White Paper on Studying the Safety of the Childhood Immunization Schedule

For the Vaccine Safety Datalink

National Center for Emerging and Zoonotic Infectious Diseases
Immunization Safety Office

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List of 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

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 be 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.

Next, 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 Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code specific for vaccine refusal is presented. Lastly, there is a description of how VSD health care utilization data can be used to help address confounding and misclassification of vaccination and outcome data.

After groups of undervaccination have been identified, health care utilization behaviors and the potential for missing vaccination data can be further evaluated through primary data collection. *Stage 4* describes two methods of data collection: manual medical record review and surveys with parents. These approaches can be used to confirm vaccination status, to determine if reasons for undervaccination are due to parental refusal or delay, and to assess whether the child is receiving care outside of the MCO, which may lead to misclassification of outcome status if an adverse event occurs.

Outcomes: plausible adverse events that could be studied relative to the entire childhood immunization schedule (Chapter 3)

In addition to identifying meaningful exposure groups of undervaccination and alternative schedules, the IOM's 2013 report stressed the importance of identifying plausible health outcomes that could be evaluated in the context of the immunization schedule as a whole.[1] While the IOM report did not rule out short-term acute events, it stressed the importance of studying longer-term outcomes, such as autoimmune diseases, asthma and other allergic conditions. The following three-phased approach was used to identify, categorize and prioritize such outcomes for future safety studies in the VSD:

1. Generate a list of potential outcomes
2. Subject matter expert (SME) engagement
3. Final prioritization

In *Phase 1*, the study team conducted a review of the medical literature, and three IOM reports from 2002, 2011 and 2013[1,58,62] to generate a list of 75 potential outcomes. The outcomes were first organized by system/organ type (e.g., respiratory system, neurological system) or reaction type (e.g., allergy, anaphylaxis). The study team then summarized and reviewed the available evidence related to biological and mechanistic plausibility, and appropriateness of evaluating the adverse event in the context of the childhood immunization schedule. After internal discussion among the study team using these criteria, the list was reduced to 47 plausible outcomes.

In *Phase 2*, the list of 47 outcomes was presented to the three vaccine science SMEs to gain additional insight into the appropriateness of studying specific outcomes in the context of the childhood immunization schedule and to conduct an initial prioritization of the outcomes. The SMEs concluded that four diseases could be excluded because they either rarely occur during childhood or are extremely rare in the general population. After lengthy discussion, the SMEs made several suggestions for the remaining 43 outcomes. They first stressed the importance of identifying long-term outcomes with clear diagnostic criteria, such as those having a definitive diagnostic test result or when case status could be confirmed using manual medical record review. Second, the SMEs expressed the need to strongly consider public concern when deciding on outcomes to study; in certain instances, they said that public concern may be a more important consideration than biologic plausibility. The SMEs were also concerned that many of the outcomes may be too rare to study. They requested additional age-specific incidence data on the outcomes and suggested that several of the outcomes could be grouped together. For example, the SMEs recommended that a single outcome grouping called "first demyelinating events" could include acute disseminated encephalomyelitis, chronic inflammatory demyelinating polyneuropathy, Guillain-Barre syndrome, neuromyelitis optica, optic neuritis, and transverse myelitis. The meeting concluded with an aggregation exercise in which study team and SMEs reduced the list of 43 outcomes to an initial list of 31 prioritized outcomes.

Following the SME meeting, the study team conducted a final prioritization of the 31 outcomes (P*hase 3*). In this last phase, the VSD databases were first used to calculate incidence rates of diagnosis for each outcome among children ages

3–8 years. The study team then reviewed the incidence estimates and classified each outcome as being either feasible or not feasible to study in the VSD; a rate of 5 diagnosed cases per 100,000 person-years was used as a cut-off for feasibility. This step eliminated 11 of the 31 outcomes as being too rare to study in the VSD.

After determining feasibility, the study team ranked the remaining 20 outcomes on public health significance and public health concern. The study team considered the seriousness of the condition, the rarity of the condition, whether the condition was increasing in prevalence, whether the outcome has already been studied as an adverse event, and whether vaccine hesitant parents would associate the outcome with vaccination. Using these criteria, team members ranked each of the outcomes on a 1–5 scale for public health significance and public health concern, with a ranking of 5 representing the highest priority. The two scores were then averaged across the study team and summed together, resulting in a combined score between 2 and 10 for each outcome.

To conclude Phase 3, the final rankings were reviewed and discussed by the study team. In these discussions, team members could make the case to move outcomes up, down or off the priority list. A final list of ranked outcomes is presented here:

Ranking of outcomes based on feasibility, public health significance, and public concern

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, communication and developmental 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: Study designs and statistical analyses to study the safety of the schedule (Chapter 4)

On June 27, 2014, the study team met with VSD staff and external experts on drug and vaccine safety methodology. Several important methodological recommendations were developed from the meeting. First, investigations into the safety of the vaccine schedule should plan for multi-part studies. Initial studies can be used to identify possible associations between outcomes and various vaccine schedules. This will then lead to follow-up studies to verify the observed associations and identify which aspects of the schedule(s) are responsible for them. Second, because vaccine schedule research is a field in its infancy, initial studies of vaccine schedule safety should focus on designs and methods with well-known properties – such as the cohort and case-control methods – until the various sources of bias in schedule safety research are better understood. Examples of these potential sources of bias include unmeasured confounding, health care seeking bias, reverse causality, selection bias and misclassification of exposures and outcomes.

Chapter 4 describes several methods to help address these biases in safety studies of the schedule. For example, to identify potential confounding variables, causal models such as directed acyclic graphs (DAGs) may be used. These models allow the investigator to identify whether key confounders can be controlled for using existing VSD databases, whether additional data needs to be collected, or whether certain confounders are unmeasurable. Examples of potentially important confounding variables that are not routinely collected in the VSD databases are parental education, income, and family history of chronic illness. These factors may be associated with parental vaccine decisions and may require more labor-intensive data collection to measure.

To evaluate the direct influence of uncontrolled confounding, initial safety studies should also include negative controls whenever possible. Negative control outcomes are conditions with no expected causal association with the vaccine schedule in infants and young children, such as fractures, sprains or other minor injuries. If a study finds an association between the vaccine schedule and a control outcome, it suggests that unmeasured confounding may be present. Potential remedies include collecting additional sociodemographic data, or to control for differences in health care utilization, since parents of undervaccinated children may be more or less likely to seek medical attention than parents who vaccinate according to the recommended schedule.

In addition to confounding, information bias is a concern because vaccination status, outcomes and important covariates may be imperfectly measured in the VSD databases. Chapter 4 describes, in detail, how misclassification of these factors can lead to effect estimates that are biased either toward or away from the null. Several analytic methods to address these potential sources of information bias are also discussed, including the use of health care utilization data to match fully and partially vaccinated children, or to restrict the study population to children who have had a minimum amount of utilization (e.g., three outpatient visits) while enrolled in their respective MCO during the first year of life.

Other approaches to address information bias involve quantifying the misclassification though primary data collection using cross-sectional surveys of parents and/or medical record review. For example, surveys on a sample of parents could be used to assess measurement error in vaccination history and/or to collect important covariates such as parental education or household income. After quantifying the degree of misclassification with primary data collection, sensitivity analyses using statistical simulation techniques could then be used to correct for the misclassification bias when estimating associations between the immunization schedule and outcomes of interest.

The chapter concludes with an example of a study to evaluate the association between a known immunization schedule and the risk of asthma. The example illustrates all phases of the study, including defining the study population, exposure groups, outcomes, covariates and analytic approaches.

Summary

This White Paper provides a comprehensive assessment for how the VSD could be used to study the safety of the recommended childhood immunization schedule. Guided by subject matter expert engagement, the document outlines a 4 staged approach for identifying exposure groups of undervaccinated children, presents a list of 20 prioritized outcomes, and describes various study designs and statistical methods that could be used to analyze the safety of the schedule. VSD investigators will be able to use this document as a guide when designing and conducting studies of the safety of the childhood immunization schedule, if such studies are judged to be necessary.

Chapter 1: Introduction

1.1 Significance

Routine vaccination in the U.S. has prevented millions of serious illnesses and deaths,[5-7] and vaccination is widely viewed as one of the greatest public health achievements of the past century.[8] Maintaining high vaccination coverage within the population is critical to the ongoing effort to prevent a wide array of vaccine-preventable diseases. While vaccination rates for young children in the U.S. are high relative to historical benchmarks[9,10] an increasing number of parents have expressed concerns about the safety of vaccines in the past two decades. Some of these concerned parents are choosing to refuse or delay vaccines for their children.[11-14] Vaccine refusal and delay has contributed, in turn, to the spread of vaccine-preventable diseases in the community.[15-18]

The nature of parent concerns about vaccine safety is complex and fluid, with concerns varying widely between parents and over time.[11-14] Some parents have voiced concerns about specific vaccines (e.g., measles-mumps-rubella [MMR]), vaccine ingredients (e.g., thimerosal and aluminum), and the development of certain medical conditions (e.g., autism). More recently some parents have stated that little is known about the safety of the recommended immunization schedule as a whole. Some parents have expressed the opinion, for example, that too many vaccines are given to children at too young of an age and that early childhood immunization overwhelms the immune system. These sentiments reflect concern about the number, frequency, and timing of recommended vaccines rather than about the specific properties of particular vaccines.[14,19-21]

The immunization schedule for the U.S. is established by the Advisory Committee on Immunization Practices (ACIP). In fact "the schedule" is a term used to encompass an extensive set of immunization recommendations guiding immunization delivery from birth through old age.[22,23] The schedule sets forth at what age particular vaccines should be given, with recommendations based upon a number of considerations, including disease burden, age at disease onset and peak incidence, immunogenicity, reactogenicity, and other practical considerations. Many more vaccines are recommended before 24 months of age than at any other age,[22,23] and parents appear particularly concerned about the safety of vaccines given to young children.[11-14]

1.2 IOM Report on the Childhood Immunization Schedule and Safety

In response to this public concern, the Institute of Medicine (IOM) in 2012 convened a committee to examine scientific evidence and stakeholder concerns regarding the safety of the recommended childhood immunization schedule, and to identify study designs and methods that could be used to rigorously examine this issue[1]. The IOM committee concluded that while the accumulation of available evidence indicated that the current U.S. immunization schedule was safe, few published investigations had specifically evaluated the safety of the childhood schedule as a whole. The committee concluded that new observational studies of the safety of the schedule were warranted, and stated that the Vaccine Safety Datalink (VSD) project[2] represented one of the best resources in the nation for conducting such studies.

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 comparing children vaccinated according to the recommended schedule to those 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).[1]

Although the IOM committee endorsed the need for and importance of studies of the safety of the schedule, the IOM report also emphasized the complexities of such studies, and the need to carefully consider issues of confounding and bias. In light of these considerations, the committee cautioned that decisions related to initiating further studies of the schedule should include an assessment of the following: 1) the epidemiological evidence of a potential adverse event related to the childhood immunization schedule; 2) the

biological plausibility of the association between an adverse event and the schedule; and 3) stakeholder concerns about the safety of the schedule. In this context, stakeholder concerns would prompt an examination of the epidemiological evidence and biological plausibility related to a particular adverse event of concern[1].

1.3 Objectives of White Paper

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, to focus on how the VSD could be used to study the safety of the entire childhood immunization schedule. The White Paper had the four following objectives:

1. Define types of alternative immunization schedules and patterns of undervaccination that could be evaluated;
2. Identify plausible adverse event outcomes that could be related to the childhood immunization schedule;
3. Suggest methodological approaches that could be used to assess the safety of the recommended schedule as a whole; and
4. Propose next steps for studying the safety of the childhood immunization schedule within the VSD.

1.4 Process of Developing White Paper

The White Paper was designed and written between September 2013 and December 2014. All funding for the White Paper came from the CDC, through the contract for participation in the VSD project. No funding was provided from any other sources. The team of collaborators involved in developing the White Paper is listed in the preface material. None of the White Paper study team members had any relevant conflicts of interest to declare. The protocol for completing the White Paper was submitted to the institutional review board (IRB) at Kaiser Permanente Colorado, and was deemed not to constitute human subjects research.

Initially, the study team reviewed the IOM report in detail. Although other published literature was also reviewed in detail, we did not conduct a formal literature review, because a comprehensive literature search and review was recently conducted as a part of the IOM committee information gathering process.

The work of the White Paper was divided into three separate but related content areas: defining exposure to different immunization schedules; defining health outcomes that could be studied in the context of the entire immunization schedule; and developing methods to study the safety of the schedule. For each content area, an iterative approach was taken, with the development of initial strategies and challenges, presentation of this material to subject matter experts (SMEs), and revision of the content based upon feedback from SMEs.

Engagement with SMEs was conducted primarily through two in-person meetings. In February 2014, at Emory University in Atlanta, Georgia, an all-day meeting was held with three vaccinologists: Drs. Walter Orenstein, Stanley Plotkin, and Edgar Marcuse. These three individuals are internationally regarded experts in the area of vaccine science. In June 2014, a meeting was held in Seattle, Washington with Drs. Martin Kulldorff and M. Alan Brookhart, two individuals with particular expertise in the areas of research methods and statistical analyses.

At each of the in-person SME engagement meetings, the discussion was audio-recorded and later professionally transcribed. The study team also kept detailed paper notes of the discussion. After the meetings, the transcript and paper notes were reviewed by the study team to identify the key themes emerging from the meeting. The team then met as a group to review and refine key themes through an iterative process.

As will be described later in this report, one of the themes to emerge from SME engagement was that evaluating the feasibility of studying specific health outcomes was dependent upon knowledge of how common or rare these outcomes were in the VSD population. Because of this feedback, as part of the White Paper process we used the VSD databases to calculate crude incidence rates of diagnoses for health outcomes of interest.

1.5 Studying the Safety of the Childhood Immunization Schedule: Defining Key Concepts

The Immunization Schedule

The IOM committee acknowledged that, in order to study the safety of the childhood immunization schedule, more clarity was needed about what defines the schedule. The U.S. immunization schedule, established by the ACIP, is an extensive set of immunization recommendations guiding immunization delivery from birth through old age.[22,23] The immunization schedule changes over time, as new vaccines are licensed, or the recommendations for existing vaccines change based on new knowledge. In addition, for some vaccines, the immunization schedule allows for a relatively wide age interval within which vaccines can be delivered (e.g. the third dose of inactivated poliovirus vaccine [IPV] is recommended to be administered between 6 and 18 months of age).[23] Finally, the schedule also allows for the use of different vaccine products with different dosing schedules (e.g. there are two different rotavirus vaccines currently licensed in the U.S., one which requires two doses and another which requires three doses).

For the purposes of the White Paper, we chose to focus on the schedule of vaccines routinely recommended for infants and young children before 24 months of age. The rationale for this decision is as follows. First, more vaccines are recommended before 24 months of age than at any other time of life, with multiple doses of particular vaccines recommended. Second, parents appear to be more concerned about the safety of the schedule (i.e. the timing and spacing of multiple vaccines) for young children rather than for older children and adults.[11-14] Third, several of the medical conditions of concern to parents, such as asthma and allergic disorders, may become apparent clinically in the pre-school age group, roughly corresponding to 2 to 6 years of age. Finally, long periods of time elapse between the infant immunization series, the "school entry" series at 4 to 6 years of age, and the "pre-teenager" series at 11 years of age; these long time periods create conceptual as well as methodological uncertainty about what would define the schedule in later childhood and how it could be evaluated.

Safety

For the White Paper, we chose to explicitly define safety as the absence of vaccine-associated adverse events following immunization. Parental vaccine delay or refusal leads to an increased risk of vaccine-preventable disease in children,[16-18] and safety could be defined more broadly to include the prevention of disease. However, considerations related to vaccine effectiveness, and the risks associated with vaccine refusal, were considered out of scope of this White Paper. Nonetheless, any new knowledge generated about adverse events related to the immunization schedule could be used in the future by national policy makers when weighing all available evidence about the benefits and risks of vaccination.

Focus on Long-term Outcomes

While there is not a uniform definition of what constitutes a short- versus long-term adverse event, short-term adverse events are typically thought to occur in the hours, days, or weeks following vaccination. For example, VSD studies of vaccine safety will generally evaluate adverse events in the 1-2, 1-7, 1-14, or 1-42 days following vaccination. Long-term outcomes can be thought of as occurring in the months to years following vaccination.

After stakeholder engagement and a review of existing literature, the IOM committee concluded that while both short- and long-term adverse events were important, the study of long-term outcomes following the routine schedule was a higher priority. The current safety surveillance systems such as the VSD,[2] and the Post-Licensure Rapid Immunization Safety Monitoring (PRISM)[24] system of the Food and Drug Administration (FDA), already have extensive systems in place to assess short-term outcomes. Parents have expressed more concerns about long-term than short-term health outcomes, and have argued that long-term health outcomes have been less well-studied in the context of vaccine safety. Finally, because the childhood immunization schedule is essentially a long-term exposure, occurring over 18 to 24 months, long-term adverse events may be more biologically plausible than short-term events. Therefore, for the purposes of the White Paper we chose to focus primarily on long-term adverse events.

Summary

In summary, the following key decisions and concepts guided the work of the White Paper:

- The schedule was defined as those vaccines routinely recommended for children prior to 24 months of age;
- Safety was defined as the relative absence of adverse events following immunization; and
- Long-term adverse events were viewed as the primary area of focus, as opposed to more acute events following immunization.

1.6 Organization of the White Paper Report

The White Paper is organized into 5 chapters and 5 appendices. The first, introductory chapter, presented a brief background, describes the objectives of the White Paper, and introduces several key concepts and decision points. The second chapter defines the types of alternative immunization schedules and patterns of undervaccination that could be evaluated in safety studies. The third chapter identifies adverse event outcomes that could possibly be related to the childhood immunization schedule. The fourth chapter focuses on the methodological approaches that could be used to assess the safety of the recommended schedule as a whole. The final chapter presents a summary of the findings of the White Paper, addresses limitations to the methods and scope of the White Paper, and proposes several recommended next steps that should be considered when evaluatong the safety of the recommended childhood immunization schedule.

Chapter 2: Exposure

2.1 Introduction

In this chapter, we describe various approaches for how the VSD can be used to create cohorts of undervaccinated children. 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 ACIP (i.e., an alternative immunization schedule). Accurately identifying undervaccinated children in the VSD can be quite challenging. While numerous studies have confirmed the validity of electronic vaccination data compared to vaccination data from manual medical record review,[25-27] the validity of missing pediatric vaccination records in the VSD is currently not known. In other words, if a child has electronic vaccination records in VSD databases, there is a high likelihood that the child actually received those vaccines. However, if the child appears undervaccinated in the databases, the lack of vaccination may be attributed to several causes. One cause is actual vaccine delay, which can be intentional or unintentional. Parents may consciously refuse or delay vaccines for their children, while other families may be experiencing barriers to care. In both instances, these children would be considered undervaccinated. In contrast, lack of vaccination records in the EHR may also be due to missing immunization records, which can occur when children have gaps in managed care organization (MCO) enrollment or when they are receiving vaccines outside of the MCO. These children would be misclassified as being undervaccinated. Minimizing such misclassification of vaccination status is particularly important because it can threaten the validity of future safety studies of the schedule.

We begin the chapter with a description of prior research on undervaccination in the VSD, and then suggest a staged approach by which cohorts of undervaccinated children can be identified and verified using the VSD databases and primary data collection. The overall goal of this staged approach is to identify groups of undervaccinated children that could be included in safety studies with minimal bias from misclassification and confounding.

2.2 Summary of methods subject matter expert meeting

On June 27th, 2014, Group Health Research Institute hosted a meeting of VSD collaborators and outside experts in drug safety methodology. The meeting's objectives were to elicit recommendations from the outside experts on analytic approaches for assessing the safety of the childhood immunization schedule. The outside experts were Martin Kulldorff, of Harvard Medical School, and M. Alan Brookhart of the University of North Carolina. The experts made several recommendations on study designs, statistical approaches, methods to address confounding and bias, and approaches for defining patterns and categories of undervaccination. In this chapter, we incorporate their recommendations for defining undervaccination patterns; their other recommendations are addressed in the fourth chapter on methodological approaches for studying the safety of the schedule.

2.3 Prior work on undervaccination in VSD

The VSD recently conducted a population-based cohort study of undervaccination,[3] the results of which were presented to the IOM committee assessing the safety of the childhood immunization schedule. The objective of this feasibility study was to examine patterns and trends of undervaccination and alternative vaccination schedules to inform future studies of the safety of the recommended childhood immunization schedule.

The VSD databases were first used to identify a cohort of 323,247 children enrolled from birth to 24 months of age. In this large cohort, the average number of days undervaccinated (ADU) was calculated for each child. ADU is a continuous metric that quantifies immunization status over the first two years of life (details of how ADU is calculated are described in section 2.4 below). In brief, ADU measures the difference in time between when a child actually received his or her vaccines and when the vaccines should have been

received according to the ACIP recommended schedule, allowing for a grace period. At two years of age, children who are age-appropriately vaccinated have an ADU = 0, while completely unvaccinated children have an ADU = 479 days (Appendix 2.a).

After calculating ADU, the cohort was divided into two groups: children who were undervaccinated for at least one day and children who were age-appropriately vaccinated. Undervaccinated children were further categorized according to whether or not they received an ICD-9 code for parental vaccine refusal (V64.05, V64.06), or if they were on a known alternative immunization schedule (Table 2.a). A medical record review was then conducted to better understand the reasons for undervaccination and to assess the potential for missing immunization data. Separate medical record reviews were conducted for undervaccinated children with and without an ICD-9 code for vaccine refusal. For the medical record reviews, abstractors looked for documentation that the parents had explicitly delayed or refused vaccines for their children. Lastly, a matched cohort analysis compared health care utilization rates between undervaccinated and age-appropriately vaccinated children.

Table 2.a: Specific alternative schedules previously identified in VSD data[3,28,30]

- No vaccines before age 24 months
- No hepatitis B, polio, MMR, or varicella vaccines before age 24 months, but other vaccines received (consistent with the Selective Schedule in *The Vaccine Book* by Dr. Robert Sears)[28]
- First 3 doses of Hib and pneumococcal vaccines given on the same day, but on a different day than the first 3 doses of DTaP (consistent with the Alternative Schedule in *The Vaccine Book* by Dr. Robert Sears)[28]
- Delaying start to vaccination until 4, 6 or 12 months of age
- Consistent shot-limiting: limiting vaccinations per visit to 2 or fewer

The results from this study[3] showed that 48.7% (n=157,454) of the cohort was undervaccinated for at least one day before age 2 years, while only 1.9% (n=6,172) had an ICD-9 code for vaccine refusal and only 2.8% (n=8,939) were identified as being on a known alternative immunization schedule. In the overall cohort of undervaccinated children, distinct patterns of undervaccination were identified by categorizing each of eight childhood vaccines into one of three groups: all doses received on-time, no doses received, or some doses either missing or not received on-time. With this method, 1399 different patterns of undervaccination and alternative immunization schedules were identified. Among children with an ICD-9 code for vaccine refusal, there were 756 different patterns of undervaccination. Since these patterns only considered three broad categories for each vaccine, this calculation did not consider other factors related to the schedule such as the age, spacing, or order of vaccinations. Considering these other factors could result in millions of different combinations of vaccination patterns, which presents potential challenges in identifying clinically meaningful cohorts for future safety studies.

The medical record review among undervaccinated children without an ICD-9 code for vaccine refusal showed that reasons for undervaccination were only present in 40% of records, thus highlighting the potential for misclassification due to missing information. In contrast, the medical record review among undervaccinated children with an ICD-9 code showed a high confirmation rate of 94% for parental vaccine refusal. It is therefore likely the immunization data for these latter children were accurately captured, implying that they could be included in safety studies with minimal exposure misclassification.

Lastly, the matched cohort analysis showed differences in rates of health care utilization between age-appropriately vaccinated and undervaccinated children. Undervaccinated children had lower rates of outpatient utilization and higher rates of inpatient utilization compared to age-appropriately vaccinated children.

In summary, these results demonstrate that there are numerous methodological challenges to consider when creating undervaccinated cohorts to study the safety of the recommended schedule (Table 2.b). While undervaccination is common, there is a considerable amount of variability in vaccination patterns, as well as potential for missing vaccination data and bias from differences in health care seeking behaviors. Misclassification of vaccination status can be minimized among children with an ICD-9 code for vaccine refusal, but these children are small in number and could not be used to study uncommon outcomes in safety studies. Next we describe a four-staged approach to help address these methodological barriers.

Table 2.b: Summary of methodological challenges identified from previous VSD research on undervaccination

- Considerable variability in patterns of undervaccination
- Few children with an ICD-9 code indicating parental refusal of vaccination
- Potential for misclassification of vaccination status in electronic health record data
- Potential for information bias and confounding from differences in health care seeking behavior between fully vaccinated and undervaccinated children

2.4 Staged approach for identifying patterns of undervaccination

In this section, we describe a four staged approach for creating cohorts of undervaccinated children for future safety studies. Within each stage, we suggest several possible methods that VSD investigators can consider when designing their studies. In stage 1, we describe four different methods for identifying undervaccinated children. In stage 2, we suggest various methods by which undervaccinated children can be characterized and grouped. Once children have been grouped, stage 3 presents methods for addressing issues related to sample size, exposure misclassification and potential confounding. Lastly, stage 4 describes approaches for collecting primary data on the groupings of undervaccinated children to further assess the potential for misclassification and confounding.

Stage 1: Identify undervaccinated children

Described below are four different methods that can be used to identify undervaccinated children in the VSD cohort. We also briefly describe state immunization registry data, which have the potential to be combined with the electronic health record (EHR) data used in the VSD.

Days Undervaccinated

Being age-appropriately vaccinated is based on the recommended schedule of the ACIP. The ACIP recommends that all healthy children receive their primary series of immunizations at birth, 2, 4, 6, 12 –15, and 18 months of age.[23] In 2005, Luman et al.,[4] calculated the total days undervaccinated for 6 childhood vaccines in a large, nationally representative population of children ages 18-36 months. Days undervaccinated is a metric that quantifies the number of calendar days a child is undervaccinated for any recommended vaccine.[4] For each vaccine, days undervaccinated is calculated by taking the difference between when each vaccine dose was administered and when the vaccine dose should have been administered according to the ACIP schedule.

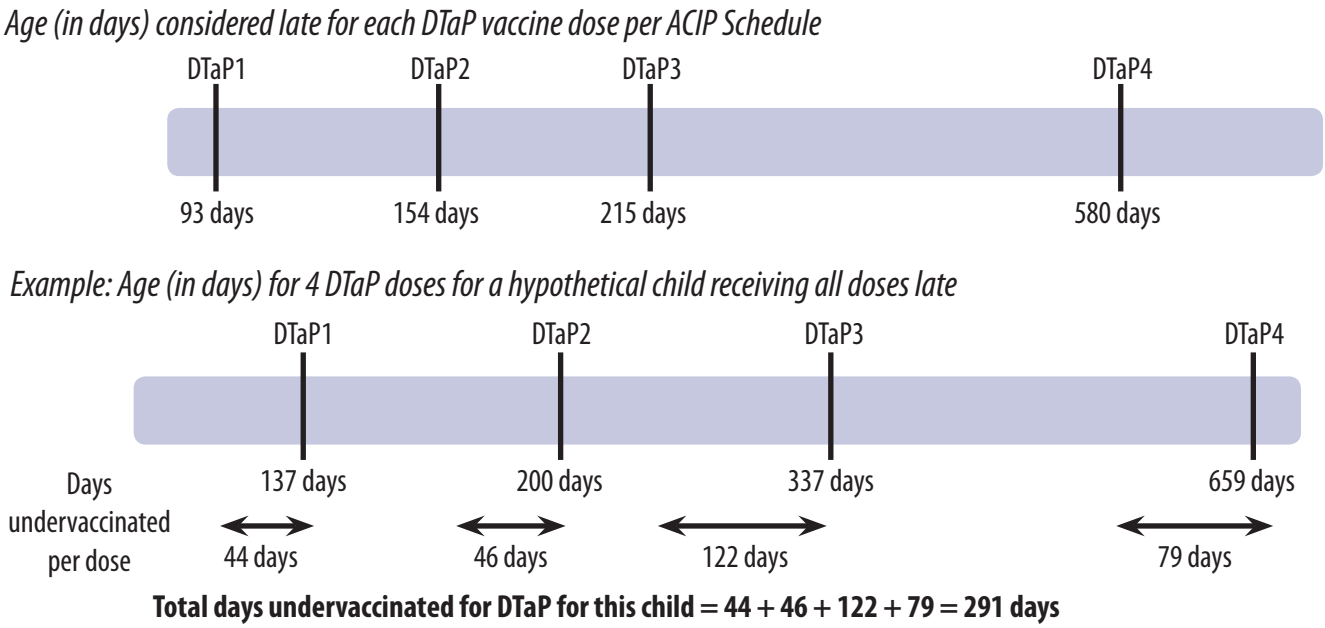
There is a grace period around ACIP's recommended age for each vaccine dose. For example, ACIP recommends giving the first dose of diphtheria-tetanus-acellular pertussis (DTaP) vaccine at age 2 months; however, a child is not considered undervaccinated for DTaP unless he or she turns 3 months of age (age 93 days) without receiving the vaccine. That is, the count for undervaccination for the first dose of DTaP is not started until age 93 days. When calculating days undervaccinated, if a child is undervaccinated for more than one vaccine on a given day, that day is only counted once in the calculation (Figure 2.a).

Full details on the criteria used to evaluate days undervaccinated before age 2 years for Hepatitis B (Hep B), rotavirus, DTaP, *Haemophilus influenzae* type b (Hib), pneumococcal conjugate (PC), inactivated polio (IPV), measles, mumps, and

rubella (MMR), and varicella vaccines is available in Appendix 2.a. These criteria include the minimum recommended age for each dose, the minimum interval between doses for the same vaccine, and the age in days when the count for undervaccinated days is initiated for each vaccine dose. Over calendar time, some criteria have been altered due to policy changes, vaccine shortages, and brand-specific dosing instructions (Appendix 2.b).

The days undervaccinated metric has some limitations because it does not account for the fact that children can be undervaccinated for more than one vaccine on a given calendar day. For example, if a child is undervaccinated for DTaP and Hib vaccines on the same calendar days, they would be assigned the same number of days undervaccinated as a child who was undervaccinated only for DTaP on those same days. If accounting for undervaccination across multiple vaccines is of interest, we suggest two metrics described in the next two sections: average days undervaccinated and proportion of days undervaccinated.

Figure 2.a: Example of calculating days undervaccinated for DTaP vaccine[4]

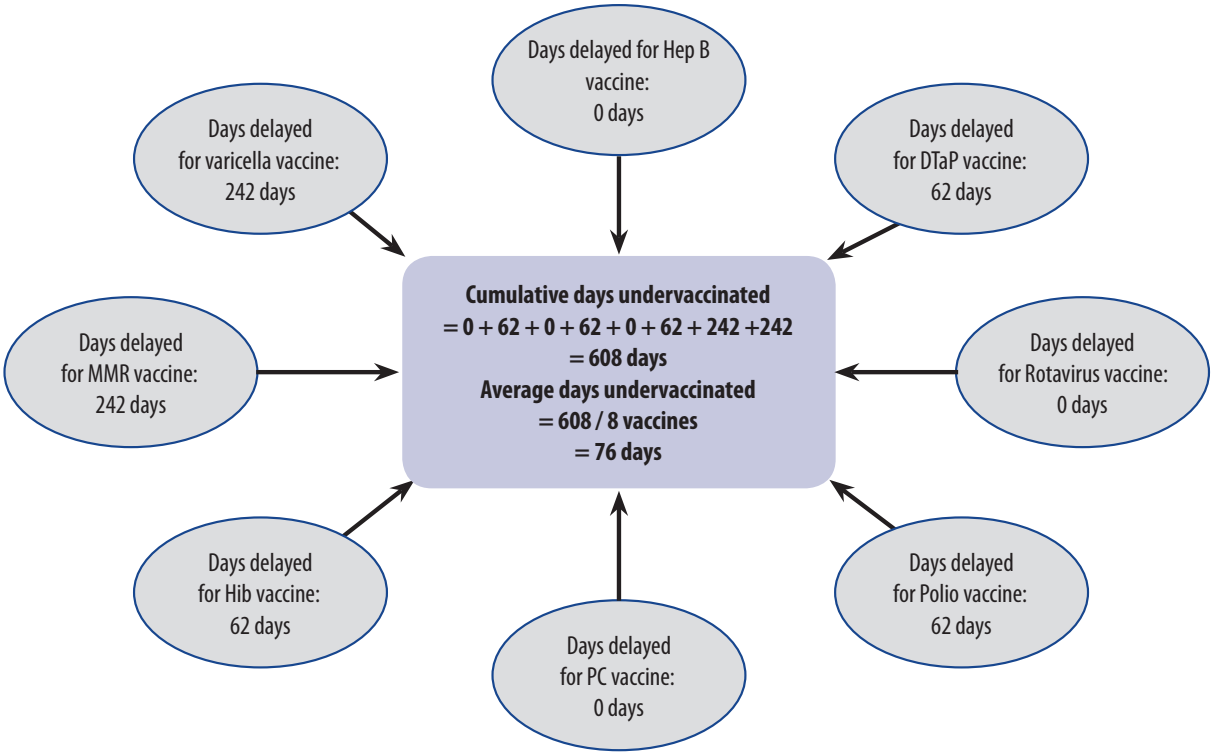


Average days undervaccinated

ADU is a summary measure of undervaccination that expands upon the metric developed by Luman et al.[3,4] by incorporating days undervaccinated across multiple overlapping vaccines. To calculate ADU, the days undervaccinated for each dose are summed across all vaccine doses to calculate cumulative days undervaccinated for each child. Then, for each child, the cumulative days undervaccinated is divided by the number of vaccines that a child should have received according to the ACIP schedule. This calculation represents the average number of days undervaccinated across all recommended vaccines.

An example of calculating ADU is provided in Figure 2.b. In this example, days undervaccinated before age 2 years have been calculated for eight recommended childhood vaccines. These days are summed to calculate the cumulative days undervaccinated. The cumulative days undervaccinated are then divided by 8 to calculate the average days undervaccinated. VSD analysts have developed a suite of SAS® macros (SAS Institute, Cary, North Carolina) to facilitate calculation of days undervaccinated and ADU.

Figure 2.b: Example of calculating average days undervaccinated (ADU) across eight recommended childhood vaccines before age 24 months[3]



Proportion of days undervaccinated

Proportion of days undervaccinated is a metric developed by Opel et al.,[31,32] and is similar to ADU. The first step is to quantify the total possible days undervaccinated over a period of time for each recommended vaccine. The sum of these days represents the denominator. The numerator is the sum of the actual number of days the child was undervaccinated for each vaccine. Table 2.c shows the proportion of days undervaccinated metric applied to the same example as Figure 2.b.

Table 2.c: Example of calculating proportion of days undervaccinated across eight recommended childhood vaccines before age 730 days[3,31,32]

Vaccine	Maximum number of possible days undervaccinated at age 730 days*	Actual number of days undervaccinated using example from Figure 2.b	Proportion of days undervaccinated
Hepatitis B	730 – 92 = 638	0	
DTaP	730 – 92 = 638	62	
Rotavirus**	252 – 92 = 160	0	
Hib	730 – 92 = 638	62	
PC	730 – 92 = 638	0	
IPV	730 – 92 = 638	62	
MMR	730 – 488 = 242	242	
Varicella	730 – 488 = 242	242	
Total	3834 (denominator)	670 (numerator)	17.48%

* The latest age a child can receive the first dose of Hepatitis B, DTaP, Rotavirus, Hib, PCV and IPV vaccines on-time per the ACIP schedule is 92 days. The latest age a child can receive the first dose of MMR and varicella vaccines on-time is 488 days.[23]

** Per ACIP recommendations, rotavirus vaccine should not be administered past age 252 days.[23]

Combined Series Completion

Another method that can be used for identifying undervaccinated children is combined series completion metrics. Combined series completion is a cross-sectional measure of whether a child is up-to-date for recommended vaccinations. Using this method, a child's vaccination status is examined at a point in time, and the doses received for recommended vaccines up until that point are compared to the number of doses the child should have received. CDC's National Immunization Survey uses several combined series completion metrics (Table 2.d) to assess whether a child is age-appropriately vaccinated at age 19-35 months.[9] As compared to ADU, combined series completion only assesses undervaccination at the point of measurement and does not capture previous periods of undervaccination. In addition, while the NIS does report rotavirus series completion separately, this series is not currently incorporated in its combined series metrics.

Table 2.d: Combined series completion metrics used by the National Immunization Survey for children ages 19-35 months[9]

Metric	≥ 4 doses DTaP	≥ 3 doses Polio	≥ 1 dose MMR	≥ 3 doses Hib	≥ 3 doses Hep B	≥ 1 dose Varicella	≥ 4 doses PCV
4:3:1:3:3:1:4	X	X	X	X	X	X	X
4:3:1:3*:3:1:4	X	X	X	3 or 4 doses*	X	X	X
4:3:1:3*:3:1	X	X	X	3 or 4 doses*	X	X	*Excluded*
4:3:1:-:3:1:4	X	X	X	*Excluded*	X	X	X
4:3:1:-:3:1	X	X	X	*Excluded*	X	X	*Excluded*

X=included in metric

* Depending on brand of Hib vaccine

Additional data sources: State immunization registries

When children appear undervaccinated in VSD databases, it is possible that these children have received vaccines outside of their MCO site. Immunization information systems (IIS) are confidential, population-based, computerized databases that record all vaccination doses administered by participating providers to people residing within a given geographic area.[33] IIS are used in clinical settings to gain access to consolidated immunization histories to assist vaccination providers in determining appropriate patient vaccinations. At the population level, an IIS provides aggregate data on vaccinations for use in assessments of coverage, program operations, and in guiding public health action to improve vaccination rates.[34] There are many initiatives underway to support interoperability of systems which are expected to result in more complete and timely immunization histories in IIS, including the Health Information Technology for Clinical and Economic Health (HITECH) Act[35] as well as aspects of the Prevention and Public Health Fund (PPHF), and the Centers for Medicare and Medicaid Services meaningful use projects.[36]

For healthcare systems, adoption of IIS as the vaccination database, or incorporation of IIS data into existing EHR records through automated data exchange, can improve the capacity to estimate vaccination coverage levels among patients. Health care systems that employ bidirectional data exchange with an IIS are well equipped to examine the prevalence of childhood undervaccination as they are able to access more complete immunization histories. Many VSD sites already link IIS records into their VSD vaccine files, and misclassification of missing vaccination data may be reduced at these MCOs.[37]

Stage 2: Characterize patterns of undervaccination

After a cohort of undervaccinated children has been identified, children can be further grouped by patterns of undervaccination using one or more of the suggested methods described below (Table 2.e). These groups of undervaccinated children can be included in safety studies, provided they are large enough to study the outcome of interest and there is minimal potential for bias from misclassification and confounding. If small sample sizes, misclassification or confounding are a concern, the groupings of children can be further refined analytically in stage 3 and then verified in stage 4 using primary data collection.

Table 2.e: Approaches for characterizing patterns of undervaccination using VSD data[3,28,30,38]

- Completely undervaccinated (zero vaccines)
- Published alternative schedules (ex: *The Vaccine Book by Dr. Robert* Sears[28].
- Limiting the number of vaccines given per visit ("shot-limiting")[30]
- Delaying start to vaccination
- Vaccine series not received
- Vaccine doses not received
- Age of receipt of each vaccine dose
- Spacing of vaccines
- Order of vaccines
- Cumulative exposure to vaccine antigens
- Cumulative exposure to other vaccines ingredients (ex: aluminum)

Completely unvaccinated (zero vaccines)

In the VSD, identifying children with no vaccination records is straightforward. A previous VSD study estimated that approximately 1% of children had no vaccine records before age 24 months[3]. However, children who appear completely unvaccinated in VSD data are likely a mix of the truly unvaccinated and children whose vaccination status is misclassified. The misclassification can be due to children receiving vaccines outside of the MCO or missing electronic vaccine records. Additional utilization and health plan criteria could be applied to increase the likelihood that completely unvaccinated children were receiving regular care within the managed care organization (MCO).

Published alternative schedules

VSD data can be used to identify vaccination patterns associated with known alternative vaccination schedules, such as those created by Drs. Robert Sears, Elizabeth Mumper, Donald Miller, Stephanie Cave, and Kenneth Bock.[28,39-42] Features of these alternative schedules include spacing vaccinations over multiple visits, delaying the start of any vaccinations until a later age, and forgoing certain vaccine series altogether. While vaccination patterns consistent with these alternative schedules have been identified within the VSD pediatric cohort, the percentage of vaccine-hesitant parents strictly adhering to one of these schedules is small.[3,14] For example, in a previous VSD study, only 0.68% of children appeared to be receiving vaccinations according to the Alternative or Selective Schedules recommended by Dr. Robert Sears in The Vaccine Book.[3,28]

Limiting the number of vaccinations per visit ("shot-limiting")

Shot-limiting refers to a parental behavior of requesting fewer than the recommended number of vaccine doses at a given immunization visit.[30]

While the term "shot-limiting" implies injections, the total number of vaccines (injected or oral) per visit can also be examined. Factors influencing how many vaccines a child should receive are the MCO's formulary and the child's age. Per current ACIP guidelines, children should receive between three and six vaccines at 2- and 4-month well-child visits.

To examine the behavior of limiting the number of vaccinations per visit in VSD data, children can be categorized by the proportion of visits where shot limiting behavior was observed (consistent or episodic). Children can also be categorized by the extent of shot limiting; for example, the average number of vaccine doses per visit over a period of time. Shot limiting could also be assessed by the average number of antigens per visit or average ingredient exposure (ex: milligrams of aluminum) per visit. A study using Oregon state immunization registry data found that 4.6% of their study population received 2 or fewer immunizations at all visits before age 9 months, suggesting that these parents were consistently limiting the number of shots given to their children.[30] Data from a current VSD study indicate that 1.36% of children appear to receive 2 or fewer vaccines at all immunization visits before age 12 months.[43]

Delaying start to vaccination

In VSD data, children with a delayed start to vaccination have no immunization records until a certain age, after which they may have received some or all recommended vaccines. In prior VSD work, children who received their first vaccines at ages 4-5, 6-11, 12-23 and 24 months were identified.[3] Approximately 1.29% of children received their first vaccination at age 4 months or later. Children with a delayed start to vaccinations can catch up and be considered up-to-date at a later age. When evaluating ADU or up-to-date status, the ACIP catch-up schedule should be considered.[23]

Vaccine series not received

Immunization patterns can be classified by vaccine types not received. Such classification is especially helpful in describing parental refusal of entire vaccine series. When using this metric, potential misclassification of vaccination data should be evaluated (i.e., children may be receiving vaccines outside the MCO). Additional utilization and health plan criteria could also be implemented to increase the likelihood that a child is getting regular care within the MCO. Also, as the number of recommended childhood vaccines considered increases, so does the dimensionality of this metric. For example, if considering whether or not a child started each of eight recommended vaccine series (yes/no) before age 2, there are $2^8 = 256$ possible patterns. In a recent VSD analysis, 156 such patterns were observed before age 2 among a cohort of about 240,000 children.[43]

Vaccine doses not received

Alternative vaccination schedules can be further classified by the number of recommended doses of a vaccine not received. This metric can be applied to each specific vaccine or more broadly across all vaccines. The denominator of how many doses a child should have received should be considered and is influenced by several factors: (1) calendar time, as new vaccines are added to the ACIP schedule, (2) age, since the number of recommended doses vary by age, and (3) vaccine brand, since the number of recommended doses for some vaccines differs by brand. This metric can be easily quantified using VSD data. However, potential misclassification of missing doses merits additional evaluation, and the high dimensionality of this metric may cause challenges in identifying large groups with similar patterns of undervaccination. For example, in a recent VSD analysis, the number of doses not received was assessed for each of eight recommended vaccines before age 2. Within a cohort of about 240,000 children, 2376 distinct patterns of doses not received across the eight vaccines was observed.[43]

Age of receipt of each vaccine dose

Children's vaccination patterns can be described by the age of receipt of each vaccine dose. In the general population the distribution of age at each dose will be centered on the ACIP-recommended age. Among undervaccinated children, these age distributions will be more variable. Days, weeks or months are appropriate units of age when describing age of receipt of vaccine doses for young children.

Spacing of vaccines

The spacing of vaccine doses can refer to the amount of time that elapsed between doses of the same vaccine series, or to the amount of time between administrations of different vaccine series. When evaluating a cumulative vaccination schedule, examining the spacing of doses as a metric can be complex given the number of vaccine series and doses that can be spread across the first few years of life.

Order of vaccines

For undervaccinated children, the order in which vaccines are given can differ from the order specified on the ACIP schedule. When describing a vaccination schedule using this method, researchers are typically interested in the order vaccine doses were administered over multiple immunization visits, not on a single visit.[44] As with other metrics relating to the timing of vaccines, evaluating a cumulative vaccination schedule based on vaccine order can be cumbersome given the numerous possibilities for how all of the recommended vaccines can be ordered.

Exposure to vaccine antigens

Exposure to vaccine antigens can be estimated using VSD data. When describing a child's vaccination pattern, exposure to antigens can be measured at various points in time (e.g., at each immunization visit) or summed as a cumulative measure over time. Cumulative antigen exposure has previously been studied with VSD data. For example, Iqbal et al., used a combination of MCO vaccination records and parent-reported data to examine the association between cumulative exposure to antigens and neuropsychological outcomes.[38]

Exposure to other vaccine ingredients

Along with antigens, vaccines contain other components used in the manufacturing process. Such non-antigen vaccine ingredients include small amounts of preservatives, adjuvants, additives, and residual substances.[45,46] Metrics summarizing exposure to some of these ingredients is possible with VSD data. Preliminary data from a recent VSD study demonstrated that it is feasible to quantify vaccine aluminum exposure in a study population of more than 400,000 children from birth to 24 months of age. Considerable variability in aluminum exposure was observed in this large cohort, suggesting the potential to compare outcomes in children with varying levels of exposure to aluminum from vaccinations. The key to this analysis was the completeness of manufacturer data in the VSD vaccination data file, which could be linked to the vaccine package inserts to quantify the ingredient amounts in each vaccine dose. Manufacturer data was approximately 70% complete between years 2004 and 2013.[43]

Stage 3: Use additional VSD data to address sample size, exposure misclassification & potential confounding

As shown in stage 2, there are numerous approaches for characterizing patterns of undervaccination in the VSD. For stage 3, we describe three methods for addressing potential issues with small sample sizes, misclassification and confounding. For small sample size concerns, we describe a data mining analytic approach for creating groupings of undervaccinated children. To address misclassification of vaccination data, we discuss a method using the ICD-9 code for vaccine refusal. Lastly, we describe how VSD utilization data can be used to help address confounding and misclassification of vaccination and outcome data.

Application of data-mining techniques

Pattern discovery techniques, such as cluster analysis (or data segmentation)[47] may be used to help identify distinct groups of undervaccinated children with closely-related immunization patterns. After a large dataset of undervaccinated children has been identified, cluster analysis can be implemented in three steps. First, children's vaccination patterns are defined using the approaches outlined in Stage 2. Second, a measure of proximity (also referred to as a distance measure) is used to quantify how similar every child's pattern of vaccination is to every other child in the dataset. Third, a clustering technique is applied to identify groups with similar vaccination patterns.

For this last step, two general methods can be considered: k-means clustering and agglomerative hierarchical clustering.[47,48] For k-means methods, a *k* number of cluster "centers" are pre-defined by the user.[48,49] For example, these centers could reflect published alternative schedules, and children would be assigned to their closest center based on established algorithm. With agglomerative hierarchical clustering, pre-defined cluster centers are not required. Each child is considered its own cluster, and children are linked together to form larger and larger clusters until all children are in one cluster (consisting of the entire dataset). Once this hierarchical representation is established, data are examined at various cut-points to determine the appropriate number of clusters.[47,48]

Along with cluster analysis, other techniques such as principal component, latent variable, and factor analysis may be considered. In general, these other methods can aid in reducing the dimensionality of a dataset, or in identifying latent groups or constructs to help identify groupings of undervaccination.

One notable limitation of clustering methodologies are their computational time and space. Some clustering methods will involve creating an *N* x *N* matrix; since pediatric VSD cohorts often have hundreds of thousands of children, creating such a relational dataset may be a challenge. Statistical packages such as R (R Foundation for Statistical Computing, Vienna, Austria) and SAS Enterprise Data Miner® (R Foundation for Statistical Computing, Vienna, Austria) should be considered for conducting these large-scale analyses.

ICD-9-CM code for parental refusal of vaccination

As described, previous VSD work has shown that there is minimal misclassification of vaccination exposure status among children with a diagnosis for parental refusal or delay of vaccination (V64.05 and V64.06) in their electronic health record data.[3] As such, if cohorts of undervaccinated children are restricted to only those with these ICD-9 codes, then misclassification of vaccination status is likely low and no additional primary data collection may be needed. However, a major limitation is that only a small percentage (≈ 12%) of undervaccinated children has this diagnosis code recorded in their electronic health record, and prevalence of this code varies by VSD site.[49] Since the recording of this ICD-9 code in a child's electronic health record is a provider-level behavior, it should not be assumed that children with this code recorded are representative of all undervaccinated children.

Utilization data

The potential for information bias among MCO members with low levels of health care utilization has been previously noted within the VSD.[3,50] For example, one VSD study initially observed a positive association between Hib and Hep B vaccination and the incidence of asthma, but the association was no longer evident once the study's cohort was restricted to children with at least two outpatient visits. The authors hypothesized that children with fewer than two outpatient visits were more likely to be receiving care outside of the MCO and to have misclassified vaccination and outcome data.[50] In addition to misclassification, differences in health care utilization between vaccination and undervaccinated children may lead to confounding if the utilization is associated with both the likelihood of receiving vaccines and being diagnosed with an adverse event.

To avoid this potential for bias, researchers may consider restricting their study populations to children with a minimum amount of health care utilization. There are two main challenges with this approach. One, the baseline level of utilization that is needed to minimize bias is currently not known. This could be potentially assessed through primary data collection such as medical record review or surveys (see stage 4). Two, VSD does not have an encounter-level data file, so utilization must be assessed by proxy from diagnoses and procedures data. In addition, certain types of utilization—such as phone and email encounters—are also excluded from the VSD data files. The VSD may want to consider including all procedure code data, and collect additional information from EHR encounters, including encounter subtypes and department codes.

Stage 4: Validate with primary data collection (manual medical record reviews/surveys)

After groups of undervaccination have been

identified, health care utilization behaviors and the potential for missing immunization data can be further evaluated through primary data collection. For stage 4, we describe two methods of data collection: manual medical record review and surveys with parents. These methods can either be applied in one large comprehensive VSD study, or VSD investigators can apply the methods on a smaller scale to address issues specific to their individual studies.

Medical record review

A manual medical record review could be used to confirm vaccination status, to determine if reasons of undervaccination are due to parental refusal or delay, and to assess whether the child is receiving care outside of the MCO. The review could be conducted across strata of undervaccination and/or strata of health care utilization. A formal abstraction tool should be developed, and Table 2.f shows examples of data elements that could be collected with the tool. Many of these data elements were captured with a tool developed for the recently published study on undervaccination in the VSD.[3] The data collected from the tool can be used to calculate confirmation rates, representing the following: the proportion of children who were undervaccinated due to intentional refusal or delay, the proportion with missing immunization data, and the proportion who were receiving their primary care outside of the MCO. Confirmation rates can be calculated for each specific pattern of undervaccination to help identify exposure groups in which misclassification of vaccination status is minimized.

Table 2.f: Example of data elements to be collected within a chart abstraction tool

Item	Notes
VSD ID	
Date of 1st vaccination	
Any documentation that the parent intentionally refused recommended vaccines?	
Any documentation that the parent intentionally delayed receiving recommended vaccines?	
Any documentation that the provider specifically recommended delaying vaccines due to current illness?	
Any documentation that the provider specifically recommended delaying vaccines for a non-medical reason?	
Any documentation that the parent specifically requested delaying vaccines due to current illness?	
Any documentation that the child had a medical contraindication to vaccination?	Contraindications would include immunosuppression (for certain vaccines), anaphylactoid reaction to a prior vaccine dose, severe egg allergy (for certain vaccines)
Any documentation that the child was in fact up-to-date on vaccines?	For example, because of vaccines documented in record or received at outside location
Any documentation that the child/family faced barriers to vaccination other than parental vaccine refusal/delay?	Examples of barriers include lack of transportation to appointments, having to take time off from work to bring to appointment, having unintentionally missed well-child visits, having temporarily moved out of state
Any other documentation regarding why the child was undervaccinated?	
Any indication within records that the child has ever obtained health care from an alternative medicine provider (such as a chiropractor, naturalist, homeopath, or acupuncturist)?	
Any evidence that the child is receiving primary care outside of the MCO?	

Survey of parents

It is possible that a medical record review will yield inconclusive results, since prior work has demonstrated that reasons for undervaccination are frequently absent from the medical records. A survey of parents may therefore be used to provide more accurate data on the following: 1) whether children who appear undervaccinated are truly undervaccinated or have received vaccines elsewhere; 2) whether undervaccination is due to parental vaccine refusal/delay or other reasons; and 3) whether undervaccinated children have received health care outside of the system. In addition, the survey could assess information that is typically not available from the medical record, including child and family characteristics, health care seeking behaviors, the general health status of undervaccinated children, and vaccination guidance given by providers and medical staff.

A two-step approach can be used to develop the survey instrument. The first step is to develop the survey questions and a preliminary survey; the second step is to pilot test the survey.

Develop survey questions

To develop the survey questions, the research team could first identify relevant questions based upon previously administered surveys, such as the National Immunization Survey[51,52] and the National Survey of Children's Health.[53] After identifying previously published questions, the team can develop questions that are tailored to the children's particular vaccination patterns. In key content areas, researchers can include several questions with similar content but different wording, which will facilitate survey revision after pilot-testing. A table of the main content domains and example survey questions are shown in Appendix 2.c.

Pilot test preliminary survey

After a preliminary survey has been developed, it can be pilot tested using a variety of methods. Cognitive interviews can be conducted with a small sample of 5-10 parents to elicit feedback on each question, focusing on wording, tone and comprehension. The results from these discussions can be used to further refine the survey, by adding, eliminating or changing the wording of questions.

In addition to cognitive interviews, the survey can be administered to a larger sample of parents and analyzed using an exploratory factor analysis. A factor analysis on the survey questions will identify the number of constructs (factors), determine which survey questions load on to the constructs, and determine which survey questions can be excluded from the final survey instrument.[54,55] After the factor analysis, the reliability (or internal consistency) of the latent constructs can be measured with a Cronbach's alpha.[56] This analysis can be used as a guide to eliminate survey questions that do not contribute to the constructs.

At the conclusion of the pilot testing, investigators will have a final version of the survey that can be administered to formally assess vaccination status, vaccination behaviors and health care seeking behaviors among parents of undervaccinated children.

Survey administration

Researchers should strive for a 50% or greater response rate on their surveys. This can likely be achieved using one or more acceptable methods of survey administration, including telephone, conventional mail, or email. The timing and sequence of these methods can be based on the Dillman protocol for survey administration.[57] Since resources may be limited, both conventional mail and email should be strongly considered, as VSD sites generally have accurate mailing addresses on their patient populations and email addresses are available for approximately 80% of the members at many of the VSD MCO sites.

Sampling scheme for medical record review and parent survey

The following factors should be considered when determining the appropriate sample size for a medical record review or survey:

- Whether the sample is stratified (e.g., undervaccination, health care utilization, VSD site)
- Range of estimated confirmation rates
- Desired confidence interval width
- Available resources

Appendix 2.d shows estimated sample sizes across a range of confirmation rates and confidence interval widths for a hypothetical medical record review and/or survey study.

Analysis of medical record and survey data

The data collected from a medical record review and survey will help provide estimates of misclassification of exposure and health care utilization, which in turn will inform how to define exposure groups for future safety studies. In the analytic methods section (chapter 4), we describe sensitivity analyses and simulation methods to incorporate the confirmation rates into the design and analysis of safety data.

Chapter 3: Outcomes

3.1 Background

As described in chapter 1, the IOM's 2013 report[1] recommended additional observational studies to better understand the safety of the entire childhood immunization schedule. In addition to identifying meaningful exposure groups of undervaccination and alternative immunization schedules, the report stressed the importance of assessing plausible adverse event outcomes that could be studied in relation to the childhood immunization schedule as a whole. In particular, the IOM suggested three criteria for identifying possible outcomes: epidemiological evidence, biologic plausibility, and stakeholder concern.

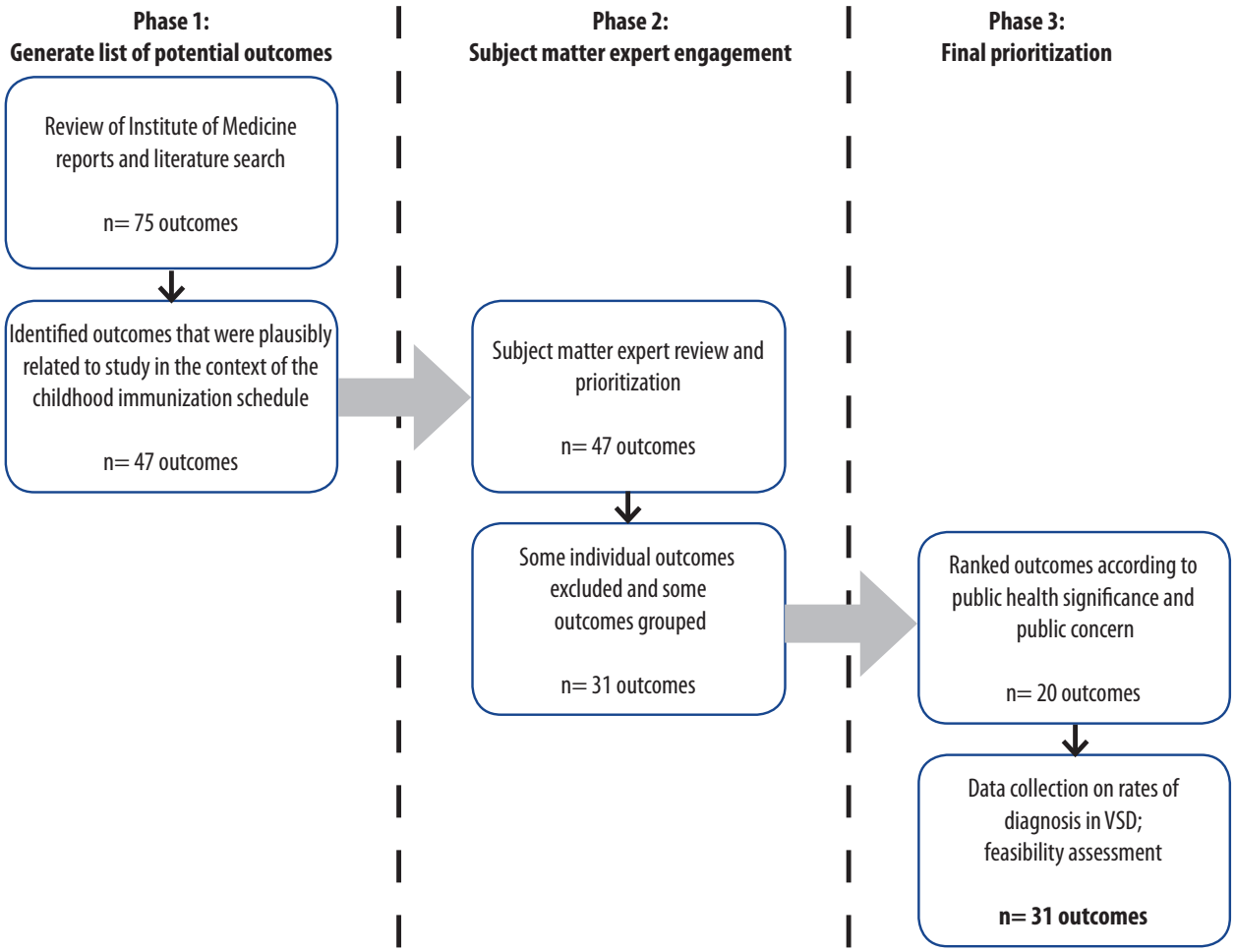
Identifying outcomes for observational studies in the VSD are typically conducted in four steps. In step 1, potential adverse events are identified in the automated medical encounter databases using ICD-9-CM codes. In step 2, trained abstractors – blinded to vaccination status – conduct a medical record review on the potential events to record the onset and timing of the events. The medical record review also documents additional clinical information that is not captured in the automated databases, such as symptoms, sequelae, medications administered, alternate diagnoses, referrals to specialists, and laboratory test results. In step 3, clinician investigators adjudicate the potential cases by validating the onset and timing of the event, and whether or not the event could be attributed to a cause other than vaccination. The results from the medical record review are used to calculate a confirmation rate, measuring the proportion of validated cases identified by ICD-9-CM codes. Past VSD studies show that confirmation rates for outcomes can range from 10% to 90%.[26,59-61] Lastly, in step 4, the validated cases are linked to their immunization records and prepared for analysis. With a case-control study, the cases are typically matched to non-disease controls by age, sex and MCO; for a cohort study, the cases are merged with a large population of vaccinated and unvaccinated individuals. All of these methods are then used to determine if vaccination is associated with a hypothesized adverse event.

In this chapter, we describe a rigorous multi-phased approach by which we identified, categorized and prioritized outcomes that the VSD could evaluate in the context of the childhood immunization schedule. This process was conducted in the following 3 phases (Figure 3.a):

1. Generate list of potential outcomes
2. Subject matter expert (SME) engagement
3. Final prioritization

Throughout the process we considered several criteria, including biologic plausibility, feasibility to study in the context of the entire immunization schedule, existing epidemiological evidence, feasibility to study in the VSD, public health significance, and public concern.

Figure 3.a: Process overview for identifying and evaluating outcomes



3.2 Generate list of potential outcomes (Phase 1)

The objective of the first phase was to compile a large, inclusive list of potential adverse outcomes that could be associated with the complete childhood immunization schedule. The initial sources of information were IOM reports from 2002, 2011 and 2013.[1,58,62] In addition to the IOM reports, Pubmed searches were conducted with the following search terms to broadly address vaccine-associated adverse events: "vaccine OR vaccination OR immunization" AND "adverse event OR adverse OR post-immunization OR post-vaccination". There were no time restrictions applied to the publication dates of the search.

References generated from the search were directly downloaded into EndNote (version X4, Thomson Reuters), and reviewed by the study team to identify articles related specifically to vaccine adverse events (e.g., vaccine efficacy or effectiveness studies were removed). This yielded epidemiological studies that either supported or rejected causal associations, as well as case reports suggesting potential linkages between vaccines and suspected adverse events. These outcomes were then grouped with the outcomes from the IOM reports, resulting in an initial list of 75 outcomes (Table 3.a) organized by either organ type (e.g., respiratory system, neurologic system) or reaction type (e.g., allergy, anaphylaxis).

For each outcome, the study team summarized and reviewed available evidence related to biological and mechanistic plausibility, and appropriateness of evaluating the adverse event in the context of the childhood immunization schedule. To determine biological plausibility, the study team assessed existing evidence of potential associations between specific aspects of the immunization schedule and particular adverse health outcomes. Moreover, the team

evaluated potential mechanisms by which receipt of all childhood immunizations could impact biological functions leading to the development of an adverse event. To assess appropriateness of evaluating an outcome relative to the entire schedule, the study team considered the acute/chronic nature of the outcome and the age at peak incidence. In addition, the team reviewed the existing epidemiological evidence to determine if outcomes could be clearly linked to a specific vaccine or combination of vaccines, suggesting that such outcomes should not be studied in relation to the entire schedule.

After internal discussions among the study team using these criteria, 28 outcomes were removed from the list. For example, outcomes such as stroke and myocardial infarction were not considered plausible for evaluation relative to the childhood immunization schedule given the later age of peak incidence and relatively low incidence among children. Additionally, outcomes such as serum sickness/Arthus reaction and measles inclusion body encephalitis were not considered plausible because of the direct association with specific vaccines and lack of biological plausibility for an association with the immunization schedule as a whole. Similarly, thrombocytopenia and immune thrombocytopenic purpura were excluded since they are known acute adverse events of specific vaccines.

At the conclusion of phase 1, the list of 75 outcomes was reduced to 47 plausible outcomes that could be studied relative to the childhood immunization schedule as a whole (Table 3.a).

Table 3.a: List of 75 outcomes identified for evaluation; 47 bolded outcomes were initially considered plausible to study relative to the childhood immunization schedule

All Cause
- **1. All cause morbidity**
- **2. All cause mortality**

Allergy/allergic condition
- **3. Allergy development**
- **4. Asthma development**
- **5. Anaphylaxis**
- **6. Chronic urticaria**
- **7. Asthma exacerbation**

Autoimmune disease
- **8. Crohn's disease and ulcerative colitis**
- **9. Kawasaki's disease**
- **10. Type 1 Diabetes**
- **11. Autoimmune hepatitis**
- **12. Psoriatric arthritis**
- **13. Juvenile rheumatoid arthritis**
- **14. Systemic lupus erythematosus**
- **15. Multiple sclerosis**
- **16. Autoimmune thyroiditis (Hashimoto's)**
- **17. Autoimmune thyroiditis (Grave's)**
- **18. Rheumatoid arthritis**

Blood/circulatory system disorders
- 19. Hypercoaguable states
- 20. Immune thrombocytopenia purpura
- 21. Polyarteritis nodosa
- 22. Thrombocytopenia
- 23. Thromboembolic events

Bone/joint
- 24. Ankylosing spondylitis
- 25. Arthropathy / chronic arthropathy
- 26. Arthalgia (chronic and transient)
- 27. Juvenile idiopathic arthritis
- 28. Polymyalgia rheumatica
- 29. Reactive arthritis

Demyelinating neurologic disorders
- **30. Acute disseminated encephalomyelitis**
- **31. Chronic inflammatory demyelinating polyneuropathy**
- **32. First demyelinating event**
- **33. Guillain-Barre syndrome**
- **34. Neuromyelitis optica**
- **35. Optic neuritis**
- **36. Transverse myelitis**

Cardio/cerebro-vascular system
- 37. Myocardial infarction
- 38. Myocarditis and pericarditis
- 39. Stroke

Seizures
- **40. Epilepsy**
- **41. Infantile spasms**
- **42. Afebrile seizures**
- **43. Febrile seizures**
- **44. Other seizures**

Other:
- 45. Erythema nodusum
- 46. Fibromyalgia
- 47. Oculorespiratory syndrome
- 48. Pancreatitis
- 49. Serum sickness and arthus reaction
- 50. Sudden infant death syndrome
- 51. Uveitis

Neurologic system
- **52. Autism spectrum disorders**
- **53. Bell's Palsy**
- **54. Brachial neuritis**
- **55. Cerebellar ataxia/ ataxia**
- **56. Encephalitis**
- **57. Encephalopathy**
- **58. Meningitis**
- **59. Narcolepsy and cataplexy**
- **60. Syncope and vasovagal reaction**
- **61. Learning, communication, and developmental disorders**
- **62. Attention deficit disorder**
- **63. Tourette's syndrome**
- **64. Tics**
- **65. Chronic fatigue syndrome**
- **66. Amyotrophic lateral sclerosis**
- **67. Chronic headache**
- **68. Hearing loss**
- **69. Opsoclonus myoclonus syndrome**
- **70. Small fiber neuropathy**

Varicella-zoster virus related conditions
- 71. Disseminated Oka varicella zoster virus, with subsequent infection
- 72. Disseminated Oka varicella zoster virus without organ involvement
- 73. Varicella zoster virus reactivation with subsequent infection
- 74. Varicella zoster virus reactivation without organ involvement

Measles virus related conditions
- 75. Measles inclusion body encephalitis

3.3 Subject Matter Expert (SME) engagement (Phase 2)

Once the initial list of 47 outcomes was in place, Emory University hosted a day-long meeting on February 25th, 2014, with VSD staff and three outside, internationally regarded experts in the area of vaccine science. The subject matter experts were Dr. Walter Orenstein of Emory University, Dr. Stanley Plotkin of the University of Pennsylvania, and Dr. Edgar Marcuse of the University of Washington. The objective of the meeting was to gain additional insight into the appropriateness of studying specific outcomes in the context of the childhood immunization schedule and to conduct an initial prioritization of the outcomes.

For the first two hours of the meeting, the study team and SMEs had an open discussion about each of the 47 outcomes, focusing on biologic plausibility, relevance to the entire immunization schedule, and feasibility to study in the VSD. After the discussion, the SMEs were instructed to classify each outcome as "include" or "exclude". The SMEs were also asked to comment on whether additional information (or data) was needed to determine the feasibility of studying the outcome relative to the entire immunization schedule within the VSD.

Of the 47 outcomes, the SMEs concluded that the following 4 outcomes could be excluded: Hashimoto's thyroiditis, Grave's disease, opsoclonus myoclonus syndrome and small fiber neuropathy. The first two were excluded because they rarely occur during childhood; the latter two were eliminated because they are extremely rare in the general population.

For the remaining 43 outcomes, the SMEs made several suggestions. First, since the emphasis was on long-term outcomes, the SMEs were concerned that outcomes with insidious onsets, long latencies, or unclear diagnostic characteristics (e.g., narcolepsy, fibromyalgia) would be difficult to study. They therefore stressed the importance of focusing on outcomes with clear diagnostic criteria, such as those having a definitive clinical diagnostic test or by having the ability to confirm case status with a manual medical record review. Second, the SMEs expressed the need to strongly consider public concern when deciding on outcomes to study. They said that, in certain instances, public concern may be a more important consideration than biologic plausibility. Some of the outcomes on the list – such as all cause morbidity/mortality and attention deficit disorder – reflect this opinion. Finally, the SMEs were concerned that many of the outcomes may be too rare to study in the VSD, and requested additional age-specific incidence data. They further suggested that several of the outcomes represented classes of conditions that could be grouped together (Table 3.b). For example, the SMEs recommended that a single outcome grouping called "first demyelinating events" could include acute disseminated encephalomyelitis, chronic inflammatory demyelinating polyneuropathy, Guillain-Barre syndrome, neuromyelitis optica, optic neuritis, and transverse myelitis.

Table 3.b: Individual outcomes that were grouped

Outcome group	Individual Outcomes
First demyelinating event	• Acute disseminated encephalomyelitis • Chronic inflammatory demyelinating polyneuropathy • Guillain-Barre syndrome • Neuromyelitis optica • Optic neuritis • Transverse myelitis
Seizures	• Febrile seizure • Afebrile seizure • Other seizures (seizures not otherwise specified)
Tics	• Tics • Tourette's syndrome

Despite the emphasis on long-term outcomes, there was also considerable discussion on the appropriateness of studying anaphylaxis, which is generally considered to be an acute event triggered by an acute exposure. However, since hypersensitivity reactions need prior sensitization to occur, it is possible that repeated exposures to a particular antigen or vaccine component could lead to the development of an underlying hypersensitivity state, which could be triggered by a follow-up booster dose. Therefore, it was concluded that anaphylaxis represents an acute event that may be evaluated in the context of the childhood immunization schedule. The final result of the SME meeting was an initial list of 31 prioritized outcomes.

3.4 Final prioritization (Phase 3)

Between April and July 2014, the study team reviewed the transcripts and formally prioritized the list of 31 outcomes using an iterative process.

The prioritization incorporated estimates of incident diagnoses to determine if outcomes could be feasibly studied in the VSD, and a newly developed rating system to estimate the public health concern and public health significance of each outcome. This final phase was conducted in 4 steps. For the first step, SAS® programs (SAS Institute, Cary, North Carolina) were run against each VSD site's data files to estimate age-specific incidence rates of diagnosis for 29 of the 31 outcomes identified in phase 2. Incidence rates were not estimated for all-cause morbidity and all-cause mortality since they are not readily estimated from ICD-9-CM codes. For the 29 conditions, incidence rates were calculated in a cohort of 321,522 children born between 2004 and 2010. Each child in the cohort had 3 years of continuous enrollment from birth (allowing a 6 week grace period), and children were followed for a maximum of 8 years. Outcomes in the cohort were represented by electronic ICD-9-CM codes determined by the study team (Table 3.c). The first occurrence of each outcome during a child's follow-up was identified, and crude incidence rates were calculated for the 0–2 year and 3–8 year age groups.

Table 3.c: ICD-9-CM codes used to estimate age-specific incidence rates in VSD data

	Description	ICD-CM-9 codes
1	Development of allergy	372.14, 477.x , 495.8x, 495.9x, 558.3x, 558.4, 691.8x, 692.x , 708.x , 995.3x, V15.0x
2	Asthma	493.x
3	Anaphylaxis	995.0x, 995.1x, 995.2x, 995.3x , 995.4, 995.6x, 999.4x
4	Chronic urticaria	708.x
5	Crohn's disease and ulcerative colitis	555.x, 556.x
6	Kawasaki's disease	446.1x
7	Type 1 Diabetes	250.x
8	Chronic hepatitis	571.4x
9	Psoriatic arthritis	696.0x
10	Juvenile rheumatoid arthritis	714.3x
11	Lupus	710.0
12	Multiple sclerosis	340.x
13	First demyelinating event	323.6x, 341.0x, 341.2x, 357.0x, 357.81, 377.30, 377.31, 377.32, 377.39
14	Autism spectrum disorders	299.x
15	Bell's Palsy	351.0x
16	Brachial neuritis	723.4x
17	Cerebellar ataxia	334.3x, 334.4x
18	Encephalitis	049.9x, 323.5x, 323.6x, 323.8x
19	Encephalopathy	348.3x
20	Meningitis	047.9x, 322.x
21	Cataplexy and narcolepsy	347.x
22	Syncope and vasovagal reaction	780.2x
23	Learning, communication, developmental disorders	315.x
24	Attention deficit disorder	314.x
25	Tics and Tourette's syndrome	307.2x
26	Chronic fatigue syndrome	780.71
27	Epilepsy	345.x but not 345.6x
28	Infantile spasms	345.6x
29	Seizures	780.3x but not 780.33
30	All-cause mortality	Incidence rate not assessed
31	All-cause morbidity	Incidence rate not assessed

ICD-9-CM=International Classification of Diseases, 9th edition, Clinical Modification

In step 2, the study team reviewed the incidence rates and classified each outcome as being either feasible or not feasible to study in the VSD. A cut-off incidence of 5 cases per 100,000 years of follow-up among children ages 3 to 8 years was used, as this is generally the smallest rate by which outcomes have been studied in the VSD.[61,63,64] This step eliminated 10 of the 31 outcomes (Table 3.d).

For step 3, study team members ranked each of the remaining 21 feasible outcomes on public health significance and public concern. For public health significance, team members were asked to consider the seriousness of the condition, the rarity of the condition, whether the condition was increasing in prevalence and whether the outcome has already been studied as an adverse event. For the last criterion, we assumed that if an outcome has been extensively studied as a vaccine adverse event, additional studies would not have a significant public health impact. For public concern, team members considered the seriousness of the outcome, and whether vaccine hesitant parents would associate the outcome with vaccination. Team members based this determination on existing vaccine hesitancy research in the literature, our own ongoing vaccine hesitancy research, and (where applicable) our own clinical experiences. Using all of these criteria, team members ranked each of the 21 outcomes on a 1 to 5 scale for public health significance and public concern. A score of 1 represented the lowest ranking and 5 the highest. The two scores were then summed together and averaged across the study team, resulting in a combined score between 1 and 10 for each outcome.

In the final step, the rankings were reviewed and discussed by the study team. In these discussions, team members could make the case to move outcomes up, down or off the priority list. For example, *first demyelinating event* was initially classified as not being feasible, but was moved up the priority list because it is a potentially serious outcome that was ranked highly on public concern. *Autism*, in contrast, was moved off the priority list because it has been extensively studied relative to the vaccination schedule,[38,65-67] despite its high public concern ranking. The final ranked list of outcomes is displayed in Table 3.e.

Table 3.d: Outcomes classified as feasible or not feasible based on age-specific incidence rates estimated with VSD data

	Estimated incidence rate of diagnosis per 100,000 person-years	
	Birth - Age 2	**Ages 3 - 8**
Feasible		
All-cause morbidity	Not estimated	Not estimated
All-cause mortality	Not estimated	Not estimated
Allergy development	14,996	4,455
Anaphylaxis	2,139	1,373
Asthma development	4,481	2,688
Attention deficit disorder	13	655
Autism spectrum disorders	236	297
Bells' Palsy	15	11
Chronic urticaria	2,453	1,415
Crohn's disease and ulcerative colitis	6	5
Encephalopathy	16	9
Epilepsy	159	105
First demyelinating event*	4	4
Juvenile rheumatoid arthritis	9	9
Kawasaki's disease	34	16
Learning, communication, developmental disorders	3,196	1,387
Meningitis	33	7
Seizures	1,066	209
Syncope and vasovagal reaction	66	111
Tics	52	235
Type 1 diabetes	21	25
Not feasible		
Brachial neuritis	1	<1
Cataplexy and narcolepsy	<1	1
Cerebellar ataxia / ataxia	5	3
Chronic fatigue syndrome	1	<1
Chronic hepatitis	4	1
Encephalitis	4	3
Infantile spasms	12	<1
Multiple sclerosis	<1	<1
Psoriatic arthritis	1	<1
Systematic lupus erythematosus	1	<1

* Although first demyelinating event was initially classified as not being feasible due to low incidence, it was re-classified as feasible to study because it is a potentially serious outcome that was ranked highly on public concern

Table 3.e: Ranking of outcomes on feasibility, public health significance, and public concern

		Average public concern ranking	Average public health significance ranking	
		Ranked from 1 (lowest) to 5 (highest)		Final combined ranking
1	Asthma development	4.33	4.17	8.50
2	Anaphylaxis	3.67	4.67	8.34
3	Encephalopathy	4.75	3.50	8.25
4	All-cause mortality	4.17	3.83	8.00
5	Meningitis	4.00	4.00	8.00
6	Learning, communication, developmental disorders	5.00	2.83	7.83
7	Epilepsy	4.00	3.83	7.83
8	Type 1 diabetes	4.00	3.83	7.83
9	First demyelinating event	4.17	3.66	7.83
10	Allergy development	4.17	3.33	7.50
11	Attention deficit disorder	4.67	2.83	7.50
12	All-cause morbidity	4.17	3.17	7.34
13	Crohn's disease and ulcerative colitis	4.17	3.17	7.34
14	Syncope and vasovagal reaction	3.17	3.17	6.34
15	Seizures	3.50	2.67	6.17
16	Kawasaki's disease	3.33	2.83	6.16
17	Juvenile rheumatoid arthritis	3.50	2.50	6.00
18	Tics	3.50	2.17	5.67
19	Chronic urticaria	2.83	2.00	4.83
20	Bells' Palsy	2.67	1.50	4.17

Chapter 4: Methods

4.1 Introduction

Chapter 2 of this White Paper identified various methods for defining childhood vaccine exposures at the level of the immunization schedule. These included continuous measures, such as average days undervaccinated, and categorical measures, identified either from known alternative schedules or from data mining techniques. Chapter 3 covered health outcomes of interest and developed a priority listing of outcomes based on plausibility and feasibility. This chapter reviews key considerations for the design and analysis of vaccine schedule safety studies. It begins with a summary of key points from the methods expert meeting conducted as part of this paper's development, and general principles derived from the meeting. It then discusses specific study design considerations, framed in terms of the biases that may affect immunization schedule safety studies in the VSD. This is followed by a review of the strengths and limitations of various study designs, and a discussion of analytic approaches. This chapter closes by describing an example study of asthma risk associated with different vaccine schedules, with illustrations of how various biases may be handled.

4.2 Summary of subject matter expert meeting

On June 27th, 2014, Group Health Research Institute hosted a meeting of VSD contributors and outside experts in drug and vaccine safety methodology. The meeting's objectives were to elicit recommendations from the outside experts on principles and analytic approaches for assessing the safety of the childhood immunization schedule. The outside experts were Martin Kulldorff, of Harvard Medical School, and M. Alan Brookhart of the University of North Carolina. They were joined by Mike Jackson and Lisa Jackson from Group Health; Jason Glanz and Sophia Newcomer of Kaiser Permanente Colorado, and (by teleconference) David McClure of Marshfield Clinic Research Foundation. The methodology experts made a number of recommendations for VSD studies of vaccine schedule safety:

- Plan for multi-step investigations
  - » Initial studies can determine outcomes and schedules for which an association exists
  - » Follow-up studies can investigate which aspects of the schedule(s) are responsible for the associations
  - » Initial studies should focus on identifying or ruling out large risks (which are less likely to be affected by bias) rather than on small increases in risk
- Defining immunization schedules
  - » Continuous summary measures are preferable to categorizing subjects into groups due to increased statistical power
  - » Comparing fully vaccinated children to totally unvaccinated children would likely be highly confounded
  - » Data-driven methods can be used to create summary measures, such as "distance" from various defined schedules.
  - » Alternatively, multiple measures of vaccination receipt and timing can be incorporated into a single multivariable regression model to assess which aspects of a schedule may need further investigation (although collinearity of covariates is a concern with this approach)
  - » "Per Protocol" approach is another alternative for events that occur before the completion of the schedule
- Methods
  - » Initial studies should use designs and methods whose properties are well-known (cohort and case-control studies in particular).
  - » Cohort studies can either use survival analysis to properly censor subjects when they experience events of interest, or define age at cohort entry such that exposure has occurred before entry and all events of interest occur after.

- Confounding and bias
  - » Focus on ruling out (or identifying) large effects, as small effects could more easily be the result of unmeasured confounding
  - » It may be important to collect data on confounders that are not typically measured in administrative data, such as parental education
  - » Measures of healthcare utilization will be important
  - » Negative controls can be used to test for the presence of bias and uncontrolled confounding
  - » Confounding due to differences in healthcare utilization is less likely for severe outcomes (i.e., those requiring hospitalization)
  - » Restricting may be an important tool for controlling confounding, at the possible expense of generalizability
- Possible opportunities for ecological studies
  - » Comparing vaccination rates and outcomes across clinics within the VSD MCOs
  - » Comparing outcome rates over time (e.g., pre- and post-introduction of rotavirus vaccines)

General principles from the expert meeting

Both the White Paper VSD team and the external methods experts agree that the field of vaccine schedule safety is in its infancy. As such, we recommend that VSD studies should begin by ruling out (or identifying) large differences in risk of adverse events between children who receive the ACIP recommended vaccines vs. undervaccinated children. This work should be conducted using common study designs whose properties and biases are well understood. For most of the outcomes of interest, this would involve cohort studies to estimate incidence rate ratios or hazard ratios. For certain outcomes that might require confirmation via medical record review, case-control studies would be preferred. More sophisticated methods such as two-stage sampling,[68] counter-matching,[69] or case-only designs[70] should be reserved until after basic methods have provided more insight into confounding and biases in schedule-level studies.

There is also agreement on the need to plan for multi-stage investigations when designing schedule safety studies. The first stage involves identifying whether an outcome of interest is associated with a particular schedule (or vaccination summary measure). If an association is detected, this should be followed by additional studies investigating what aspects of the schedule/summary measure are associated with the outcome. The specific aspects will depend on the observed association but will likely include timing of doses, number of concomitant vaccines, and/or specific vaccines excluded or delayed.

4.3 Study design considerations

As with any observational study, the goal of good design for VSD schedule-level safety studies is to rule out non-causal explanations for the study findings: chance, selection bias, information bias, and confounding, as well as reverse causality.[71] We first review these alternative explanations and their likely impacts on vaccine schedule safety studies. We then present a sample VSD study to illustrate the design considerations in practice.

Reverse causality

Reverse causality, where onset of the study outcome may influence the exposure (i.e. completion of a particular vaccine schedule), is a concern whenever the study outcome can occur prior to completion of one of the immunization schedules of interest. Parents may alter their intended immunization schedules for a child who experiences a negative health outcome, particularly if the outcome is perceived to be a result of a vaccine. For example, a child receiving vaccines according to the ACIP schedule could have an anaphylactic reaction following the third dose of DTaP vaccine. In response, the child's parents or provider may defer or refuse future vaccine doses, so that the child does not complete the ACIP schedule. In schedule safety studies, vaccination and event times must be carefully measured, and subjects must be censored after they experience a study outcome.

Of greater difficulty are studies of outcomes that are diagnosed after the age at which the schedule is completed, but that have a gradual or insidious onset. In such cases, early signs or indications of disease may be apparent to the parents, who may alter their child's vaccination patterns in response, but in advance of any clinical diagnoses. VSD schedule safety studies using endpoints that may have gradual onset should consider the possibility of reverse causality.

Confounding

Confounding is likely to be a serious threat to the validity of schedule-level safety studies. Children who receive the ACIP-recommended vaccines differ in meaningful ways from children who do not. Parental refusal or delay of childhood vaccines varies by race/ethnicity, household income, parental education, and household size, among other factors.[13,52] The incidence of many safety outcomes of interest also varies by these factors. Incidence of physician-confirmed asthma, for example, varies by race/ethnicity, number of siblings, and household socioeconomic status (often mediated through differences in environmental exposures), among many other factors.[72,73] Any studies of vaccine schedule and risk of incident asthma in children will be potentially confounded by these factors.

A particular challenge for vaccine schedule safety studies is that many potential confounders are difficult to measure using EHR data. Household size and socioeconomic status, for example, are very difficult to capture based on administrative data. Linking enrollees together based on insurance plans or addresses can give approximate measures of household size but will miss any household members who have different insurance plans, and do not include any measure of household density. Careful consideration must be given to identify potential confounders that must be measured, perhaps through the use of causal models such as directed acyclic graphs (DAGs),[74] prior to beginning any schedule safety study. In a causal DAG, the investigator describes variables (nodes) representing exposure and outcome, and covariates that the investigator believes to be causally related to exposure and outcomes. The investigator connects these nodes using arrows to represent the expected direction of causal action. For example, if maternal education is expected to affect childhood vaccination, the investigator would draw an arrow from the "maternal education" node to the "childhood vaccination" node. After the investigator has used the DAG to describe all of the assumptions about the relevant variables, the DAG can be used to identify potential confounders and variables whose control can reduce confounding in estimates of the exposure-disease association. Use of these causal models can help investigators identify whether key confounders can be controlled for by administrative healthcare data, whether additional data collection will be necessary, or whether important confounders may be unmeasurable.

Given the expected difficulties in measuring potential confounders, we recommend that VSD studies of vaccine schedule safety incorporate methods to detect the influence of uncontrolled confounding. One feasible approach is to analyze the association between the vaccine schedule and one or more "control" outcomes.[75] In this context, control outcomes are diseases that have no expected causal association with the vaccine schedule. If a study finds an apparent association between the vaccine schedule and the control outcome(s), this is evidence that important differences exist in baseline health status, socioeconomic status, healthcare utilization, or other covariates between exposure groups, suggesting that uncontrolled confounding may be present in the main study results. Depending on the outcome under study, possible control outcomes could include injuries, well-child visits, or neoplasms.

To illustrate, minor injuries might be a useful control outcome for safety studies where the outcome would typically not require hospitalization. These might be defined as outpatient visits with an ICD-9-CM code of 800-829 (fractures), 840-848 (sprains and strains), or 940-949 (burns) for which there is no hospitalization for similar codes within the two preceding or following months. There is no plausible biologic pathway by which vaccines could cause these minor injuries. Any association between immunization schedule and minor injuries must be due to confounding from sociodemographic factors that put some children at an increased risk of minor injuries, or to

parental healthcare seeking preferences for non-emergency conditions. *A priori* we might expect that confounding due to parental preferences for healthcare utilization might be similar for minor injuries as for outcomes such as allergies, asthma, or attention deficit disorder, making minor injuries a potential control outcome for these outcomes. VSD investigators could use a retrospective cohort study to assess whether minor injuries are appropriate control.

To illustrate with incident asthma in children 2-4 years of age as the safety outcome of interest, the population would consist of all children enrolled in the VSD from birth through 23 months of age who were fully vaccinated according to the ACIP schedule. These children would be stratified into groups based on measurable sociodemographic data (e.g., census tract, race/ethnicity) and healthcare utilization (e.g., number of outpatient visits prior to the second birthday). Children would be followed from their second birthday until the earliest of MCO disenrollment, death, or their fifth birthday. The investigators would calculate the rates of incident asthma and of incident minor injury within each sociodemographic/utilization stratum. If this incidence rate ratio is the same across strata, this suggests variations in sociodemographics and utilization have similar effects on incident diagnoses of asthma and minor injuries, independent of vaccination history (since all children are fully vaccinated). Under the assumption that vaccination does not impact minor injuries, this would be evidence that minor injuries are an appropriate control outcome for asthma.

Information bias

Information bias results whenever exposures, outcomes, or model covariates are measured imperfectly. Misclassification of vaccination history or covariates that is non-differential with respect to the outcomes will tend to bias effect estimates towards the null. The same is true for misclassification of outcomes or covariates that is non-differential with respect to vaccine history. Differential misclassification, in contrast, can bias effect estimates either toward or away from the null.

In vaccine schedule safety studies, a particular concern is differential misclassification of outcomes and covariates based on vaccination history. Children who are undervaccinated due to parental choice have lower rates of healthcare utilization (both outpatient visits and emergency department encounters) than fully vaccinated children.[3] Differential healthcare utilization between fully vaccinated and undervaccinated children has several consequences for information bias. First, data on covariates such as body mass index and comorbid illnesses may be less available for undervaccinated children than for fully vaccinated children. This can lead to differential misclassification of covariates, such as greater missing data among undervaccinated children or falsely considering undervaccinated children to be disease-free with respect to comorbidities of interest.

Second, differences in healthcare utilization mean that adverse outcomes may be less likely to be detected in undervaccinated children compared to fully vaccinated children. Severe adverse outcomes may be detected later in undervaccinated children, if parents delay seeking healthcare or specialty care to confirm possible diagnoses. Delayed or missing outcome data in undervaccinated children will falsely reduce the observed incidence in these children, biasing effect estimates such that undervaccination appears safer than it truly is.

Several general approaches can be used to reduce the problem of differential misclassification between fully vaccinated and undervaccinated children. First, study populations can be restricted to children for whom similar information is likely to be available in EHRs and administrative databases, perhaps by matching fully and partially vaccinated children on the number of well-child visits or total outpatient visits they have as of a specified age. This could be done by setting some minimum utilization criteria for all study participants, such as restricting the study population to children who have been continuously enrolled since birth and who have had at least, for instance, three MCO outpatient visits during the first year of life. Alternatively, the investigators could match fully vaccinated subjects to undervaccinated subjects on number of outpatient medical encounters.

Where restriction is not possible, attempts should be made to define the sensitivity/specificity or medical record confirmation rate of the measured outcome and key covariates in fully vs. undervaccinated children (perhaps through a limited medical record review, although such records may not contain the necessary information). These can be used to correct effect estimates for misclassification.[76,77] or, at a minimum, perform sensitivity analyses to put bounds on the error due to misclassification.

Selection bias

VSD cohort studies are relatively resistant to selection bias, as the study population generally includes all members of the enumerated VSD population who meet some eligibility criteria, independent of exposure or outcome status. Selection bias in VSD vaccine schedule safety studies can be minimized by ensuring that all exclusion criteria are applied equally to fully vaccinated and undervaccinated children (in cohort studies) or to cases and controls (in case-control studies). As a simplistic example, consider a study comparing children vaccinated according to the ACIP schedule (where all doses are completed by 18 months of age) with unvaccinated children. The investigators might want to reduce possible information bias due to apparently unvaccinated children actually receiving vaccines outside the VSD MCOs. For this, they might exclude unvaccinated children who had fewer than four outpatient visits during the first two years of life. If they do not also exclude fully vaccinated children with fewer than four outpatient visits during the first two years of life, selection bias could be introduced into the study. Since unvaccinated children are selected to be more frequent users of the MCO than vaccinated children, outcome rates may appear to be higher in unvaccinated children than vaccinated children due to this selection rather than to a true vaccine effect.

Chance

Random chance is ruled out as an explanation for study findings when studies are adequately powered to detect the effect size of interest. Power/sample size calculations should be performed before beginning any VSD study. To provide some general guidance on the feasibility of certain types of studies, this section presents detectable effect sizes for some hypothetical studies of vaccine schedules and various outcomes of interest.

A current VSD study on vaccine ingredients[43] defined a cohort of VSD children born between 2004 and 2011 who were continuously enrolled from 2 to 24 months of age, had more than one outpatient visit during that time, and received no vaccines for which the manufacturer was unknown. This cohort consisted of 303,070 children. Of these, 152,871 (50.9%) were fully vaccinated according to the ACIP schedule, 5,492 (1.8%) were vaccinated consistent with a defined alternative schedule, 3,404 (1.1%) had no vaccination records in the VSD databases, and 1,898 (0.6%) had no vaccines and at least one V-code for vaccine refusal. Based on this cohort, we estimated the minimum detectable incidence rate ratios from a cohort study comparing rates of events after two years of age in the fully vaccinated children to either children following a defined alternative schedule or to unvaccinated children with a V-code for refusal. In this design we assume that unvaccinated/partially vaccinated children are matched 1:10 with fully vaccinated children based on variables such as number of outpatient visits.

The preliminary calculations shown in Table 4.a suggest that studies of adverse events in children vaccinated according to the ACIP schedule compared to unvaccinated children or children vaccinated with an alternative schedule should be well powered to detect meaningful differences in risks of common events. These power calculations did not take into account any potential for confounding. For a given outcome, direct adjustment or cohort restriction may be necessary to address confounding. These power calculations should therefore only be used as a general guide. The incidence of asthma development and allergy development all exceed 1,000 per 100,000 person-years in VSD children 3-8 years of age. For such outcomes, VSD studies with two or more years of follow-up can detect 30% increases in risk associated with the ACIP schedule relative to other specific schedules. In contrast, VSD studies may only be able to rule out large differences in risk for rare outcomes such as meningitis, encephalopathy, and development of type I diabetes, which have incidence of <30 per 100,000 person-years in children 3-8 years of age.

Table 4.a: Minimum detectable incidence rate ratios (IRR) at different expected incidence rates in comparison children and durations of follow-up, assuming 80% power, 25% annual loss to follow-up, and a Type I error rate of 0.05

Incidence per 100,000 person-years in comparison group	Comparison group	Minimum detectable IRR assuming:	
		Five years of follow-up	Two years of follow-up
1,000	Alternative schedule	1.24	1.33
1,000	Unvaccinated	1.44	1.6
100	Alternative schedule	1.9	2.26
100	Unvaccinated	2.75	3.56
10	Alternative schedule	5.19	7.42
10	Unvaccinated	10.66	16.43
5	Alternative schedule	8.16	12.28
5	Unvaccinated	18.37	29.38

4.4 Study designs: strengths and limitations

Case-control, cohort, risk-interval, and ecological designs have all been used in assessments of vaccine safety. Each design has advantages and disadvantages that make it more or less fit to specific vaccine safety questions. The general strengths and limitations of basic epidemiological study designs will not be discussed here, as they have been extensively covered in numerous sources.[78,79] Rather, this section discusses the strengths and limitations of these designs relative to possible sources of bias in vaccine schedule safety studies conducted in the VSD.

Cohort studies

Cohort designs are often the design of choice for VSD studies,[80-82] particularly those requiring only administrative healthcare data. Cohort designs offer several advantages for studying vaccine schedule safety. Because the VSD population is fully enumerated, with detailed data on MCO enrollment, VSD cohort studies typically avoid problems of selection bias, so long as all eligibility restrictions are applied equally to all study subjects regardless of exposure status. When steps are taken to ensure that cohort members are disease-free as of the start of follow-up, cohort studies with careful attention to exposure times and with appropriate censoring avoid problems of reverse causality. Cohort studies are also very well suited to the use of control outcomes, which are likely to be of considerable importance for detecting residual bias and confounding. Another benefit of cohort studies is ease of calculation of attributable risk, which is often an important metric for policy-making.

Cohort designs are, of course, more difficult for studies that may require primary data collection on all study subjects via surveys, medical record reviews, or other measurements. Due to the potential information biases when comparing fully vaccinated children to undervaccinated children who lack an ICD-9-CM code for vaccine refusal, there may be many safety questions of interest that require additional data collection to overcome information biases. Cohort studies have limited utility for these situations.

Case-control studies

Case-control studies are less common than cohort studies in the VSD, but they are used occasionally.[83] For vaccine schedule safety studies, case-control studies are likely to be of use when information biases would result from relying solely on administrative healthcare data and additional data collection is needed. As an example, a study could identify children diagnosed with a health outcome (for example, Type 1 diabetes) between ages 3 and 8 and match them to children without that health outcome. Then, researchers could look back and determine whether each child was fully vaccinated per ACIP recommendations or whether they were on an alternative vaccination schedule. Primary data collection may be necessary since complete immunization histories may not be available for

cases or controls who enrolled in their MCO later in childhood. In that study, it may also be important to conduct medical record reviews or parental surveys of children apparently following the alternative schedule, to verify that the children were not receiving vaccines outside of the VSD MCOs. The cost of additional data collection is typically more feasible in a case-control design than in a cohort design.

Case-control designs tend to be more susceptible to selection biases than cohort designs. Choosing an improper control group in particular can often lead to selection biases in case-control designs. Within the VSD, some of the typical problems of control selection (such as selecting appropriate control groups from hospitals with uncertain catchment areas) may be reduced because the case-control sample is nested in an enumerated cohort. Case-control studies are also more susceptible to errors of reverse causality than cohort studies, and require careful definitions of outcome onset times and exposure periods. Due to the challenges of studying multiple outcomes in a case-control study, control outcomes to detect bias are difficult to use with case-control designs.

Risk-interval designs

Self-controlled case series and other similar risk-interval methods have been used with increasing frequency in the VSD.[59,64] Self-controlled designs are well suited to control for confounding due to time-invariant factors, and greatly reduce problems with selection bias from sampling cases and controls or from defining groups based on exposure history. However, self-controlled designs have two main disadvantages for vaccine schedule safety studies. First, self-controlled designs are best suited to events occurring in a short risk window following exposure.[84] In contrast, many of the schedule safety outcomes of interest occur months or years after the completion of the vaccination schedule. Second, self-controlled designs have generally been applied to exposures that occur over a short period of time, such as an individual vaccination or a cellular telephone conversation.[85] Little work has been done on the use of risk-interval designs with long-term exposures such as vaccination schedules.

Another design recently developed for VSD studies is the case-centered approach. This design is not self-controlled, and it relies on examining risk intervals for the exposure (vaccination) rather than the outcome. With the case-centered design, the observed odds of vaccination during a time interval before an outcome is compared to the expected odds of vaccination in that same interval.[82] Like other risk interval methods, application of this method has not been extended to studies of entire immunization schedules and long-term outcomes.

Ecological studies

The external experts suggested several possible ecological studies that could be conducted to examine vaccine schedule safety. One suggestion was to compare rates of adverse events between countries that have different recommended vaccination schedules. This type of comparison is outside the scope of the VSD and is not considered further here. A second suggestion was to compare rates of adverse events within the VSD population from different time periods. For example, event rates from 2005-2006 could be compared to event rates from 2007 and after to assess the impact of the addition of rotavirus vaccines to the schedule.[86] ACIP has made relatively few additions to the recommended vaccines for children <2 years of age in the past decade (rotavirus, universal influenza vaccine,[86] switch to PCV13 from PCV7[87]), which limits the schedule safety questions that can be answered with time-based ecological studies.

A third suggestion was to compare adverse event rates for clinics within the VSD MCOs. Pediatricians and family medicine physicians vary in the degree to which they encourage adherence to the ACIP schedule among their patients.[89] If there is clinic-level variation in the promotion of the ACIP schedule, there may be clinic-level variation in childhood immunization and in corresponding rates of adverse events. There may also be clinic-level variation in diagnosis of outcomes; for example, variations in prevalence of referrals for neurodevelopmental assessment. A clinic-level ecological study may be feasible within the VSD. To assess feasibility, a preliminary study could assess whether there is clinic-level variation in vaccination summary measures such as days undervaccinated, and whether the variability is exists across clinics within an MCO or only across MCOs. These types

of group-level studies are prone to ecologic fallacy and bias from confounding, and such studies should be approached with caution.

4.5 Analytic methods

Precise analytic methods for any vaccine schedule safety study will depend on the exposures and outcomes of interest, the study design, and the study population, among other factors. With that in mind, this section provides some general guidance for study analysis.

Statistical methods and effect measures of interest

In cohort studies, the effect measures of interest for causal inference are generally either hazard ratios, incidence rate ratios, or risk ratios. The choice of effect measure depends on scientific interest, on available data, on the assumptions deemed to be reasonable by the investigators, and (to some degree) on computational power. Where individual-level data are available on entry, event, and censoring times, and where proportional hazards can be assumed (or deviations from proportional hazards can be modeled) investigators can estimate hazard ratios using Cox regression models. These will likely be the most common data for vaccine schedule safety studies, as careful attention will need to be given to exposures times and dates of start and stop of follow-up to avoid reverse causality.

With similar data but when the proportional hazards assumption is not met, or where the population size makes Cox regression computationally intractable, incidence rate ratios can be estimated using Poisson or negative Binomial regression models. Incidence rate ratios can also be estimated when only aggregate data on person-time and events are available, although this is rarely a limitation in VSD studies. Due to detailed person-level data available on the VSD population, it is uncommon for VSD studies to have only data on the fact of an event without the corresponding person-time at risk. In this event, however, risk ratios can be calculated using Poisson regression with robust variance estimates[89] or via log-binomial regression.

Case-control studies typically involve estimating odds ratios to estimate (when using incidence density sampling) or approximate (when using a cumulative design) risk ratios.[79] Odds ratios are generally estimated using logistic regression models.

Models for exposure

As discussed above, vaccine exposures can either be modeled by grouping subjects into categories (perhaps defined by data mining techniques) or by using continuous summary measures of exposure or by deviation from specific schedules. If we conduct a cohort study of outcome risk using a categorical exposure measure, we might collapse subjects into categories based on exposure categories and covariates and calculate total events and person-time in each category. In this approach, each unique vaccination schedule would be represented by a binary covariate indicating whether a subject was compliant (=1) or not (=0) with that particular schedule.

To illustrate, consider a study comparing the incidence rate of some event in children 2-3 years of age between children who are fully vaccinated, children who are unvaccinated, and children vaccinated according to "Dr. Bob's selective schedule."[28] In this study, incidence rate ratios could be estimated using a Poisson regression model such as this:

$$\log(E(Y|x\_1,x\_2,z))=\alpha+\beta_1 ACIP+\beta_2 Dr.Bob+\beta z+\log(pt)$$

where Y is the count of events, **z** is a vector of covariates, and pt is person-time. The *ACIP* and *Dr.Bob* variables indicate compliance with either the ACIP or Dr. Bob's selective schedules, with unvaccinated children serving as the reference group. The parameters β_1 and β_2 are the log rate ratios for the ACIP schedule or Dr. Bob's selective schedule, respectively, relative to no vaccination.

Note that, if the study design involved following children for outcomes that could occur prior to the completion of the schedule, it is possible that a subject could be compliant with more than one vaccination schedule at some time point. For example, multiple categories might involve giving no doses prior to one year of age. For follow-up time prior to one year of age, subjects receiving no vaccines would be classified as compliant with all such schedules.

Alternatively, we may conduct a study using a summary measure such as average days undervaccinated (ADU). Consider conducting a survival analysis for time to first event, with ADU as the primary exposure of interest. Hazard ratios could be estimated from a model such as:

$$\log(E(\lambda(t|ADU,z)))=\log(\lambda\_0)+\beta_1 ADU+\beta z$$

where $\lambda(t)$ is the hazard function and $\lambda_0(t)$ is the baseline hazard. In this model, β_1 is the log hazard ratio for a one-unit increase in ADU. This model assumes that there is a linear relationship between ADU and $\log(\lambda(t))$. In practice, the association between ADU and outcome may not be expected to follow a linear function. In that case, ADU could be parameterized using a polynomial or spline function, or by dividing ADU into clinically relevant categories and including these as a set of binary variables in the model.

Sensitivity analyses for misclassified data

As mentioned above, measurement error in vaccination history, important confounders, or outcomes can bias study results. Collecting data using gold-standard measurements (such as medical record review or interview with parents) is, naturally, the most effective method for reducing measurement error. However, it is often impractical or impossible to collect data on all study subjects using these labor-intensive methods. Another approach to possible information bias is to first quantify the measurement error present in the administrative data (through surveys or medical record reviews conducted within the VSD MCO populations).

To illustrate the additional data collection, consider important covariates such as parental education or household socioeconomic status. These are generally not captured by administrative healthcare data and must either be measured using separate surveys or by proxies such as census tract data. A proposed study to estimate misclassification associated with use of census tract data is to conduct a cross-sectional survey of VSD households. For this, VSD investigators would select a random sample of children in the VSD population as of the study start data, with block randomization based on some measures of census tract characteristics such as median income. Surveys would be sent to these households, requesting data on key features such as race/ethnicity, parental education, and measures of socioeconomic status. The investigators would then estimate the sensitivity and specificity of census tract data for these factors, relative to the gold standard of self-reported data.

Alternatively, VSD investigators could conduct a systematic literature review and meta-analysis of published studies on the accuracy of census tract data relative to individual-level data. This approach may provide more comprehensive data and greater statistical power than a survey conducted within the VSD. However, it has the limitation of not being specific to the VSD population, making extrapolation to VSD studies uncertain.

After quantifying the expected degree of misclassification, these quantifications can be used to adjust the effect estimates of interest for the presence of misclassification.[90] Where this is not feasible, the measurement error data can still be used to put bounds on the effects of misclassification, via sensitivity analyses or simulation studies.

One approach to simulation studies for misclassification is to create simulated datasets of the study population. These simulated dataset are based on the observed study data, but with the exposure, outcome, or covariate data of the simulated subjects randomly altered based on estimates of misclassification in the observed data.[91] Consider a study comparing fully vaccinated children to unvaccinated children, so defined based on MCO vaccination records. Suppose that analyses of VSD populations suggested that 20% of apparently unvaccinated children had in fact received all the recommended vaccines, but outside the MCOs, and so were actually fully vaccinated. The investigators could then simulate a series of datasets. In each dataset, simulated subjects would be randomly sampled from the observed study populations. Sampled unvaccinated subjects, would randomly be classified as vaccinated (using, for example, Monte Carlo methods).[92] The association between vaccination and outcome would be estimated in each simulated dataset. The median (2.5^{th}, 97.5^{th} percentiles) estimate from the simulated datasets would represent the expected association (with 95% confidence limits) accounting for the misclassification.

Sensitivity analyses could also be used to put bounds on the expected effects of misclassification on study results. Using the example of 20% misclassification of unvaccinated subjects above, investigators could repeat the study analyses but reassigning 20% of the unvaccinated children to the fully vaccinated category. The bounds of the effect of misclassification could be estimated by first reclassifying only children who experienced the outcome of interest (moving effect estimates maximally toward a beneficial effect of unvaccination), and then by reclassifying only children who did not experience the outcome (moving effect estimates maximally toward a beneficial effect of vaccination).

Healthcare utilization: design and analysis methods

Differences in healthcare utilization between fully vaccinated and undervaccinated children poses particular problems for vaccine schedule safety studies. As discussed in the information bias section, one concern is the potential for information bias due to differences in utilization. Several options are available to handle differences in utilization. Perhaps the most effective would be to restrict the study population on the basis of healthcare utilization, though this may limit generalizability.

4.6 Sample proposed study: Vaccine schedule and risk of asthma

Asthma was highly ranked as an outcome of public health significance by the VSD White Paper team and external experts (Table 3.e). With an estimated incidence of 2,688 cases per 100,000 person-years among children 3-8 years of age, studies within the VSD should be adequately powered to detect meaningful differences in risk of asthma between children vaccinated according to the ACIP schedule and three separate comparison groups:

- Fully unvaccinated children
- Children vaccinated according to "Dr. Bob's Alternative Schedule" or "Dr. Bob's Selective Schedule"[28]
- Children vaccinated according to a shot-limiting schedule during the first year of life

The aim of this study is to estimate the association between the childhood vaccine schedule during the first two years of life and risk of developing asthma in the third and fourth years of life.

Study population

The proposed study population consists of VSD enrollees born from 2006–2011, who are continuously enrolled from 2 to 23 months of age, and have more than one outpatient visit before 24 months of age. The restriction to continuous enrollees and those with multiple outpatient visits is intended to exclude children who may be receiving vaccines outside of the VSD medical systems or their associated state immunization information systems. This reduces information bias by reducing misclassification of vaccination history. Requiring enrollment through 23 months of age gives all study subjects the opportunity to fully comply with the ACIP schedule (which must be completed before 2 years of age) and schedules defined in The Vaccine Book by Dr. Bob Sears, which must be completed by 19 (Alternative) or 16 (Selective) months of age.[28] This reduces selection bias by applying the same eligibility criteria to all study subjects. Subjects with an ICD-9 code for asthma prior to 24 months of age will be excluded. This exclusion avoids reverse causality that could result if incident asthma alters the vaccination schedule a child would otherwise have received.

Exposure groups

Fully unvaccinated children will be identified as having no recorded vaccines from birth through 23 months of age and who also have at least one ICD-9-CM code for vaccine refusal (V64.05 or V64.06) prior to 24 months of age. Children with a vaccination pattern consistent with the Alternative schedule from The Vaccine Book by Dr. Robert Sears will be identified by receipt of the first three doses of pneumococcal and Hib vaccines on the same day, but on a different day than the first three doses of DTaP. Children with a vaccination pattern consistent with the Selective schedule from The Vaccine Book will be identified by the absence of Hepatitis B, polio, MMR, or varicella vaccines (but at least one recorded dose of another vaccine).[28] Children on a consistent shot-limiting schedule will be identified as those children who received 2 or few vaccinations at all immunization visits before age 2 years,[30] but

who do not appear to be following the Alternative schedule as described above.

Each child in a comparison group (unvaccinated, "Dr. Bob", or shot-limiting) will be matched to ten fully vaccinated children based on birth year and the number of outpatient visits during the first 12 months of life. Matching on number of outpatient visits helps restrict the study population to children with similar patterns of healthcare utilization. This reduces information bias by reducing differential misclassification of outcomes between fully vaccinated children and comparison children. It also reduces confounding due to factors that are correlated with healthcare utilization. Matching on year of birth reduces confounding due to any potential secular changes in vaccination patterns and in asthma incidence.

Follow-up and outcomes

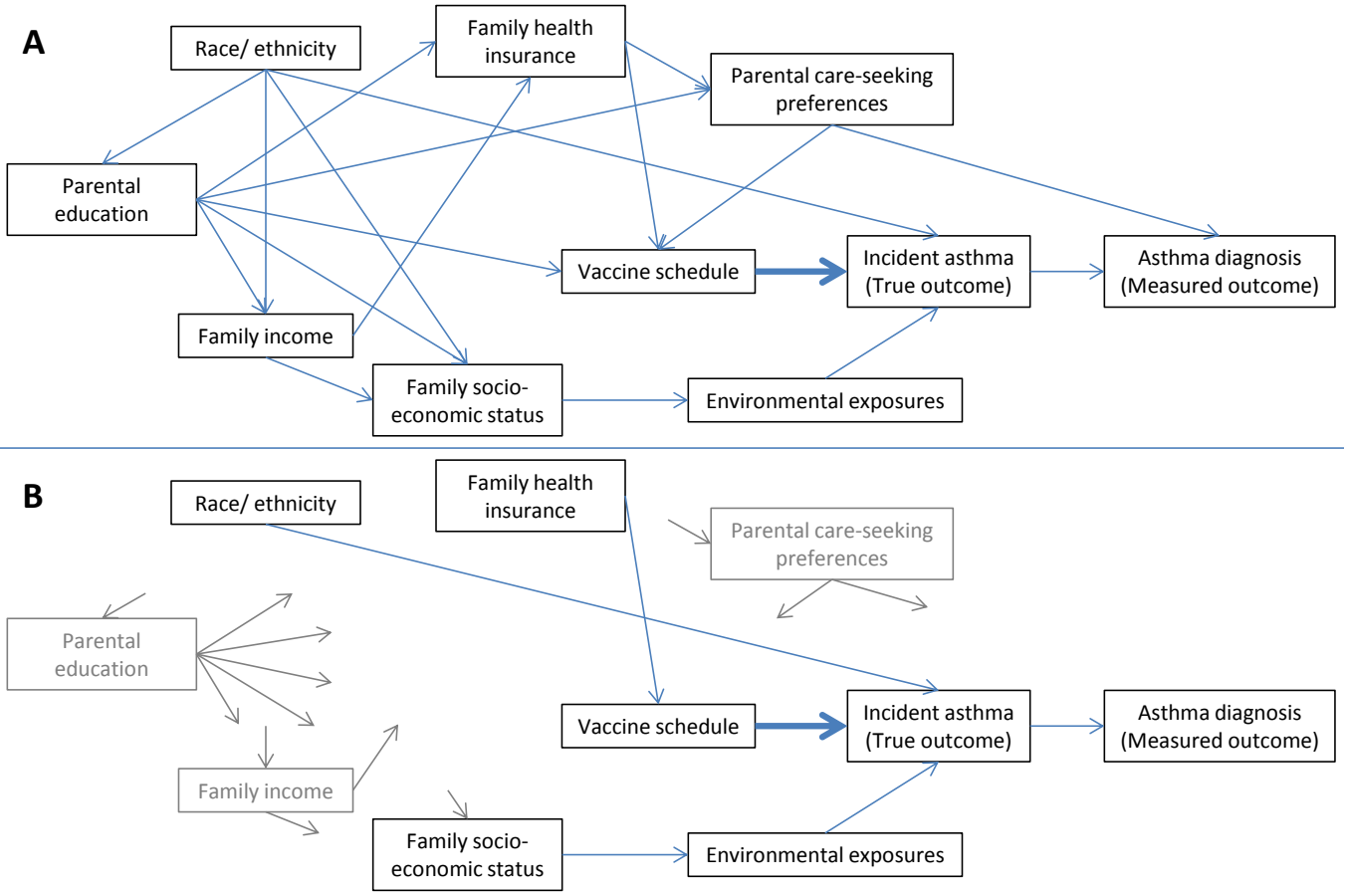
The outcome of interest is first diagnosis of asthma, defined as incident diagnosis of ICD-9-CM code 493 between 24 and 48 months of age. Subjects will be followed from their second birthday until the earliest of: death, disenrollment from their VSD MCO, first diagnosis of asthma, fourth birthday, or the end of the study on December 31st, 2015. The end of the study is chosen so that all study subjects will have equal opportunity for two full years of follow-up after their second birthday. This prevents possible information bias that could result if follow-up time is differential by birth year. Censoring subjects at MCO disenrollment prevents information bias from outcomes that may not be detected among subjects who are no longer MCO members. Censoring subjects after death or first diagnosis of asthma prevents selection bias that would result if subjects no longer at risk of first asthma were allowed to contribute further person-time to the analysis.

Covariates

For this project, data on covariates are collected in order to measure and control for potential confounders. Identification of covariates is guided by a DAG (Figure 4.a). Assuming that a DAG adequately captures the relevant causal associations, the DAG can be used to identify which variables should be controlled for (by matching, restriction, or adjustment) to remove confounding between the exposure and the outcome of interest. In the hypothetical DAG of Figure 4, controlling for parental care-seeking preferences, parental education, and family income would be sufficient to reduce confounding in the estimate of the association between vaccine schedule and asthma risk (Figure 4.a). This is because control of these factors leaves no open "backdoor" paths from exposure to outcome through which confounding could operate.

In practice, none of these three factors are directly captured in automated data that are readily available in the VSD. Instead, the investigators must rely on proxy measures that, ideally, will be well correlated with the true confounders of interest. For example, neighborhood of residence may be correlated with income and education, so census-block data on socio-economic factors, linked via geocoded subscriber addresses, may be a partial proxy for household income and education. Number of well-child visits, or vaccination history of older siblings, may be a proxy for parental care-seeking preferences.

Figure 4: A) Directed acyclic graph of predictors of vaccine schedule receipt and risk of asthma in children; B) Graph illustrating removal of backdoor paths from vaccine schedule to measured outcome



Analysis

Univariate statistics will describe the distribution of exposures, outcomes, and covariates in the study population. Bivariate statistics will describe the distribution of covariates by exposure and by outcome, and distribution of outcomes among the exposure groups. Length of follow-up will be calculated for each subject, beginning at the second birthday and continuing until the earliest of death, MCO disenrollment, end of the study, or incident asthma diagnosis. Follow-up should be started at the second birthday rather than at the start of the vaccination schedule. The schedules begin at different ages, so starting follow-up at the start of vaccination would introduce immortal time bias in favor of the schedule with the earliest age at first vaccination.[93]

Assuming the number of covariates is manageable, the population will be stratified into mutually exclusive groups based on unique combinations of exposure category and study covariates. Within each group, total person-time and number of events will be calculated. Incidence rate ratios for asthma in the fully vaccinated group vs. each comparison group will be calculated, adjusted for the covariates, using Poisson or Negative Binomial regression as appropriate. If the number of covariates (or number of levels of covariates) is too large, Cox regression could be used to estimate the corresponding hazard ratios.

Chapter 5: Summary and Recommendations

In this White Paper, we provided a comprehensive assessment for how the VSD could be used to study the safety of the recommended childhood immunization schedule. Guided by subject matter expert engagement, we outlined a 4 staged approach for identifying exposure groups of undervaccinated children, developed a list of 20 prioritized outcomes, and described various study designs and statistical methods that could be used to assess the safety of the schedule.

It is important to re-emphasize that defining patterns of undervaccination and alternative immunization schedules is complex. There are numerous reasons why children may be undervaccinated in the VSD data, including parental choice, missing vaccine data, barriers to care, gaps in insurance, or receiving their vaccines outside of the MCO. For these reasons, there are numerous different patterns of undervaccination in the VSD, and the potential for misclassification of vaccination data among undervaccinated children is relatively high. While it is possible to identify groups of undervaccinated children in which misclassification would be minimized – such as those with an ICD-9 code for vaccine refusal – these groups are small in number and would therefore lead to low statistical power in studies of uncommon outcomes. To address the potential for misclassification, we recommend primary data collection, but this requires additional resources and could significantly increase the timeline of a study. We also described a data driven approach for identifying patterns of undervaccination, but this would likely result in exposure groups that are not as clinically meaningful as groups of children on known alternative schedules. All of these factors need to be carefully considered when designing future studies of the safety of the schedule.

We used a rigorous, systematic approach for identifying potential outcomes for future safety studies. We engaged subject matter experts, and our assessment of the feasibility of studying outcomes relative to the schedule as a whole was based on age-specific incidence rates calculated directly from the VSD databases. However, it is also important to stress that our methods for prioritizing outcomes were somewhat subjective. Our rankings of public health significance and public concern, as an example, were based on our research experience, existing literature, clinical experiences and clinical judgment. Some of the outcomes that ranked highly on public health significance and public concern were particularly rare in children and had to be combined into groupings of similar conditions so that they would be feasible to study. However, it is not entirely clear that these groupings are clinically appropriate. *First demyelinating events* is an example of one disease grouping; if deemed by the CDC to be important outcome to examine, it would be advisable to consult with specialists (e.g., pediatric neurologists) to adequately define and adjudicate cases for a specific study. It is also important to note that the prioritization of outcomes may change over time, based upon new knowledge, public concern, or changing incidence.

Throughout the IOM report, it was implied that public stakeholders were primarily concerned with long-term outcomes, such as asthma, autoimmune diseases, and neurologic conditions. In response to the report, our outcomes assessment focused on conditions diagnosed in children older than 2 years of age, representing months to years after the primary infant immunization series has been completed. Such long-term outcomes will, in turn, allow us to evaluate the childhood immunization schedule as a whole. In contrast, short-term acute outcomes occurring before 2 years of age pose challenges to studying the safety of the entire schedule because they are typically associated with short risk periods following specific vaccines, doses or combinations of vaccines. Short-term acute outcomes may also influence parents' future vaccine decisions and lead to reverse causality – a potential source of bias described in chapter 4.

As shown in chapter 4, there are numerous considerations when deciding on study designs and analytic plans to examine the schedule. In addition to reverse causality, studies of the schedule may be susceptible to misclassification, confounding and selection bias. These sources of bias stem from the fact that undervaccinated

children likely differ from age-appropriately vaccinated children by several important variables, including baseline health status, socioeconomic status, parental education, race/ethnicity, health care utilization, and family history of illness. Such differences are problematic because many of these variables are not routinely collected in the VSD databases. We therefore encourage investigators to strongly consider using the methods highlighted in chapter 4, including DAGs, control outcomes, restriction/matching, primary data collection, and sensitivity analyses.

This White Paper has some notable limitations. First, we only engaged 5 subject matter experts to help develop the content. However, it is important to stress, however, that our SMEs were highly regarded experts in the fields of vaccine science and applied statistical methods, and it is unclear if our findings would have changed had we engaged a larger group of subject matter experts. Second, we did not engage any parents or parental groups throughout the process. While parental input could have affected our results, the White Paper was heavily informed by the 2012 IOM report which incorporated a rigorous public stakeholder engagement process. Lastly, the IOM report questioned the VSD's representativeness, and we did not explore this potential limitation of the VSD in the White Paper.

Despite the limitations described above, it appears feasible to study the safety of the childhood immunization schedule within the VSD. This finding is consistent with the IOM report conclusion that the VSD represented one of the nation's best resources for studies of this nature. We believe that VSD investigators can use this document when designing and conducting studies of the safety of the childhood immunization schedule.

Appendices

Chapter 2

Appendix 2.a: Criteria used to evaluate days under-vaccinated for 8 recommended early childhood vaccines and calculation for maximum average number of days undervaccinated

Appendix 2.b: Policy changes, vaccine shortages, and brand-specific dosing considerations for assessing undervaccination in a retrospective VSD cohort, 2004-2013

Appendix 2.c: Examples of potential survey domains and questions within a survey of parents of under-vaccinated children.

Appendix 2.d: Estimated sample sizes for primary data collection across a range of estimated confirmation rates and desired confidence interval widths (alpha= 0.05)

Appendix 2.a: Criteria used to evaluate days under-vaccinated for 8 recommended early childhood vaccines and calculation for maximum average number of days undervaccinated

Vaccination dose[a,b]	Recommended age per ACIP (months)	Minimum acceptable age (days) allowing for 4 day grace period	Minimum acceptable interval between doses (days) allowing for 4 day grace period	Age in days when count for undervaccination initiated	Maximum possible days undervaccinated at 730 days (no doses received)
Hepatitis B					**730-92=638**
Dose 1	0-2	0		93	
Dose 2	1-4	24	24	154	
Dose 3	6-18	176	38[c]	580	
Rotavirus					**252-92=160**
Dose 1	2	38		93	
Dose 2	4	66	24	154	
Dose 3	6	94	24	215	
Diphtheria, tetanus, and pertussis (DTaP)					**730-92=638**
Dose 1	2	38		93	
Dose 2	4	66	24	154	
Dose 3	6	94	24	215	
Dose 4	15-18	361	179	580	
***Haemophilus influenzae* type b (Hib)**					**730-92=638**
Dose 1	2	38		93	
Dose 2	4	66	24	154	
Dose 3	6	94	24	215	
Dose 4	12-15	361	52	580	
Pneumococcal conjugate vaccine (PCV)					**730-92=638**
Dose 1	2	38		93	
Dose 2	4	66	24	154	
Dose 3	6	94	24	215	
Dose 4	12-15	361	52	580	
Polio (IPV)					**730-92=638**
Dose 1	2	38		93	
Dose 2	4	66	24	154	
Dose 3	6-18	94	24	580	
Measles, mumps, and rubella (MMR)					**730-488=242**
Dose 1	12-15	361		489	
Varicella					**730-488=242**
Dose 1	12-15	361		489	
Maximum Average Number of Days Undervaccinated: = (638 + 160 + 638 + 638 + 638 + 638 + 242 + 242) / 8 vaccines = **479.25**					

From Glanz et al. 2013[3] adapted from Luman et al. 2005[4] and Opel et al. 2011[31]

ACIP=Advisory Committee on Immunization Practices

[a] Influenza vaccine was not included the analysis because days undervaccinated cannot be calculated with a seasonal vaccine in which children can receive the vaccine at varying ages; Hepatitis A vaccine was not included because recommendations are relatively new and the low coverage rate suggests low adherence to the recommendations by physicians.

[b] For vaccines administered as combination vaccines (e.g., Pentacel®, Pediarix®, ProQuad®) the components of the combination vaccines were treated individually.

[c] The minimum acceptable interval between doses 2 and 3 was changed from 52 days (per Luman et al. 2005)[4] to 38 days because Pediarix® doses may be administered in 6-week intervals.

Appendix 2.b: Policy changes, vaccine shortages, and brand-specific dosing considerations for assessing under vaccination in a retrospective VSD cohort, 2004-2013

	Description	Modification to calculating average days undervaccinated (ADU)
Policy Changes		
Change in recommended age for varicella vaccine	In 2007, the recommended age for the varicella vaccine changed from 12-18 months to 12-15 months[94]	Prior to the policy change and for three months after, count for days under-vaccinated starts when the child turns 19 months of age. Starting three months after the policy change, count for days under-vaccinated starts when the child turns 16 months of age.
Recommendation for rotavirus vaccination	Rotavirus vaccine was universally recommended in August, 2006[95]	Days under-vaccinated for rotavirus vaccine incorporated into ADU calculation starting two months after the recommendation. At one VSD site, rotavirus vaccination introduction occurred much later, so days undervaccinated for rotavirus is not included until September 2007.
Vaccine Shortages		
Pneumococcal vaccine shortage in 2004	Shortage of PCV7 in 2004 led to short-term recommendations to delay or not administer 3rd and 4th doses in children[96-98]	Children born January 2004 - May 2004 are not penalized for any delay in the 3rd or 4th dose of pneumococcal vaccine.
Hib vaccine shortages in 2007-2009	Shortages of Hib vaccines led to short-term recommendations to not administer 4th booster dose[99,100]	If a child was age 12-15 months between Dec 18th, 2007 and July 30th, 2009, he/she is not penalized for not receiving 4th dose of Hib.
Brand-specific dosing		
Different dosing recommendations for rotavirus vaccines	ACIP recommends 2 doses of Rotarix® or 3 doses of Rotateq® by age 6 months[23]	If Rotarix® is administered for the first 2 doses, then a 3rd dose of rotavirus vaccine is not required.
Different dosing recommendations for Hib vaccines	ACIP recommends 2 doses of PedvaxHib® or Comvax® or 3 doses of ActHIB® by age 6 months[23]	If PedvaxHib® or Comvax® is administered for the first 2 doses, then a 3rd dose of Hib vaccine is not required.

Appendix 2.c: Examples of potential survey domains and questions within a survey of parents of undervaccinated children.

Example Questions	Source/Notes
Survey Domain Assessment of Vaccination Status	
Our records indicate that [your child] has not received all of [his/her] recommended vaccines. Is that correct?	
Our records indicate that [your child] did not receive any vaccines before 6 months of age. Is that correct?	Can ask about specific patterns of undervaccination.
Our records indicate that [your child] has not received the measles-mumps-rubella, also called MMR, vaccine. Is that correct?	Can ask about specific patterns of undervaccination.
Not counting a dose of Hepatitis B vaccine that [your child] may have received in the hospital after birth, has [your child] received any vaccines at any place other than at [MCO]?	
Assessment of Reasons for Undervaccination	
Introduction: Now I'd like to ask you about times when you decided not to get a vaccination for [your child], and the about times when you delayed getting a vaccination for [your child].	From 2009 National Immunization Survey
Has there ever been a time when you refused or decided not to get a vaccination for [your child]?	From 2009 National Immunization Survey
Now, has there ever been a time when you delayed or put off getting a vaccination for [your child]?	From 2009 National Immunization Survey
Please tell me all the reasons why you refused or delayed getting vaccines for [your child]? Was it because…	From 2009 National Immunization Survey; however, this level of granularity may not be needed for current survey.
Your child was ill at the time?	
You have safety or side-effect concerns?	
You heard or read bad things through the media?	
You missed or couldn't get an appointment?	
You feel that there are too many shots?	
You wonder about the effectiveness of the vaccine?	
You have concerns about cost?	
You have transportation problems?	
Getting vaccines was not convenient?	
You have concerns about autism?	
Any other reason?	
Health Care Utilization	
Not counting the time in the hospital after [he/she] was born, have you ever taken [your child] to someplace other than [MCO] to get health care?	
If [your child] had an urgent need for health care, would you take [him/her] to [MCO] to get that care?	
Have you ever taken [your child] to an alternative medicine provider, such as a chiropractor, naturalist, homeopath, or acupuncturist, when your child was sick?	
Child General Health Status	
In general, how would you describe [your child's] health? Would you say [his/her] health is excellent, very good, good, fair, or poor?	From National Survey of Children's Health 2012
Does [your child] need or use more medical care, mental health, or educational services than is usual for most children of the same age?	From National Survey of Children's Health 2012
Is [your child] limited or prevented in any way in [his/her] ability to do the things most children of the same age can do?	From National Survey of Children's Health 2012
Family Characteristics	
Parental education level	Note that some data regarding child and family will be available from electronic health records
Annual family income categories	May not be needed
Do you have any health insurance that covers [your child], other than your insurance at [VSD site]?	

Appendix 2.d: Estimated sample sizes for primary data collection across a range of estimated confirmation rates and desired confidence interval widths (alpha= 0.05)[101,102]

	Desired confidence interval width		
Estimated confirmation rate	**0.05**	**0.075**	**0.10**
10%	138	61	35
20%	246	109	61
30%	323	143	81
40%	369	164	92
50%	384	171	96
60%	369	164	92
70%	323	143	81
80%	246	109	61
90%	138	61	35

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