



Studying the safety of the childhood immunization schedule in the Vaccine Safety Datalink

Advisory Commission on Childhood Vaccines (ACCV) meeting
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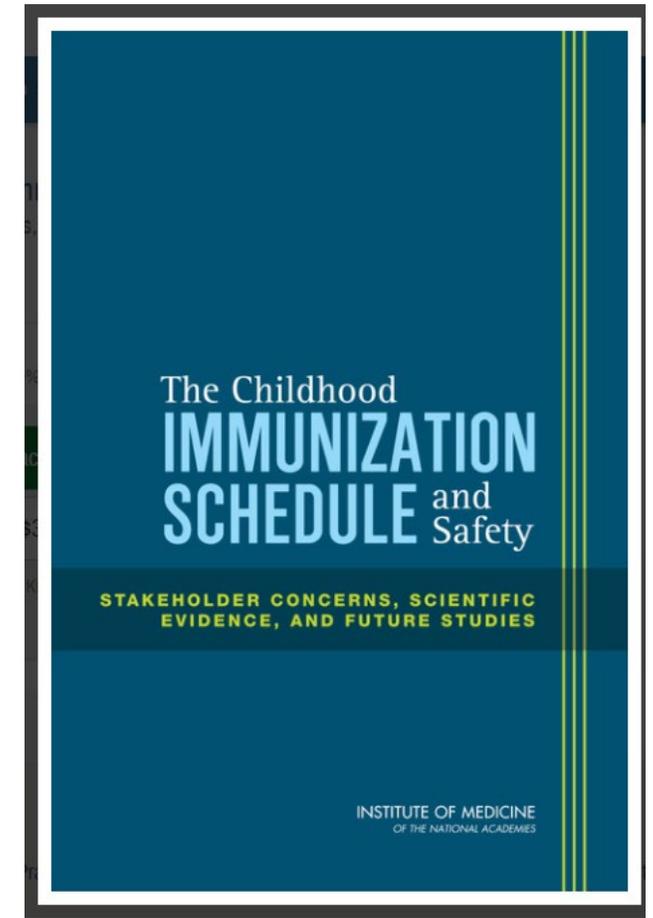
Presentation outline

- 2013 Institute of Medicine (IOM) report
- 2016 Vaccine Safety Datalink (VSD) white paper on studying the safety of the childhood immunization schedule
- VSD childhood immunization schedule studies published to date

Institute of Medicine (IOM) report

The Childhood Immunization Schedule and Safety: Stakeholder Concerns, Scientific Evidence, and Future Studies

- Requested by the National Vaccine Program Office
- Published in 2013
- Available at: <https://doi.org/10.17226/13563>



The charge to the committee

- 1) review scientific findings and stakeholder concerns related to the safety of the recommended childhood immunization schedule
- 2) identify potential research approaches, methodologies, and study designs that could inform this question, considering strengths, weaknesses, as well as the ethical and financial feasibility of each approach

BOX S-2

Leading Research Questions of Interest to Select Stakeholders

1. How do child health outcomes compare between those who receive no vaccinations and those who receive the full currently recommended immunization schedule?
2. How do child health outcomes compare between (a) those who receive the full currently recommended immunization schedule and (b) those who omit specific vaccines?
3. For children who receive the currently recommended immunization schedule, do short- or long-term health outcomes differ for those who receive fewer immunizations per visit (e.g., when immunizations are spread out over multiple occasions), or for those who receive their immunizations at later ages but still within the recommended ranges?
4. Do potentially susceptible subpopulations—for example, children from families with a history of allergies or autoimmune diseases—who may experience adverse health consequences in association with immunization with the currently recommended immunization schedule exist?

Selected conclusions from the report

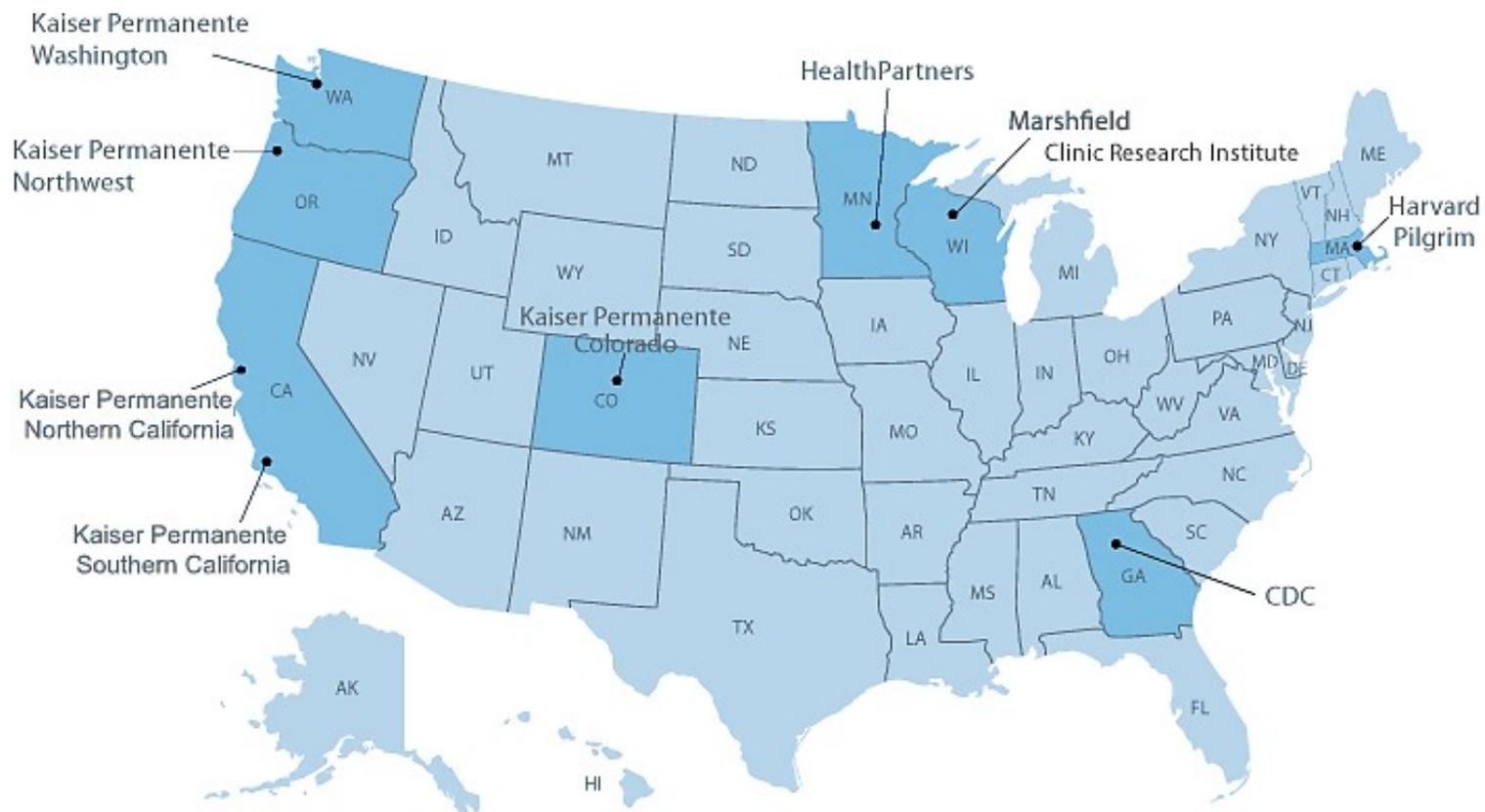
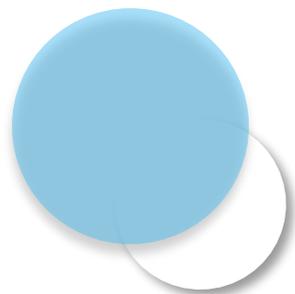
- “There are concerns from some stakeholders that merit exploration through research if epidemiological signals are detected and an indication of biological plausibility is available.”
- “However, the committee concludes that it is not ethical to implement any study requiring that some children receive fewer vaccines than recommended as part of the childhood immunization schedule because this would needlessly endanger children’s lives.”
- “The committee concludes that data from existing surveillance systems, such as the Vaccine Safety Datalink, could be used and offer the best means for ongoing research efforts regarding the safety of the schedule.”

Vaccine Safety Datalink (VSD) white paper on studying the safety of the childhood immunization schedule



VSD

Vaccine Safety Datalink



8 participating integrated healthcare organizations

White Paper on studying the safety of the childhood immunization schedule in the Vaccine Safety Datalink



White Paper on studying the safety of the childhood immunization schedule in the Vaccine Safety Datalink^{☆,☆☆}



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- The document was developed and written between September 2013 and December 2014.
- Final version published in Feb 2016
- Available at: <http://dx.doi.org/10.1016/j.vaccine.2015.10.082>

White Paper content areas

1. Defining exposure to different immunization schedules
2. Identifying health outcomes to study in the context of the immunization schedule
3. Describing epidemiological and statistical methods to study the safety of the schedule

Defining exposure to different immunization schedules

- Undervaccination is broadly defined as children who are either behind on their immunizations or on an immunization schedule that differs from the recommended schedule of the Advisory Committee on Immunization Practices
- Comparisons of undervaccinated children to children who are age-appropriately vaccinated poses numerous methodological challenges that could threaten the validity of future safety studies, including information bias, confounding, and lack of statistical power
- The White Paper describes a four staged approach for identifying cohorts of undervaccinated children for safety studies

Identifying health outcomes to study

- A three-phased approach was used to identify, categorize, and prioritize outcomes for future safety studies in the VSD
- Based on the IOM report, the focus was on:
 - plausible health outcomes that could be evaluated in the context of the immunization schedule as a whole
 - the importance of studying longer-term outcomes, such as autoimmune diseases, asthma and other allergic conditions

Final list of outcomes in the VSD white paper

Rank	Outcome	Rank	Outcome
1	Asthma	11	Attention deficit disorder
2	Anaphylaxis	12	All-cause morbidity
3	Encephalopathy	13	Crohn's disease and ulcerative colitis
4	All-cause mortality	14	Syncope and vasovagal reaction
5	Meningitis	15	Seizures
6	Learning and devel. disorders	16	Kawasaki disease
7	Epilepsy	17	Juvenile rheumatoid arthritis
8	Type 1 diabetes	18	Tics
9	First demyelinating event	19	Chronic urticaria
10	Allergy development	20	Bell's palsy

Methods to study the safety of the schedule

- Observational immunization schedule safety research could be prone to potential sources of bias including unmeasured confounding, health care seeking bias, reverse causality, selection bias and misclassification of exposures and outcomes
- The White Paper describes several methods to help address these biases in safety studies of the schedule
- The White Paper describes various study designs and statistical methods that could be used to analyze the safety of the schedule

White Paper conclusions

- While it appears feasible to study the safety of the recommended immunization schedule in settings such as the VSD, these studies will be inherently complex, and as with all observational studies, will need to carefully address issues of confounding and bias.
- VSD investigators will be able to use this document as a guide when designing and conducting studies of the safety of childhood immunization schedule, if such studies are judged to be necessary.



VSD childhood immunization schedule studies published to date

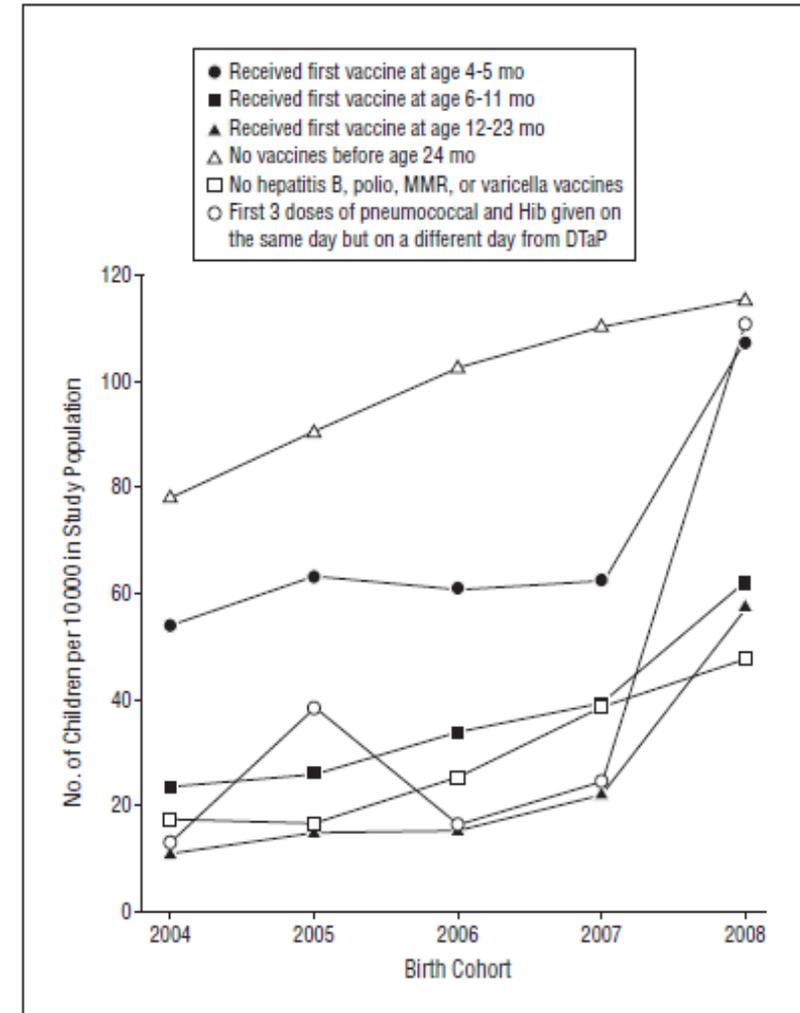
Assessment of undervaccination in the VSD

- Objectives: To examine patterns and trends of undervaccination in children aged 2 to 24 months and to compare health care utilization rates between undervaccinated and age-appropriately vaccinated children.
- Findings:
 - Among 323,247 children born between 2004 and 2008, 48.7% were undervaccinated for at least 1 day before age 24 months.
 - Compared to children who were age-appropriately vaccinated, undervaccinated children had lower outpatient visit rates and increased inpatient admission rates
 - Children who were undervaccinated because of parental choice had lower rates of outpatient visits and emergency department encounters
- Conclusion: Undervaccinated children appear to have different health care utilization patterns compared with age-appropriately vaccinated children

Available at: <https://pubmed.ncbi.nlm.nih.gov/23338829/>

Trends in delayed start to vaccinations and select vaccination patterns by birth cohort before age 2 years

- 2.8% of children were on specific nonstandard vaccination schedules
- Approximately 1% of children had no record of receiving any doses of 8 recommended vaccines before age 2 years



Papers addressing methodological issues

- Assessing misclassification of vaccination status: Implications for studies of the safety of the childhood immunization schedule. (<https://pubmed.ncbi.nlm.nih.gov/28285983/>)
- Bias from outcome misclassification in immunization schedule safety research. (<https://pubmed.ncbi.nlm.nih.gov/29292551/>)
- Assessing potential confounding and misclassification bias when studying the safety of the childhood immunization schedule. (<https://pubmed.ncbi.nlm.nih.gov/29604461/>)
- Use of three summary measures of pediatric vaccination for studying the safety of the childhood immunization schedule. (<https://pubmed.ncbi.nlm.nih.gov/30709727/>)
- Cumulative and episodic vaccine aluminum exposure in a population-based cohort of young children. (<https://pubmed.ncbi.nlm.nih.gov/26518400/>)

Papers assessing adverse event outcomes

- Increasing exposure to antibody-stimulating proteins and polysaccharides in vaccines is not associated with risk of autism. (<https://pubmed.ncbi.nlm.nih.gov/23545349/>)
- Number of antigens in early childhood vaccines and neuropsychological outcomes at age 7-10 years. (<https://pubmed.ncbi.nlm.nih.gov/23847024/>)
- Patterns of childhood immunization and all-cause mortality. (<https://pubmed.ncbi.nlm.nih.gov/29061349/>)
- Association between estimated cumulative vaccine antigen exposure through the first 23 months of life and non-vaccine-targeted infections from 24 through 47 months of age. (<https://pubmed.ncbi.nlm.nih.gov/29509866/>)
- Order of live and inactivated vaccines and risk of non-vaccine-targeted infections in US children 11-23 months of age. (<https://pubmed.ncbi.nlm.nih.gov/32032310/>)

Papers assessing the risk of vaccine preventable disease

- Association between undervaccination with diphtheria, tetanus toxoids, and acellular pertussis (DTaP) vaccine and risk of pertussis infection in children 3 to 36 months of age.
(<https://pubmed.ncbi.nlm.nih.gov/24019039/>)

Papers assessing special populations

- Vaccination patterns in children after autism spectrum disorder diagnosis and in their younger siblings.
(<https://pubmed.ncbi.nlm.nih.gov/29582071/>)

Papers that included a comparison of children who did or did not receive a specific vaccine

- Lack of association between hepatitis B birth immunization and neonatal death: a population-based study from the vaccine safety datalink project. (<https://pubmed.ncbi.nlm.nih.gov/15247605/>)
- Protective association between rotavirus vaccination and childhood seizures in the year following vaccination in US children. (<https://pubmed.ncbi.nlm.nih.gov/24265355/>)
- Incidence of Herpes Zoster Among Children: 2003-2014. (<https://pubmed.ncbi.nlm.nih.gov/31182552/>)

Summary

Summary

- The Institute of Medicine identified the CDC's Vaccine Safety Datalink (VSD) system as one of the best resources for research regarding the safety of the childhood immunization schedule
- Observational studies of the immunization schedule pose numerous methodological challenges and require careful planning to control for potential sources of bias
- To date, the VSD has completed many studies related to the immunization schedule
- Additional VSD studies of the immunization schedule are ongoing and planned to address the priorities outlined in the VSD White Paper

Thank You

For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

