer follow up time
  - Exposure: aluminum before 12 months of age
  - Eczema: treat eczema as covariate
  - Outcome: asthma diagnosed at a later age (60 through 84 months of age); asthma diagnosed earlier may represent viral-induced wheezing (not asthma)
- Additional consideration of other data sources which could help assess relationship between vaccine aluminum exposure and subsequent asthma risk

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The Schedule and Safety: Broader Context

- Totality of available evidence continues to support the safety of the routine childhood vaccination schedule
- Existing federal vaccine safety surveillance systems robust and responsive to concerns expressed by parents of young children
- Precipitated by 2013 IOM Report on schedule, new field of study is being developed:
  - Examine cumulative, repeated exposures to vaccines and vaccine ingredients
  - Examine long-term health outcomes
- At time of IOM Report, few studies of the safety of the schedule "as a whole"
- Evidence accumulating around specific testable hypotheses; results which can be communicated to parents
- Additional studies related to aluminum and asthma risk planned and ongoing
- Benefits of vaccination strongly outweigh known and potential risks


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