



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



Jason M. Glanz^{a,*}, Sophia R. Newcomer^b, Michael L. Jackson^c, Saad B. Omer^d,
Robert A. Bednarczyk^e, Jo Ann Shoup^f, Frank DeStefano^g, Matthew F. Daley^h

^a Institute for Health Research, Kaiser Permanente Colorado, Denver, CO; University of Colorado School of Public Health, Aurora, CO, United States

^b Institute for Health Research, Kaiser Permanente Colorado, Denver, CO, United States

^c Group Health Research Institute, Group Health Cooperative, Seattle, WA, United States

^d Emory University Schools of Public Health and Medicine, Atlanta, GA, United States

^e Emory University School of Public Health, Atlanta, GA, United States

^f Institute for Health Research, Kaiser Permanente Colorado, Denver, CO, United States

^g Immunization Safety Office, Centers for Disease Control and Prevention, Atlanta, GA, United States

^h Institute for Health Research, Kaiser Permanente Colorado, Denver, CO; University of Colorado School of Medicine, Aurora, CO, United States

ARTICLE INFO

Keywords:

Vaccine safety
Recommended immunization schedule
Alternative immunization schedule
Parental vaccine concerns
Parental vaccine refusal
Vaccine safety methods

ABSTRACT

While the large majority of parents in the U.S. vaccinate their children according to the recommended immunization schedule, some parents have refused or delayed vaccinating, often citing safety concerns. In response to public concern, the U.S. Institute of Medicine (IOM) evaluated existing research regarding the safety of the recommended immunization schedule. The IOM concluded that although available evidence strongly supported the safety of the currently recommended schedule as a whole, additional observational research was warranted to compare health outcomes between fully vaccinated children and those on a delayed or alternative schedule. In addition, the IOM identified the Vaccine Safety Datalink (VSD) as an important resource for conducting this research. Guided by the IOM findings, the Centers for Disease Control and Prevention (CDC) commissioned a White Paper to assess how the VSD could be used to study the safety of the childhood immunization schedule. Guided by subject matter expert engagement, the resulting White Paper outlines a 4 stage approach for identifying exposure groups of undervaccinated children, presents a list of health outcomes of highest priority to examine in this context, and describes various study designs and statistical methods that could be used to analyze the safety of the schedule. 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. In light of these considerations, decisions about conducting studies of the safety of the schedule will also need to assess epidemiological evidence of potential adverse events that could be related to the schedule, the biological plausibility of an association between an adverse event and the schedule, and public concern about the safety of the schedule.

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Abbreviations: ACIP, Advisory Committee on Immunization Practices; ADU, average days undervaccinated; CDC, Centers for Disease Control and Prevention; DAG, Directed Acyclic Graph; DTaP, diphtheria and tetanus toxoid and acellular pertussis vaccine; EHR, electronic health record; Hep B, Hepatitis B Vaccine; Hib, Haemophilus Influenzae Type b Vaccine; ICD-9-CM, International Classification of Diseases, 9th revision, Clinical Modification; IIS, Immunization Information Systems; IOM, Institute of Medicine; ISO, Immunization Safety Office; MCO, Managed Care Organization; MMR, Measles, Mumps, and Rubella Vaccine; PC, Pneumococcal Vaccine; PCV7, Pneumococcal 7-valent Conjugate Vaccine; PCV13, Pneumococcal 13-valent Conjugate Vaccine; SME, Subject Matter Expert; VDW, Virtual Data Warehouse; VSD, Vaccine Safety Datalink.

[☆] **Notice:** The project that is the subject of this report was approved and funded by the Immunization Safety Office, Centers for Disease Control and Prevention. The contributors responsible for the content of the White Paper were funded by Task Order contract 200-2012-53582/0004 awarded as a prime contract to Kaiser Foundation Hospitals.

^{☆☆} 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.

* Corresponding author. Tel.: +1 303 614 1313.

E-mail address: Jason.M.Glanz@kp.org (J.M. Glanz).

Executive summary

Routine vaccination in the United States is widely viewed as one of the greatest public health achievements of the past century. Despite this success, an increasing number of parents have been expressing concerns about vaccine safety over the last two decades. Parental vaccine worries have traditionally focused on specific vaccines, ingredients and types of adverse events. More recently, parents have been voicing concerns about the safety of the recommended immunization schedule as a whole, with opinions that children receive too many vaccines at too young of an age, and that early childhood immunization overwhelms the immune system. These sentiments reflect the number, frequency and timing of recommended vaccines, leading some parents to refuse or delay vaccinations for their children.

In response to these concerns, the Institute of Medicine (IOM) in 2012 convened a committee to gather stakeholder input and scientific evidence on the safety of the recommended childhood immunization schedule [1]. The committee concluded that, while available evidence indicated that the current U.S. immunization schedule was safe, few published investigations had specifically examined the safety of the recommended childhood schedule as a whole. The committee recommended that additional observational studies of the safety of the schedule were warranted, and stated that the Vaccine Safety Datalink (VSD) project [2] represents one of the best resources in the nation for conducting such studies. The VSD is an established collaboration of nine managed care organizations (MCOs) where electronic health record (EHR) data on over 9 million people are used to conduct observational studies on vaccine safety.

The IOM report also highlighted four research questions of highest priority to stakeholders: (1) how do child health outcomes compare between fully vaccinated and unvaccinated children; (2) how do child health outcomes compare between fully vaccinated children and children whose parents have refused specific vaccines; (3) do short- and long-term health outcomes differ when comparing children vaccinated according to the recommended schedule to children receiving fewer vaccines per visit or receiving vaccines at later ages; and (4) are some subpopulations of children at increased risk of adverse events following immunization (for example, children with a family history of allergic or autoimmune disease).

To address these research questions, the IOM report emphasized the need to carefully consider the potential impact of confounding and bias. In particular, the committee stressed that decisions to initiate future safety studies should include an assessment of the following: (1) epidemiological evidence of adverse events; (2) biologic plausibility of associations between the immunization schedule and adverse events of interest; and (3) stakeholder concerns about the safety of the schedule.

Guided by the IOM committee's assessment of the unique and important role the VSD could play in this area of study, the Immunization Safety Office (ISO) of the Centers for Disease Control and Prevention (CDC) issued a request for a White Paper. The focus of the White Paper was to determine how the VSD could be used to study the safety of the entire childhood immunization schedule.

The White Paper had the following four objectives:

Four objectives of White Paper:

1. Define types of alternative immunization schedules and patterns of undervaccination that could be evaluated, focusing on the first 24 months of age
2. Identify plausible adverse event outcomes that could be related to the childhood immunization schedule, with an emphasis on long-term adverse events

3. Suggest methodological approaches that could be used to assess the safety of the recommended schedule as a whole
4. Propose next steps for studying the safety of the childhood immunization schedule within the VSD

The document was developed and written between September 2013 and December 2014. All funding for the project was obtained through a CDC VSD contract. No funding was provided by pharmaceutical companies or other sources. The White Paper study team had no conflicts of interest to declare.

Three separate but related content areas were addressed: defining exposure to different immunization schedules, identifying health outcomes to study in the context of the immunization schedule, and describing epidemiological and statistical methods to study the safety of the schedule. The study team first reviewed the IOM report in detail and conducted a review of published literature. Two in-person meetings with subject matter experts (SME) were then held. The first meeting occurred in February 2014 in Atlanta, Georgia, with three internationally regarded vaccinologists: Drs. Walter Orenstein, Stanley Plotkin and Edgar Marcuse. The second meeting was in June 2014 in Seattle, Washington, with two expert statisticians: Drs. Martin Kulldorff and M. Alan Brookhart. These meetings were audio recorded and transcripts were analyzed to identify key themes to guide the final report.

Below, we summarize each of the three main content areas in the White Paper.

Exposure: Defining patterns of undervaccination and alternative immunizations schedules (Chapter 2)

The objective of this chapter was to describe various approaches for using VSD databases to create cohorts of undervaccinated children for future safety studies of the recommended immunization schedule. 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 (i.e., an alternative immunization schedule) [3,4]. In theory, the safety of the recommended immunization schedule could be evaluated by comparing rates of adverse events between cohorts of undervaccinated children and children who are age-appropriately vaccinated. As shown in prior VSD research, however, defining these cohorts poses numerous methodological challenges that could threaten the validity of future safety studies, including information bias, confounding and lack of statistical power [3].

To help address these challenges, chapter two describes a four staged approach for creating cohorts of undervaccinated children for safety studies. Within each stage, there are several suggested methods that investigators can consider when designing future studies.

In *Stage 1*, different methodological approaches for identifying a cohort of undervaccinated children are presented. After a cohort of undervaccinated children has been identified, children can be further grouped by different patterns of undervaccination. *Stage 2* provides details on 11 different methods for characterizing patterns of undervaccination, including using the VSD databases to identify published alternative schedules, shot limiting, delayed start to vaccination, vaccine series not received, spacing of vaccines, order of vaccines, and exposure to vaccine components such as antigen and non-antigen vaccine ingredients.

Stage 3 describes approaches to address issues arising with small sample sizes, misclassification and confounding. For small sample size concerns, a data mining analytic approach for creating groupings of undervaccinated children is proposed. To address misclassification of vaccination data, a method using an International

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