Centers for Disease Control and Prevention's Immunization Safety Office Scientific Agenda

Immunization Safety Office, Division of Healthcare Quality Promotion National Center for Emerging and Zoonotic Infectious Diseases

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Overview

In response to a 2005 Institute of Medicine (IOM) recommendation (IOM, 2005), and to guide the scientific direction of the Centers for Disease Control and Prevention's (CDC's), Immunization Safety Office (ISO), a draft ISO Scientific Agenda (referred to as the Agenda) was developed to be implemented over a 5-year period. ISO received input from experts during three planned meetings with external, federal, and industry scientists, and vaccine manufacturers' representatives. ISO also gathered input from other partners and CDC experts in vaccine safety. A companion background document highlights the differences between the initial 2008 draft Scientific Agenda and this finalized 2010 Scientific Agenda. The background to the 2008 draft also provides additional information on the ISO research and surveillance infrastructure, and the Agenda's rationale and scope. The entire process used is described in an earlier document that can be found at: http://www.cdc.gov/vaccinesafety/00_pdf/agenda_background_080321.pdf.

At the request of CDC, the National Vaccine Advisory Committee (NVAC) Vaccine Safety Working Group advised on the content and priorities of the Agenda. CDC finalized the Agenda and responded to NVAC feedback. The NVAC Vaccine Safety Working Group reviewed the Agenda and made 32 recommendations in three categories: general, capacity, and research needs recommendations. The prioritization criteria included significance of the exposure to a vaccine, prevalence of the adverse health event following immunization, public concern, scientific concern and degree to which further study is warranted, impact on policy, and feasibility of the study. A summary of the NVAC recommendations is included in *Appendix C: Summary of NVAC Recommendations*. The NVAC recommendations to the Agenda were approved by the Assistant Secretary for Health of the US Department of Health and Human Services (HHS) and sent to CDC on July 29, 2009 (NVAC, 2009).

The Agenda was informed by NVAC's request for broad public engagement to identify public concerns and priorities related to vaccine safety research. Public input was solicited in four ways: 1) at community meetings held in Birmingham, Alabama, Ashland, Oregon, and Indianapolis, Indiana; 2) at a writing group meeting in Salt Lake City, Utah; 3) at a stakeholder meeting held in Washington, DC; and 4) by written comments solicited through two notices in the Federal Register.

CDC/ISO has incorporated many of NVAC's recommendations into the Agenda and is working with the National Vaccine Program Office (NVPO) to consider the best way to address activities included in the Agenda that are beyond the scope of ISO. Considerations in implementing the Agenda include resources, feasibility, advances in science, and alignment with CDC/ISO missions.

HHS has developed a Strategic National Vaccine Plan (http://www.hhs.gov/nvpo/vacc_plan/), which was drafted concurrently with this ISO Agenda. The ISO Agenda was written to be consistent with the draft national plan.

Separate from this process, the NVAC Vaccine Safety Working Group has also taken up a second charge to review the current federal vaccine safety system and develop a white paper describing the infrastructure needs for a federal vaccine safety system that includes CDC (NVAC, 2009) (www.hhs.gov/nvpo/nvac/documents/vfwgwhitepaper20080410.pdf).

Ongoing Development of the ISO Scientific Agenda

ISO acknowledges that the need to formulate specific vaccine safety questions is an ongoing process. Selected studies may be required to answer complex research questions. With this in mind, ISO will generate a list of testable hypotheses to be prioritized according to the considerations outlined in the emerging issues and core activities in Section 1 of Box 1. This process may also be informed by conclusions from the Health Services and Resources Administration-sponsored IOM review currently underway of vaccine adverse events for several vaccines (http://www.hrsa.gov/vaccinecompensation/adverseeffects.htm).

ISO plans to present progress on the Agenda to NVAC periodically. Priority studies and other research activities will also be regularly updated on the CDC Web site (http://www.cdc.gov/vaccinesafety/index.html) to inform stakeholders and the public of on-going and planned research activities. ISO will review its Scientific Agenda periodically to identify new gaps and communicate research priorities.

The Agenda makes recommendations for a 5-year period in three main scientific areas: vaccine safety research, selected surveillance, and selected clinical guidance activities.

The Agenda topics are summarized in Box 1.

Box 1: Summary of Centers for Disease Control and Prevention's ISO Scientific Agenda

A. Respond to emerging issues and conduct core, required scientific activities.

B. Enhance vaccine safety public health and clinical guidance capacity in six areas:

1. **Infrastructure for Vaccine Safety Surveillance: Vaccine Adverse Event Reporting System (VAERS)**
2. **Infrastructure for Vaccine Safety Surveillance and Research: Vaccine Safety Datalink (VSD) Project**
3. **Epidemiologic and Statistical Methods for Vaccine Safety**
4. **Laboratory Research Genomics and Vaccine Safety**
5. **Case Definitions for Data Collection, Analysis, and Presentation for Adverse Events Following Immunization (AEFI)**
6. **Vaccine Safety Clinical Practice Guidance**

C. Address 5-Year Research Needs

1. **Specific Vaccine Safety Questions**
2. **Vaccines and Vaccination Practices**
3. **Special Populations**
4. **Clinical Outcomes**

Section 1. Emerging Issues and Core, Required Scientific Activities

CDC's Immunization Safety Office (ISO) leads most of the agency's vaccine safety research and surveillance activities for vaccines used in the civilian population. ISO also has integrated research and surveillance components into its activities. These components include the Vaccine Adverse Event Reporting System (VAERS), the Vaccine Safety Datalink (VSD) Project, the Clinical Immunization Safety Assessment (CISA) Network, and the Vaccine Analytic Unit (VAU). ISO collaborates on an ongoing basis with other vaccine programs at CDC, other federal agencies and programs, and various external partners. More information is available at http://www.cdc.gov/vaccinesafety/Activities/About_ISO.html.

To ensure optimal vaccine safety, ISO will continue to respond to emerging issues and conduct core scientific activities, which include:

- **Monitoring the safety of all newly licensed and Advisory Committee on Immunization Practices (ACIP) recommended vaccines and previously licensed vaccines with new or expanded recommendations.** The general monitoring approach includes reviewing existing vaccine safety data to identify potential areas of concern and developing VAERS and VSD monitoring plans, as appropriate. Sometimes vaccine safety data indicates that special studies may be needed to investigate adverse events that might be associated with a vaccine.

- **Responding to potential vaccine safety signals that may be identified in pre-licensure studies, VAERS, or other mechanisms (Table 1, Case Example 1).** Some vaccine safety concerns are apparent at the time of licensure, but potential safety problems often become apparent after a vaccine is widely used in the general population or after it is used in a new population. New vaccine hypotheses may arise from the medical literature, expert reviews (e.g., IOM, reports to VAERS, clinical consultation calls to investigators in the CISA network, the media, and the general public). The VSD Project historically has conducted most of ISO's hypothesis testing research.

- **Providing technical consultation to CDC immunization experts and other stakeholders for collaborative and multidisciplinary scientific activities (Table 1, Case Example 1).** ISO serves as a national and international resource for vaccine safety science. In addition to leading research and surveillance activities related to risk assessment, ISO provides technical safety expertise for numerous scientific activities, (i.e., those related to immunization services, risk perception, economic analyses, or risk-benefit analyses). ISO also participates in federal advisory committees related to vaccines, including the Advisory Committee on Immunization Practices (ACIP), NVAC, and the Advisory Commission on Childhood Vaccines (ACCV) (ACIP, and NVAC, and ACCV charters).

- **Monitoring vaccine safety and responding to vaccine safety emergencies in the event of a mass vaccination campaign or other vaccine safety emergency (Table 1, Case examples 2 and 3).** Monitoring for and rapidly responding to vaccine safety emergencies are core ISO public health functions (http://www.cdc.gov/vaccinesafety/emergency/).

Vaccine safety emergencies may arise during disease outbreaks or other situations when large numbers of people are vaccinated, including people who may not be recommended for vaccination in normal circumstances. They may also occur when clusters of adverse events are detected or, uncommonly, when sterility of a vaccine cannot be assured. In these situations, ISO works closely with the Food and Drug Administration (FDA), state health departments, and other partners to investigate these public health concerns. In addition, vaccine safety monitoring is an important component of national pandemic influenza preparedness (http://www.hhs.gov/pandemicflu/plan/sup6.html#safety). ISO had planned for the use of vaccines in a pandemic setting and executed those plans during the 2009 H1N1 influenza pandemic.

Table 1. Examples of Core Required Scientific and Emerging Issues Activities
Example 1. Measles, Mumps, Rubella, and Varicella (MMRV) Vaccine and Febrile Seizures[1]

Ongoing Activity	Event
Monitor safety for newly licensed and ACIP recommended vaccines and for vaccines with new recommendations.	• In 2007, VSD initiated near real-time surveillance for selected vaccine adverse events after administration of the MMRV vaccine to children aged 12–23 months. • The computerized data identified a possible risk for seizures after MMRV vaccine.
Respond to new vaccine safety signals and hypotheses, which are not always predictable.	• On the basis of the signal related to possible seizures, VSD rapidly implemented an epidemiologic chart review study to assess risk for febrile seizures using chart data. • The final results found that among 12- to 23-month-olds who received their first doses of measles-containing vaccine, fever and seizure were elevated 7 to 10 days after vaccination, with the highest rate observed after MMRV vaccine. Vaccination with MMRV results in 1 additional febrile seizure for every 2,300 doses given, a result that is separate from MMR varicella vaccines (Klein NP et al, 2010).
Provide technical consultation to immunization experts and other stakeholders.	• ISO presented this information to FDA and Merck scientists during the ACIP meeting in February 2008. • On the basis of these and other findings, FDA updated the package insert and ACIP voted to remove the preference for MMRV vaccine over MMR, and to administer varicella vaccines separately. ACIP also formed an MMRV Vaccine Safety Working Group to evaluate the data more thoroughly and develop policy options. ISO co-led this Working Group along with CDC's National Center for Immunization and Respiratory Diseases (NCIRD). Final recommendations for MMRV were published in May 2010 (CDC/MMWR, 2010).

[1] CDC, MMWR, 2008.

Table 1. (continued)
Examples 2 and 3: Response to a Public Health Emergency in a Pandemic and a Vaccine Recall Safety Concern[2]

Ongoing Activity	Event
Monitor a newly recommended vaccine for use in a pandemic. (case example 2)	• FDA licensed the first 2009 influenza A (H1N1) monovalent vaccines (H1N1 vaccines) on September 15, 2009. • ISO was fully involved in assessments of the safety profile of H1N1 vaccines in the United States (CDC MMWR, 2009). ISO reviewed vaccine safety reports received through VAERS and electronic data from people vaccinated at managed care organizations in the VSD; CISA Principal Investigators were consulted to review difficult cases. • ISO monitored safety of this vaccine in pregnancy, which is a special at-risk population. A study to VAERS summarizing ~10,000 reports after 2009 H1N1 vaccine was published in October 2010 (Vellozzi et al, 2010).
Vaccine safety recall or other vaccine safety emergency. (case example 3)	• In December 2007, ISO responded to a potential safety concern after 1.2 million doses of *Haemophilus Influenza* type b (Hib) conjugate vaccine were recalled. Because *Bacillus cereus* was isolated from the manufacturing equipment, no contamination of the vaccine was found. • VAERS conducted a rapid review of reports from recalled Hib lots. • ISO used CDC's Epidemic Information Exchange (*Epi-X*) to call for vaccine-associated *B. cereus* infections with onset since April 1, 2007 in recipients aged <6 years. • CDC found no evidence of vaccine-associated *B. cereus* infection in recipients of recalled Hib vaccine. • The *Epi-X* posting stimulated one report of vaccine-associated *B. cereus* infection in a person who received a non-recalled Hib vaccine. CDC conducted molecular typing of the isolate and it differed from the isolate from the manufacturing equipment (Huang WT et al, 2010).

[2] CDC, http://www.cdc.gov/vaccines/recs/recalls/hib-recall-faqs-12-12-07.htm

Section 2. Vaccine Safety Public Health and Clinical Guidance Capacity

This section describes existing ISO infrastructure, capacity, and proposed future needs to advance the field of vaccine safety science. Enhanced capacity will ensure that ISO can continue to conduct high quality vaccine safety research and surveillance, and provide clinical guidance. ISO could conduct initial work in these areas using infrastructure generally accessible to CDC. However, to carry out these activities, ISO may need to forge new collaborations and tap into federal infrastructure beyond ISO as recommended by the NVAV Committee. The areas are listed in Box 2.

Box 2. Summary of Draft Recommendations for Vaccine Safety Public Health and Clinical Guidance Capacity

Enhance vaccine safety public health and clinical guidance capacity in six areas:

1. **Infrastructure for vaccine safety surveillance: Vaccine Adverse Event Reporting System (VAERS)**
   - **Enhance VAERS reporting.**
   - **Improve VAERS surge capacity infrastructure and analytical capabilities.**
2. **Improve surveillance and evaluation of VAERS data infrastructure for vaccine safety surveillance and research: Vaccine Safety Datalink (VSD) Project**
   - **Conduct studies to improve and understand the data that are being used for VSD's vaccine safety research and surveillance activities.**
3. **Epidemiologic and statistical methods for vaccine safety**
   - **Improve near real-time surveillance methods.**
   - **Overcome limitations of conventional epidemiologic designs.**
   - **Laboratory research.**
   - **Collect biological specimens.**
   - **Assess lab testing methods for hypersensitivity to vaccines.**
   - **Measure single nucleotide polymorphisms (SNPs).**
4. **Genomics and vaccine safety**
   - **Develop a systematic scientific approach to studying the genetic basis for vaccine adverse events including an understanding of technology advances, analytic approaches, and public health applications of evidence.**
5. **Case definitions for data collection, analysis, and presentation for adverse events following immunization (AEFI)**
   - **Development of case definitions.**
   - **Evaluation of case definitions.**
   - **Translation of case definitions into practice.**
6. **Vaccine safety clinical practice guidance**
   - **Use evidence-based methods, including expert clinical opinion, to develop and widely disseminate clinical guidance that will assist clinicians in assessing, reporting, and managing vaccine adverse events.**

Item A: Infrastructure for Vaccine Safety Surveillance: Vaccine Adverse Event Reporting System (VAERS)

Background and Public Health Importance:

The National Childhood Vaccine Injury Act (NCVIA) of 1986 requires health professionals and vaccine manufacturers to report to HHS specific adverse events that occur after the administration of routinely recommended vaccines. In response to NCVIA, CDC and FDA established the Vaccine Adverse Event Reporting System (VAERS) in 1990 (Chen, Vaccine, 1994). VAERS is a national passive reporting system co-managed by CDC and FDA. In 2007, VAERS received approximately 30,000 primary reports, with 13% classified as serious (i.e., associated with disability, hospitalization, life-threatening illness, or death) (CDC VAERS Master Search Tool, April 2, 2008). Anyone can file a VAERS report, including healthcare providers, manufacturers, and vaccine recipients. ISO has responsibility for receiving and processing VAERS reports.

The primary objectives of VAERS are to 1) detect new, unusual, or rare vaccine adverse events (VAEs)[3]; 2) monitor increases in known adverse events; 3) identify potential patient risk factors for particular types of adverse events; 4) identify vaccine lots with increased numbers or types of reported adverse events (FDA leads); and 5) assess the safety of newly licensed vaccines. Although VAERS can rarely provide definitive evidence of causal associations between vaccines and particular risks, its unique role as a national spontaneous reporting system enables the early detection of signals that can then be more rigorously investigated. VAERS seeks reports of any clinically significant medical event that occurs after vaccination, even if the reporter cannot be certain that the event was caused by the vaccine. ISO and FDA review adverse reports; VAERS has identified important signals that after further research resulted in changes to vaccine recommendations. VAERS demonstrated its importance to public health when the system detected multiple reports for intussusceptions after RotaShield® rotavirus vaccine was administered in 1999; epidemiologic studies confirmed an increased risk, and these data contributed to the product's removal from the US market (CDC MMWR, 2004a; Varricchio, PIDJ, 2004; CDC, MMWR, 2003).[4]

CDC's Immunization Safety Office Role and Contribution:

VAERS is the most broad-based federal system to detect adverse events, which makes it a critical component of vaccine safety surveillance. ISO shares responsibility with the VAERS staff of the FDA's Center for Biologics Evaluation and Research for reviewing and analyzing reports and developing scientific projects. ISO leads activities that involve close collaboration with its internal research and surveillance teams: the Vaccine Safety Datalink (VSD) Project and the Clinical Immunization Safety Assessment (CISA) Network. When the need arises to investigate adverse events, CDC plays an important role in partnering with the state departments of health, including state epidemiologists, to coordinate the investigation. In certain cases, CDC also conducts special laboratory analysis of clinical specimens. Because CDC manages the

[3] The terms vaccine adverse event following immunization (VAE) and adverse event following immunization (AEFI) are used interchangeably throughout this document and do not imply that an event was caused by a vaccine.
[4] Two different rotavirus vaccines, Rotateq® and Rotarix, are currently licensed and recommended for use in the United States.

VAERS contract, ISO often leads projects to evaluate and further develop the VAERS infrastructure to optimize the infrastructure for vaccine safety scientific activities. In addition, CDC commonly assists FDA in its surveillance and evaluation efforts related to vaccine lot safety.

Priority Scientific Areas:

With the goal of enhancing VAERS scientific capacity, ISO and FDA groups have prioritized three major areas for VAERS infrastructure improvement.

1) Enhance VAERS reporting.
Specific activities include:

- Determine the most effective and efficient mechanisms to communicate to healthcare providers about reporting to VAERS.
- Identify ways to facilitate reporting to VAERS by primary healthcare providers and specialists (e.g., neurologists and rheumatologists), who may be less familiar with VAERS than primary care providers.
- Evaluate ways to increase reporting to VAERS by vaccine recipients who do not have a primary healthcare provider. We recognize that relying only on clinician reports may result in underreporting to VAERS.

2) Improve VAERS surge capacity infrastructure and analytical capabilities.
In recent years, the number of reports to VAERS has increased. During 2007, VAERS received more than 30,000 reports compared to approximately 16,000 reports received in 2002 (CDC VAERS Master Search Tool, April 2, 2008). In addition to handling an increased amount of reports under routine conditions, VAERS was recently enhanced to handle the surge capacity during the H1N1 emergency response to pandemic influenza. VAERS developed standard operating procedures (SOPs) that were instituted in a timely manner, including developing and implementing new VAERS electronic reporting mechanisms and training additional staff to meet these public health needs. Currently, VAERS accepts reports through mail, facsimile, and Internet/Web-based submission. However, the paper reports represent approximately 80% of yearly reports and are the most resource consuming.

In a recent pilot project, VAERS partnered with the Massachusetts Department of Health and Harvard Medical School to integrate VAERS with existing systems, including state registries and electronic medical records that contain vaccine adverse event (VAE) information via the Health Level 7 (HL7) messaging standard (CDC, MMWR, 2004b). This project builds upon federally-required information system standards for state and local preparedness capacity (e.g., HL7 messages) (CDC, MMWR, 2004b). In the pilot project, data about adverse events contained within an HL7 message is sent via the Public Health Information Network Messaging System (PHINMS) through a data transport mechanism to VAERS. In turn, a VAERS report is generated using data in the HL7 data file. This mechanism has the potential to reduce report processing time, improve quality of medical reports, and decrease underreporting.

Specific activities include:

- Improve VAERS capacity to handle significant increased reporting, particularly in an emergency setting.
- Evaluate ways to improve electronic reporting to VAERS (e.g., Internet submissions) by various entities. Electronic reporting is the most efficient and cost-effective mechanism for reporting to VAERS. However, less than 20% of reports are submitted electronically.
- Enhance data quality and completeness of records to VAERS and reporting capabilities from immunization registries and healthcare providers through the development and implementation of HL7 electronic reporting.
- Enhance VAERS analytical capabilities through the receipt of individual- or population-level information (e.g., detailed immunization, medical histories, total cohort population) provided through direct linkage with registries and electronic medical records.
- Explore ways to increase reporting of especially serious adverse events to VAERS to include enhancing reporting by use of text messages; incorporating reporting alerts into electronic medical records; posting VAERS ads in professional journals (e.g., JAMA and American Academy of Neurology); and posting VAERS links to key sites in an effort to increase reporting.
- Improve educational materials for specific audiences.

3) Improve surveillance and evaluation of VAERS data.
Specific activities include:

- Evaluate the effectiveness of the *Medical Dictionary for Regulatory Activities* (*MedDRA*) (effective January 2007) coding strategies in identifying rare VAEs and standardize VAERS search terms in the CDC VAERS search tool using *MedDRA* coding.
- Develop standardized protocols for monitoring and evaluating adverse events following immunization with new and established vaccines, including during emergency situations.
- Identify the most effective and efficient use of resources to evaluate and obtain follow up medical information on serious VAERS reports.
- Enhance and evaluate the use of VAERS capacity for obtaining tissue specimens for pathologic, genomic, or other biologic testing, and develop further collaboration between VAERS and other CDC/ISO activities, (e.g., CISA Network).
- Enhance capabilities to identify and evaluate reports of specific adverse events that are more common for one product than for another (e.g., through advanced signal detection or data mining) (Iskander, Drug Safety, 2006).
- Explore the possibility of revising the VAERS form to include race and ethnicity to enable the conduct of studies that would address these key variables.

Item B: Infrastructure for Vaccine Safety Surveillance and Research: Vaccine Safety Datalink Project

Background and Public Health Importance:

Since 1990, the Vaccine Safety Datalink (VSD) has been a key component of ISO's research infrastructure through their testing of vaccine safety hypotheses. The productivity of this research infrastructure is reflected by the number and quality of VSD research publications (VSD Publications, 2008). Currently, the VSD infrastructure includes eight managed care organizations (MCOs) with a beneficiary population that represents 3.2% of the US population aged <18 years and 1.4 % of the population aged ≥18 years.

Ensuring high-quality vaccine safety research is one of ISO's top priorities. Despite ongoing success of VSD research, continued evaluation and quality improvement are important. Specifically, VSD researchers are currently developing methodologies to improve the timeliness of vaccine safety data analysis. To support a variety of vaccine safety studies, the VSD MCOs created annual cycle data files that contain demographic and medical information on their members, such as age and gender, vaccinations, hospitalizations, outpatient clinic visits, emergency room visits, urgent care visits, mortality data, and additional birth information (e.g., birth weight), when available. Direct identifiers such as name and social security number are not collected. Rather, each VSD member is assigned a unique, randomized VSD study ID that is not associated with their MCO member ID. The VSD study IDs can be used to link data on demographics and medical services. Using data from electronic systems, VSD creates a standardized data dictionary so that data across plans are collected in a similar manner.

In 2004**,** VSD changed its paradigm of collecting data from using a centralized data model wherein data were sent to CDC annually to a distributed data model (DDM) wherein anonymous patient data reside at sites and CDC is provided access through computer programs. Although the change to the distributed data model (DDM) enhanced data confidentiality, there have been some challenges. Programming through the DDM is more difficult. VSD sites also must monitor submitted programs to ensure data quality and compliance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

In addition to creating data files annually, in 2006, VSD began creating files that are updated weekly through extracts of computerized data from the participating MCOs. These files are called the dynamic data files (DDF). The DDF approach is modeled after the standardized data dictionary used for cycle files and includes information on demographics, vaccinations, hospitalizations, outpatient clinic visits, urgent care clinic visits, and emergency room visits. The ability to create weekly data files has provided VSD with the opportunity to conduct near real-time surveillance of adverse events associated with newly licensed vaccines and with changes in existing recommendations. In order to conduct vaccine safety surveillance on data that are revised on a weekly basis, the VSD researchers have developed and validated methodologies such as maximum sequential ratio probability testing, sequential case series designs, and flexible sequential methods (Lieu, Med Care, 2007).

CDC's Immunization Safety Office's Role and Contribution:

VSD provides critical vaccine safety data to inform national vaccine policy. To keep up with the changes occurring with data sources and evolving health informatics technologies at the study centers, ISO must conduct studies to improve and interpret the data that are being used for VSD's vaccine safety research and surveillance activities. For example, if a specific diagnosis is added to clinic data entry software, an increase in estimates of incidence rate for that diagnosis may be observed even though the actual underlying rate has not changed.

Priority Scientific Areas:

Quality improvement efforts include:

- Studies to understand the quality of ICD-9 outcome codes commonly used in vaccine safety studies. An example of an ongoing study includes the positive predictive value of automated seizure codes, in which investigators are assessing and comparing positive predictive values of automated seizure ICD-9 codes by setting (hospital, emergency department, and clinic).
- Validity studies of both annual cycle files and DDFs to assess the quality of VSD data.
- Surveys to determine the accuracy of automated data on immunization. An example of an ongoing study includes the evaluation of MCO influenza immunization data. However, a major concern is that such data acquired from these studies may not capture immunizations that occur outside the MCO, particularly among adults.
- Studies to monitor the uptake and use patterns of new vaccines as they enter the US market and are administered at the participating MCO.
- Studies to evaluate patterns of vaccine administration, including patterns of simultaneous vaccination.
- Establishing both background rates of diseases and outcomes for selected potential vaccine adverse events, and immunization coverage rates. To quantify the occurrence of an event and its relationship to the timing of a vaccination, one must first know the seasonal and temporal patterns of the event in question. Information is also needed on whether the vaccine of interest is used within the VSD population of interest and the rate of the adverse event in that population.
- Studies to improve CDC's ability to collect socioeconomic and demographic information. Using geocode data collected from the VSD cycle files and appended data from the US Census Bureau, one proposed project would characterize VSD participants on the basis of geographical location and by socio-demographics, and compare the distribution of these characteristics across participating MCOs; evaluate VSD representativeness by comparing prevalent socio-demographic distributions within the VSD participants' area of residence with residents of the MCO service areas and with the entire US population; and explore the quality of collected geocode data and the potential for bias resulting from poor quality address matches.

Item C: Epidemiologic and Statistical Methods for Vaccine Safety

Background and Public Health Importance:

Ensuring the rapid availability of high quality risk assessment data for vaccines is important to inform clinician and patient education, guideline and policy development, and regulatory action. Post-licensure investigations of vaccine safety based on automated immunization and diagnosis data have generally used conventional observational epidemiological designs, such as retrospective cohort or case control studies. Although vaccine safety studies conducted using these methods have provided meaningful information for public health, several factors may limit their use. Conventional epidemiological designs are characterized by an inevitable delay between when an adverse event signal is reported and when an investigation is completed, which can range from months to years.

Another factor that may limit use of conventional designs in certain situations is that populations who are unvaccinated may be different from those who are vaccinated. Potential differences between vaccinated and unvaccinated groups include: underlying health conditions, socioeconomic factors status, accuracy of the information collected and analyzed (i.e., information bias), and differential risk of the outcome (i.e., confounding by indication). These differences could lead to inaccurate assessment of the relationship between a vaccine and the outcome if these unvaccinated persons were used as a comparison group (Chen, Infect Dis Clin North Am, 2001). In an era of an increasing number of new vaccines and increasing public concern about adverse events, developing novel and improved epidemiologic and statistical methods for assessing vaccine safety is imperative.

CDC's Immunization Safety Office's Role and Contribution:

ISO is well-suited to improve epidemiologic and statistical methods for vaccine safety monitoring and already serves as a national center of excellence in this area. In 1990, CDC established the Vaccine Safety Datalink (VSD) Project to overcome the limitations of passive surveillance, and VSD has provided critical vaccine safety science data to inform national vaccine policy. Scientists with VSD have substantial expertise in pharmacoepidemiology and statistical methods. They have consistently pioneered development of new statistical methods and reported these techniques in the peer reviewed literature (Vaccine Safety Datalink Pubs). VSD is recognized as a world leader in the field of vaccine safety and can serve as a model for other medical product safety monitoring initiatives. In 2006, VSD implemented population-based active surveillance to rapidly detect rare adverse events following newly introduced vaccines (Lieu, Med Care, 2007).

Priority Scientific Areas:

1) Improving near real-time surveillance methods.

To improve timeliness of detection of adverse events following immunization (AEFI), VSD investigators developed the rapid cycle analysis (RCA) project, which takes advantage of the ever-improving computational capacity at the MCOs. Instead of creating data files on an annual basis, vaccination and diagnosis files (both outpatient and inpatient) are created weekly at the MCO level and serve as the source of aggregate files that the RCA coordinating center analyzes.

Use of aggregate data maintains a high level of confidentiality. The development of RCA means that vaccine safety issues can be addressed in a continuous or periodic fashion, and represents a critical addition to VSD's capacity to assess vaccine safety, which ranges from surveillance to analytical investigations.

RCA has advantages over passive surveillance programs because it is based on systematically collected data from patients' medical records and it includes denominator data. As with other epidemiologic designs used in VSD, studies of RCA use electronic data to identify a presumptive association between a vaccine and pre-specified outcomes. Additional investigations further reveal the relationship between the exposure and the outcome. The basic structure for the RCA facilitates follow-up investigations, including reviewing medical records to confirm or refute a signal of a potential VAE. Other analyses that may be used to help determine if a signal is spurious include an evaluation of temporal clustering of events after vaccination.

The data for an RCA project are being analyzed at least monthly and more often when warranted; therefore, special statistical methods to handle multiple testing are needed. To analyze these data, VSD investigators have adapted a classical statistical test commonly used in clinical trials, the sequential probability ratio test (SPRT). A refinement, termed the maxSPRT, permits a more flexible composite alternative hypothesis compared to SPRT, which required the investigator to specify a definite hypothesis (Lieu, Med Care, 2007).

Goals:

Because RCA is a relatively new and critical VSD activity, substantial research in multiple areas is both ongoing and planned that will more fully bring out the capabilities and limitations of the RCA approach. Areas that need investigation include:

- Identifying the appropriate comparison group and how they are affected by such things as matching criteria or secular trends in the VAE of interest. The optimal method of producing expected counts for a given VAE may also be derived from unexposed time periods within individual strata (self-controlled methods).
- Improving response times to evaluate and confirm signals (values above specified thresholds) that are detected in RCA analyses.
- Identifying how increasing the length of the study influences RCA results and finding the right balance between timely data acquisition and data quality and stability.
- Defining the optimal characteristics of the outcome to be studied. In general, outcomes best suited for RCA are serious, clinically well-defined, and biologically plausible with respect to the target vaccine.

VSD investigators are working to implement the self-controlled case series (SCCS) method (described below) into the RCA. Although it may not be appropriate for every RCA study, it appears that SCCS can be configured to use the maximum available data with a minimum delay after the event onset date and still maintain subject anonymity by using aggregate data for the analysis.

2) Overcoming limitations of conventional epidemiologic designs.

VSD investigators have been evaluating and continue to explore two alternatives that address some of the limitations of conventional epidemiologic study designs. The risk interval and SCCS designs are best suited for the study of well-defined, acute onset events occurring after vaccination (Glanz, J Clin Epidemiol, 2006). One of the advantages of these designs is the ability to control for unmeasured, time-independent covariates. In addition, they are applicable to situations in which there are high rates of vaccination. However, they may be less useful if the outcomes of interest are subacute or have a delayed onset.

1) In the risk interval design, the incidence rates for risk periods (usually a relatively short period immediately after vaccination) are compared to rates in non-risk periods among those who are vaccinated (Glanz, J Clin Epidemiol, 2006). Studying only vaccinated persons eliminates the problems associated with unexposed comparison groups, which may have different characteristics.

2) In the SCCS, the probability of an adverse event occurring during a specified risk period is compared to the probability during the control periods for the same person, adjusting for baseline risk (Glanz, J Clin Epidemiol, 2006). Only cases of the outcome are included in the analysis with every case serving as their own control. However, these methods also have limitations, such as the control of time-varying covariates and types of outcomes that can be investigated.

Goals:

A goal of ongoing and planned VSD research is to identify and explain key factors that influence the performance of the case series method. For example,

- Modifications of the SCCS to improve its capacity to adjust for confounders and time-varying covariates (e.g., seasonality), which would be especially important for certain immunizations such as influenza vaccines (Fireman, 2007).
- Timing and placement of the risk windows relative to the exposure, which may depend on the vaccine and outcome among other factors.
- The effect of underlying health status and the validity with which it can be assessed within VSD's near real-time surveillance activities.
- Vaccination variables such as timing of vaccination and simultaneous vaccinations.

Item D: Laboratory Research

Background and Public Health Importance:

A variety of laboratory methods are useful for assessing adverse events following vaccination (AEFIs).[5] Understanding the association between the immune response to vaccination and AEFI is particularly important as outlined in the draft National Vaccine Plan (Chapter 2) (http://www.hhs.gov/nvpo/vacc_plan/2008plan/draftvaccineplan.pdf). In 2002, the IOM Immunization Safety Review Committee evaluated the hypothesis that multiple immunizations increase the risk for immune dysfunction (IOM, 2002b). Although their general conclusion was that available data did not support this theory, the committee recognized the benefit of identifying surrogate laboratory markers for autoimmune and allergic diseases after immunization. The committee also endorsed "current research efforts aimed at identifying genetic variability in human immune system development and immune system responsiveness as a way to gain a better understanding of genetic susceptibility to vaccine-based adverse events." By using the tools of modern molecular immunology, both humoral and cellular immunity and immune responses can be assessed. These responses can then be correlated with the frequency and severity of adverse events in an attempt to better understand and perhaps modify these responses.

CDC's Immunization Safety Office Role and Contribution:

ISO's Clinical Immunization Safety Assessment (CISA) Network is uniquely poised to obtain biologic specimens from people experiencing AEFI and to perform laboratory assessments on these samples.

Biologic Mechanisms of Adverse Events:

Basic research is a priority as outlined in the draft National Vaccine Plan (Chapter 2). ISO and CISA currently conduct clinical research on the pathophysiologic basis of adverse events following immunization. However, it may be helpful for NVPO to coordinate basic research designed to increase understanding of biological mechanisms of vaccine adverse events at a national level, including CDC and other federal partners (e.g., NIH). ISO will collaborate with experts within CDC and other federal agencies (e.g., FDA and NIH) on basic and clinical research, as appropriate, and as resources are available.

The CISA network has a bio-specimen central repository at the Columbia University CISA Center, which has the expertise and facilities to receive, process, and store clinical samples. In particular, CISA is well-suited to conduct serologic and cellular immune studies to vaccines, to assess in vivo and in vitro cytokine responses. CISA is also suited to collaborate with specialty laboratories throughout the country in the performance of additional immunologic and microbiologic studies. ISO has an established system for following up VAERS reports of rare or unusual adverse events for further studies done by CISA. CISA links with VAERS via an established mechanism to collect biological specimens for banking in the repository. ISO does

[5] The terms vaccine adverse event following immunization (VAE) and adverse event following immunization (AEFI) are used interchangeably throughout this document and do not imply that an event was caused by a vaccine.

not have the laboratory capacity needed for vaccine safety research. Indicated laboratory investigations can be conducted at selected CDC laboratories, laboratories at the CISA centers or other specialized laboratories, as needed.

Priority Scientific Areas:

1) Collecting Biological Specimens

The type of biological specimen obtained for study depends on the nature of the AEFI, the study question, and the patient population. The range of possible specimens that CISA could collect includes serum, immune cells, cerebrospinal fluid, urine, plasma, tissue samples, or DNA specimens. Genetic material can be efficiently obtained through buccal swabs, which can be shipped to the repository from other CISA sites. Each CISA site has experience with collecting patient specimens under ongoing, institutional review boards (IRB) approved protocols. In addition to IRB approval for collection of clinical samples for studies that address specific vaccine safety issues (e.g., transverse myelitis, Gullian-Barré syndrome) the network sites also have IRB approval for collection and storage of samples from people with VAEs that are not prespecified.

Goals:

Blood samples for RNA and DNA analysis, peripheral blood mononuclear cells (PBMC), and serum samples will be collected using appropriate methods and sent to the Columbia University CISA site where the repository is located. Some testing protocols will necessitate the collection of real-time samples. Such studies will require working with clinicians to collect whole blood samples during real-time of an AEFI in their patients. Whole blood samples can be processed at the Columbia specimen bank into serum, PBMCs, DNA, and RNA for long-term storage. This sample bank will be accessible for use in CDC-approved protocols to assess hypotheses relating to the genetic and immunological basis of AEFI.

2) Assessing Hypersensitivity Reactions to Vaccines

Vaccines, like all other drugs, have the potential to cause allergic reactions. Components that may be allergenic include the infectious agent or specific antigen(s) (e.g., preservatives, stabilizers, and residual media), used in preparation of the vaccine, as well as inadvertent contaminants introduced during vaccine handling. Estimates of true allergic, or immediate hypersensitivity, reactions to routine vaccines range from 1 per 50,000 doses for DTP to about one per 500,000–1,000,000 doses for most other vaccines (Zent et al., Pediatrics, 2003). The most useful system for classifying immunologically mediated reactions is based on timing, immediate or delayed. Most immediate reactions are Type I hypersensitivity reactions that are mediated by preformed IgE antibodies against a vaccine component. Delayed type reactions (e.g., type IV hypersensitivity reactions) occur hours to days after exposure and do not involve IgE mediation. Most delayed reactions are rather from formation of immune complexes with complement activation.

Goals:

CISA has developed an immediate hypersensitivity algorithm (Wood et al. 2008) and is developing a delayed hypersensitivity algorithm as practical tools to guide the clinician in the

evaluation and management of suspected vaccine allergic reactions (See Section 2. Vaccine Safety Clinical Practice Guidance). An essential part of these algorithms are recommendations for laboratory testing methods for evaluation and confirmation of the diagnosis. For immediate hypersensitivity reactions, recommendations for laboratory testing include skin (prick or scratch) tests, measurement of total IgE, and specific IgE antibodies against the suspected allergens. Because delayed-type reactions are not mediated by IgE antibodies, skin tests or in vitro IgE studies are not of value in identifying the causative antigen or vaccine constituent. Type IV hypersensitivity is primarily mediated by antibodies of the IgM or IgG classes and complement. Diagnostic testing for delayed hypersensitivity includes delayed intradermal skin testing examined 48–72 hours after injection, lymphocytic mitogen response, lymphocytotoxicity assay, and IL-2 production.

3) Measuring single nucleotide polymorphisms (SNPs)

Single nucleotide polymorphisms (SNPs) are DNA sequence variations that occur when a single nucleotide (A, T, C, or G) in the genome sequence is changed. These differences lead to humans' diversity (e.g., skin and hair color, height, creativity, and intelligence). At the same time, SNPs can also be markers of genetic changes that cause one person to be more susceptible to developing certain diseases, to be more responsive to certain medical therapies than others, or perhaps to be more susceptible to a certain AEFI. One of the most exciting developments in linking the genetic and immunological bases for AEFIs is the ability to measure SNPs for the matching specific cytokine gene among persons with specific AEFI.

Goals:

Research is needed to conduct microarray analyses to generate immune activation gene data. Serum from a sample of index cases and matched controls are assayed for candidate cytokine serum levels to confirm the findings of the microarray analyses. To further evaluate the genetic variation associated with a study question, whole human genome arrays could be performed to look for polymorphisms associated with the outcome in question.

Item E: Genomics and Vaccine Safety

Background and Public Health Importance:

Because only a small number of people develop serious AEFIs, it is important to investigate if genetically determined differences in immune responses to vaccination are partly responsible for these adverse events. Identifying genetic risk factors for serious AEFI might identify markers of susceptibility for AEFI, improve the evidence base for safe vaccination, and aid development of safer vaccines.

There is increasing appreciation of the role of human genetic variation and how it affects the risk for drug interactions and AEFI (Wilke, Nat Rev Drug Discov, 2007). Although there is substantial research, both federal and industry-wide, into the genetic basis of drug adverse events, relatively little research has been directed towards understanding the genetic basis of AEFI. In addition, a number of unique aspects of vaccine safety differentiate it from research on medication safety. Vaccines are routinely recommended for widespread use and most are administered to healthy children, adolescents, and adults.

Few studies have assessed genetic risk factors for AEFI. Examples include:

- Mitchel reported higher frequencies of HLA-DR2 and DR5 in women who developed joint symptoms after rubella vaccination (Mitchel, J Infect Dis, 1998).
- Piyasinsilp found an increased frequency of HLA-DR9 (DRB1*0901) and HLA-DR17 (DRB1*0301) in Thai patients who developed autoimmune encephalomyelitis following Semple rabies vaccination (Piyasirisilp, Ann Neurol, 1999).
- Wilson et al reported four loci preliminarily linked to myopericarditis after smallpox vaccination, including interleukin associated genes and HLA genes (Wilson, Vaccine Safety Evaluation: Post Marketing Surveillance Conference, 2007).
- Polymorphisms in Fas genes involved in regulation of immune homeostasis have been associated with anti-ganglioside antibodies that have relevance to Guillain-Barré syndrome (GBS) (Van Sorge, Neuroimmunol, 2005).

CDC's Immunization Safety Office Role and Contribution:

- Along with FDA, CDC has primary responsibility for monitoring the safety of US-licensed vaccines and contributes to developing the evidence base to inform safe vaccination practices. The draft National Vaccine Plan includes an objective to understand host risk factors, including genetic factors that may be associated with AEFI (http://www.hhs.gov/nvpo/vacc_plan/).
- The National Institutes of Health has posted Research Project Grants (R01) in vaccine safety and genomics (http://grants.nih.gov/grants/guide/pa-files/PA-08-256.html). Close coordination with other federal partners is imperative to furthering the capacity of vaccine safety genomics.
- Within this context, the objective of the genomics research initiative within ISO is to develop a scientific approach to understanding the potential genetic basis for VAEs. ISO

can play an important role in enhancing the infrastructure needed for such work, and in outlining the steps needed for collecting and analyzing such data. The long-term goal is to implement genetic studies and apply findings to enhance vaccine safety. In doing so, ISO, along with other partners, could be a leader in implementing the HHS goal of personalized healthcare.

- The Personalized Health Care Initiative will improve the safety, quality, and effectiveness of healthcare for every patient in the United States. ISO hosted a conference on "Understanding the Genetic Basis of Vaccine Safety" (2008) that was co-sponsored by NVPO, as well as a meeting in April 2010 on establishment of an HHS-wide Bio-specimen repository.
- It may also be helpful for NVPO to coordinate basic research activities with other federal partners (e.g., NIH). ISO will collaborate with experts within CDC and other federal agencies (e.g., FDA and NIH), as appropriate.

Priority Scientific Areas:

Developing a systematic scientific approach to studying the genetic basis for VAEs requires an in-depth examination and discussion of a number of issues, including an understanding of technology advances, analytic approaches, and public health applications of evidence.

ISO is currently sponsoring a variety of studies to assess the genetic factors associated with VAEs within the vaccine safety network of CISA, Vaccine Safety Datalink (VSD) and Vaccine Adverse Event Reporting Systems (VAERS), such as:

1) **Establishing a specimen repository bank for biological specimens**. ISO and CISA have developed an IRB-approved protocol for a repository of specimens from patients that have experienced a clinically significant VAE. This registry complies with the HIPAA regulations to maintain patient privacy. Specimens in the repository may be used for future studies of cytokine responses, gene expression profiles, and gene polymorphisms related to specific VAEs. Specimens stored in the repository are linked to epidemiologic data (e.g., demographic, clinical, exposure history, and risk factors) stored in the registry by an assigned code to maintain privacy. These specimens include serum, whole blood, biopsies, urine, cerebrospinal fluid (CSF), white blood cell (WBC) pellets or saliva/buccal cells. The CISA Specimen Repository resides at Columbia-Presbyterian Medical Center in New York City.
2) **Evaluating genetic risk factors for GBS after vaccination**. The association of GBS and influenza vaccine was reported in 1976 when a 7-fold increase in GBS risk was observed within 6 weeks following vaccination with swine influenza vaccine (Schonberger, Am J Epidemiol, 1979). Recent data suggest a small increased risk for GBS after MCV4 vaccination (CDC, MMWR, 2006b; Haber, JAMA, 2004). Because GBS is rare, it has been suggested that a genetic predisposition may be an important contributing factor. Enrollment in case-control studies using reports of GBS within 10 weeks of vaccination identified through VAERS, VSD, and CISA sites is ongoing. Genetic analysis by whole genome scan is planned, but may also include a more focused analysis of specific gene targets.
3) **Studying the genomics of wheezing and variable immune response after influenza vaccination in children 6–59 months of age.** Recent evidence shows that the variability

in the acute phase response to influenza vaccination may be in part mediated by genetic variants in HLA class II (Gelder, J Infect Dis, 2002) and a genetic variant in the candidate gene *NFKBIA* (Carlson, Hum Genet, 2007; Carty, Arterioscler Thromb Vasc Biol, 2006)**.** The objective of this study was to identify both the genetic and non-genetic factors that can predict whether or not a patient will have an adverse reaction to the influenza immunization. This was a retrospective study to collect DNA samples from 80 children aged 6–50 months who participated in a seasonal influenza clinical trial. As part of the clinical trial, information was collected on adverse reactions, infection with influenza during that subsequent influenza season, and basic demographic variables for every vaccinated patient. Comparisons of genotypes were made between 1) children who wheezed following vaccination and children who did not wheeze; and 2) children who were found to be infected with influenza during the season and those who were not infected.

Goals:

ISO is developing a genomics initiative with the following intent:

- To develop a scientific approach to understanding the genetic basis for AEFI and its proper public health applications.
- To promote increased awareness and cooperation between federal agencies, academia and industry for improving the understanding of the genetic basis of AEFIs.
- To perform studies to identify candidate genes that may be associated with an increased risk for AEFIs.
- To identify short- and long-term strategies for integrating genomics into vaccine safety science.

Item F: Case Definitions for Data Collection, Analysis, and Presentation for Adverse Events Following Immunization (AEFI)

Background and Public Health Importance:

Vaccines are used worldwide, and shared terminology in the field of vaccine safety is essential. Standardization of adverse events following immunization (AEFI) reporting facilitates comparability and communication of vaccine safety data and plays a key role in the enhancement of trust in current immunization programs. The need arises from the fact, unlike vaccine effectiveness, that safety cannot be measured directly. Safety can only be inferred from the relative absence of vaccine adverse events. The lack of a standard vocabulary or case definitions or guidelines for vaccine adverse event data collection or presentation has hindered our ability to compare vaccine safety data across studies. Assessing safety requires a standardized vocabulary of adverse events. Unfortunately, only limited standardization has occurred in the past (Proceedings, 1992; Braun, Pediatrics, 1998).

Experts in vaccine safety met in Brighton, England, and conceptualized the Brighton Collaboration (BC), which was officially launched in the fall of 2000. Work began with the formation of a steering committee and creation of working groups which included international volunteers with expertise in vaccine safety, patient care, pharmaceuticals, regulatory affairs, public health, and vaccine delivery. The guidelines for collecting, analyzing, and presenting safety data developed by the collaboration will facilitate sharing and comparison of vaccine data among vaccine safety professionals worldwide. Previously, medical dictionaries for regulatory affairs (International Conference, 2008; The Uppsala Monitoring Center, 2005; Iskander, Ped Annals, 2004) and case definitions for adverse drug reactions (CIOMS, Working Group, 2008) were developed and implemented. However, relatively little work has been done to develop case definitions for use in immunization safety (Braun, Pediatrics, 1998; WHO, 1997; Ball, J Clin Epid, 2002) before the establishment of the Brighton Collaboration (BC) (http://www.brightoncollaboration.org/internet/en/index.html).

The BC, in concert with the World Health Organization (WHO) (Duclos Drug Saf 2001) and the US and European Centers for Disease Control and Prevention (CDC, ECDC) is working to develop and disseminate standardized case definitions for AEFI. The case definitions are categorized by the levels of evidence available, which will differ whether data is gathered in prospective clinical trials, in post-marketing surveillance, or whether it occurs in a developed or developing country using a robust process (Kohl, Vaccine, 2007; Kohl, Adv Pat Safe, 2005; Bonhoeffer, Vaccine, 2004a; Bonhoeffer, Vaccine, 2004b; Kohl, Pharmacoepidemiol Drug Safe, 2003; Bonhoeffer, Vaccine, 2002). As of January 2010, the BC had completed a total of 28 case definitions; these include definitions on anaphylaxis, intussusception, thrombocytopenia, and unexplained sudden death in the first and second years of life (Kohl, Vaccine, 2007). A complete list of case definitions is available and can be downloaded via a quick registration process at the BC Web site, http://www.brightoncollaboration.org/internet/en/index/html. In addition, finalized definitions are published in the journal *Vaccine* (Marcy, Vaccine, 2004; Beigel, Vaccine, 2007; Tapiainen, Vaccine, 2007; Bines, Vaccine, 2004).

CDC's Immunization Safety Office's Role and Contribution:

Although ISO's scientists engage in specific BC working groups, ISO no longer leads the secretariat activities of the BC; however, ISO continues supporting the work of the BC, a consortium of more than 2,000 volunteer professional participants from over 90 countries. As a global leader in immunization safety science, ISO provides technical expertise in various BC working groups. ISO continues to play a technical role in helping the BC achieve its mission. Today, the use of BC case definitions is recommended by key organizations in vaccine safety including: WHO, IOM, FDA, and the European Agency for the Evaluation of Medicinal Products (EMEA) (WHO, Wkly Epi Record, 2006; IOM, 2002a; FDA Draft Guidance, 2007; EMEA, 2005). These case definitions were used globally during the monitoring of the 2009 H1N1 pandemic to allow comparison of vaccine safety data using one set of definitions. No other organization is dedicated to the development, evaluation, and implementation of standardized case definitions for AEFI.

Priority Scientific Areas:

To further the foundational work towards a common vaccine safety language, ISO plans to continue supporting the development of new case definitions, disseminate completed BC case definitions, and translate them into practice.

Key goals during the next 5 years are to:

- Continue to support development of case definitions to contribute to priority research and surveillance needs in vaccine safety.
- Evaluate case definitions to be used in research and surveillance.
- Support translation and dissemination of the BC case definitions into practice.

Item G: Vaccine Safety Clinical Practice Guidance

Background and Public Health Importance:

Delivery of every vaccine involves an interaction between the healthcare provider and individual patient. Vaccine providers and vaccinees (or their care givers) strive to achieve optimal benefits from vaccination, while minimizing risks to the vaccinated person. In addition to screening for contraindications and using proper vaccine delivery techniques, clinicians are responsible for managing and reporting clinically significant VAEs. Building a knowledge base for vaccine safety involves better understanding of clinical aspects of VAEs.

Clinical practice guidelines are one mechanism to better characterize adverse events and to minimize risk of further adverse events or complications if an adverse event occurs. Clinical practice guidelines are a standard part of practice in the United States and numerous professional organizations develop and disseminate guidance (AHRQ, National Guideline Clearinghouse, 2008). CDC's treatment guidelines for sexually transmitted diseases (CDC, Sexually Transmitted Diseases Treatment Guidelines, 2008) and the Advisory Committee on Immunization Practices (ACIP) recommendations (CDC, Advisory Committee on Immunization Practices, 2010, recommendations available at http://www.cdc.gov/vaccines/recs/acip/) for vaccine use are two prominent examples of clinical guidance. Availability of guidance on vaccine safety clinical practice will help clinicians investigate, diagnose, and help make revaccination decisions for their patients with VAEs. Although all clinicians, from primary care providers to subspecialists, may benefit, certain groups are particularly likely to encounter adverse events and their assessments may influence the opinions of others. Allergist-immunologists, dermatologists, and neurologists are often consulted on clinical problems that are potentially attributable to vaccines. These subspecialists could be a particular focus for vaccine safety clinical practice guidance.

Although severe VAEs are rare, they are of concern to clinicians, their patients, and their patients' caregivers. The healthcare provider needs to manage the adverse event on the basis of available clinical practice guidance, determine whether future vaccinations are indicated, and report clinically important events to VAERS. The ACIP General Recommendations provides guidance on preventing or managing some adverse events (CDC, ACIP General Recommendations on Immunization, 2006). For example, ACIP provides guidance to prevent injuries from syncope or treat anaphylaxis after vaccination. The Department of Defense Vaccine Healthcare Centers (VHC) Network (Vaccine Healthcare Network Center, 2008) provides clinical guidelines for management of adverse events for targeted military service members and their beneficiaries. However, the diversity of vaccines, adverse events, and vaccinated populations make a broader evidence base necessary.

Surveillance for VAEs must be capable of detecting rare and unexpected events, and at the same time assessing the likelihood of causal relationships. Whether VAEs are reported to VAERS or are ascertained via electronic databases such as those used by the VSD Project, each event begins at a clinical level. The quality of the data for VAE reports depends on the ability of clinicians to correctly characterize events and perform appropriate clinical investigations. Busy clinicians could use support in characterizing, diagnosing, and managing VAEs. Limitations and deficiencies at the clinical level may translate into limitations of the data used to develop public health policy.

CDC's Immunization Safety Office's Role and Contribution:

ISO is uniquely suited to lead development of evidence-based, vaccine safety clinical practice guidance. ISO is a national leader in the field of vaccine safety and has ongoing, established vaccine safety programs and access to clinicians with diverse expertise. Providing vaccine safety guidelines will improve CDC's surveillance programs, enhance its public health mission, and contribute to the HHS strategic goal of personalized healthcare (HHS, Strategic Plan, 2008). Developing clinical guidance to improve health fits in with CDC's broad goal of implementing preventive strategies as the agency disseminates guidance in a number of health areas. CDC's mission focuses on preventing disease and disability. ISO will develop guidelines to help providers make vaccination decisions, in consultation with their patients that will minimize the risk of AEFI. Specific management of clinical outcomes (e.g., febrile seizures after MMR or MMRV vaccine) that may occur after vaccination is not in the purview of ISO. However, ISO can assist the clinician in gaining easy access to best practice guidance from other federal agencies and professional societies about management of clinical outcomes that may be seen after vaccination (http://www.guideline.gov/).

Priority Scientific Areas:

Priority areas for the development of guidelines are based on the frequency and severity of the adverse events associated with vaccination, including:

- Immediate hypersensitivity reactions after vaccination (completed, Wood RA et al, 2008).
- Delayed hypersensitivity reactions after vaccination.
- Inflammatory and demyelinating neurologic disorders appearing after vaccination.
- Guidelines for minimizing VAEs for immunocompromised hosts.
- Causality assessment of individual adverse events following immunization.
- Up-to-date comprehensive document for clinicians to use to prevent and report vaccine adverse events.

Goals:

The goal is to use evidence-based methods, including expert clinical opinion, to develop and widely disseminate clinical guidance. This guidance will assist clinicians in assessing and reporting VAEs and making revaccination decisions, in consultation with the vaccinee (or caregiver), regarding experiences with adverse events following immunizations. Within CDC, the ACIP General Recommendations Working Group develops recommendations periodically on cross-cutting vaccination issues. These include areas regarding safety of vaccination, reporting adverse events to VAERS, and preventing adverse events. ISO has representation on this working group to advise on the vaccine safety sections. During the next General Recommendations update, vaccine safety information will be updated to include more detailed information to assist clinicians with vaccine safety issues. In addition, CDC will prepare a document that consolidates vaccine safety information for easy access by clinicians into one location. For example, this document will describe how to report an adverse event to VAERS, summarize guidance from the ACIP General Recommendations, and include information and resources about diagnosis and treatment of injuries included in the Vaccine Injury Table (http://www.hrsa.gov/Vaccinecompensation/table.htm).

Section 3. 5-Year Research Needs

The initial draft ISO Scientific Agenda that the NVAC reviewed had 30 research needs for the next 5 years, including 7 specific vaccine safety questions and 24 scientific thematic areas (Table 2 and Tables 3A–D). The scientific thematic areas fall into in three categories: 1) vaccines and vaccination practices (8 topics), 2) special populations (8 topics), and 3) clinical outcomes (8 topics). ISO developed these lists in collaboration with numerous internal and external experts through a multi-step process described in the earlier draft located at: http://www.cdc.gov/vaccinesafety/index.html.

Topics could be included on these lists if the following inclusion criteria were met: ISO routinely leads the topic (i.e., vaccine safety risk assessment), ISO could implement a study during the next 5 years with infrastructure generally available to CDC, and routine use of the vaccine(s) in question in the civilian population is likely to happen during the next 5 years. Other research studies or activities might occur as part of ISO's core responsibilities (see Section 1: Emerging Issues and Core Required Scientific Activities).

The technical tables were developed to assist the NVAC Vaccine Safety Working Group in reviewing and prioritizing the topics (Tables 3A–D) (see Section 4: Approaches for Prioritizing CDC's Immunization Safety Office Vaccine Safety Scientific Activities). The background material is not intended to be a comprehensive review of all potentially relevant information. Rather, it includes selected summary information from the literature, IOM reports, and ACIP recommendations. In addition, information is presented about ongoing and planned ISO research studies. Selected information is provided on selected manufacturer post-marketing studies of vaccine safety. The order of materials in the technical tables is not prioritized in order of importance. Some information has been updated since the draft Agenda was prepared in 2008 to reflect incorporation of the NVAC recommendations and advances in science.

The following general principles apply to these 5-year research needs:

1) The Agenda does not specify study aims or methods, such as comparison groups.
2) When developing research studies to address vaccine safety questions or thematic areas, factors to consider should include, but are not limited to gender, race and ethnicity, underlying medical history, and potential genetic risk factors.
3) If an association between an exposure and risk for an outcome is identified, then follow-up studies to describe the mechanisms or sequelae may be needed.
4) Addressing research gaps in the vaccine safety areas requires collaboration among ISO, its research partners such as other experts across CDC, other federal agencies, and academia. Clinical expertise in subspecialty areas may be needed.

Table 2. Summary of 30 Immunization Safety Office (ISO) 5-Year Research Needs

Item	Topic
A	**Specific Vaccine Safety Questions**
A-I	Are vaccines (e.g., influenza vaccines, meningococcal conjugate vaccine [MCV4]) associated with increased risk for Guillain-Barré syndrome (GBS)?
A-II	Is live, attenuated influenza vaccine (LAIV) associated with increased risk for asthma or wheezing, particularly in young children or persons with history of wheezing?
A-III	Is exposure to thimerosal associated with increased risk for clinically important tics or Tourette syndrome?
A-IV	Are acellular pertussis vaccines associated with increased risk for acute neurological events, particularly hypotonic-hyporesponsive episodes (HHE)?
A-V	Is immunization associated with increased risk for neurological deterioration in children with mitochondrial dysfunction?
A-VI	Is combination measles, mumps, rubella, and varicella vaccine (MMRV) associated with increased risk for febrile seizure, and if so are there sequelae?
A-VII	Are varicella vaccines (i.e., varicella, MMRV, and zoster vaccines) associated with increased risk for clinically important events related to varicella vaccine virus reactivation?
B	**Vaccines and Vaccination Practices**
B-I	Bivalent human papillomavirus (bivalent HPV) vaccine (Cervarix®)
B-II	Zoster vaccine (Zostavax®)
B-III	Annual influenza vaccination in children and adolescents (trivalent inactivated influenza vaccine [TIV] and LAIV)
B-IV	Non-antigen components of vaccines (other than thimerosal or ASO4 in bivalent HPV vaccine)
B-V	Simultaneous vaccination
B-VI	Safety of different products within the same vaccine category
B-VII	Off label use of vaccines
B-VIII	Vaccine-drug interactions
C	**Special Populations**
C-I	Premature and low birth weight infants
C-II	Pregnant women
C-III	Adults aged ≥60 years
C-IV	Persons with primary immunodeficiency
C-V	Persons with secondary immunodeficiency
C-VI	Persons with autoimmune disorders
C-VII	Children with inborn errors of metabolism
C-VIII	Race/Ethnicity minorities and gender
D	**Clinical Outcomes**
D-I	Autoimmune diseases
D-II	Central nervous system demyelinating disorders
D-III	Encephalitis/encephalopathy
D-IV	Neurodevelopmental disorders, including autism spectrum disorder (ASD)
D-V	Vasculitis syndromes
D-VI	Myopericarditis (not associated with smallpox vaccine)
D-VII	Clinically important outcomes associated with post-immunization fever
D-VIII	Post-vaccination syncope and sequelae

Table 3A. ISO 5-Year Research Needs: Specific Vaccine Safety Questions

Item	Question	Background
A-I	**Are vaccines (e.g., influenza vaccines, meningococcal conjugate vaccine [MCV4]) associated with increased risk for Guillain-Barré syndrome (GBS)? High priority**	• IOM favored acceptance of a causal relationship between the 1976 swine influenza vaccine and Guillain-Barré syndrome (GBS) in adults (IOM, 2004); found the evidence inadequate to accept or reject a causal relationship between GBS in adults and influenza vaccines administered after 1976 (IOM 2004); and favored acceptance of a causal relationship between tetanus toxoid-containing vaccines and GBS (Stratton, JAMA, 1994). • Studies of risk for GBS after influenza vaccine in years other than 1976 have found either no increased risk or a small increased risk of about one additional case per million persons vaccinated (REF 2010 ACIP statement for influenza vaccines). • During the 2009 H1N1 response, several federal systems assessed the risk for GBS after 2009 H1N1 vaccines. Data analysis in most of these systems is ongoing (REF VSRAWG report 6/2010 http://www.hhs.gov/nvpo/nvac/reports/vsrawg_report_may2010.html). • Data in VAERS suggest a small increased risk for GBS after MCV4 vaccination; however, uncertainty exists regarding this risk estimate (CDC, MMWR, 2006; Haber, JAMA, 2004). • Studies led by VSD and Harvard Medical School/ Harvard Pilgrim Health Care assessing the relationship between immunization with MCV4 and Guillain-Barré syndrome (GBS) in adolescents do not suggest an increased risk for GBS after MCV4 vaccination (REF ACIP 6/2010 meeting presentations http://www.cdc.gov/vaccines/recs/acip/slides-jun10.htm#meingvac). • The Clinical Immunization Safety Assessment (CISA) Network is conducting a study on genetics of GBS and one on the relapse of GBS following vaccination. • VSD near real-time surveillance studies specifies GBS as an outcome for several vaccines. • VSD is conducting a study to identify the risk of GBS associated with various vaccines; populations in different pediatric and adult age groups will be analyzed. • The Vaccine Analytic Unit (VAU), jointly managed by CDC and DOD, is planning studies to evaluate the risk of GBS associated with anthrax, influenza, and meningococcal vaccines (Payne DC et al, 2007). • VSD near real-time surveillance studies specify GBS as an outcome for several vaccines: Gardasil®, Menactra®, Kinrix®, and Pentacel®, Tdap, and seasonal and H1N1 influenza. • The Emerging Infections Program (EIP) is conducting active GBS case finding during the 2009–2010 influenza season. It will assess potential risk factors for GBS, including recent influenza vaccination. • CISA is creating a registry of clinical data and a repository of biological specimens in patients who develop adverse events following immunization, including specimens of GBS cases. • A final Brighton case definition for GBS has been completed (Sejvar JJ et al 2010)
A-II	**Is live, attenuated influenza vaccine (LAIV) associated with increased risk for asthma or wheezing, particularly in**	• LAIV (FluMist®) was licensed in the United States in 2003 for healthy persons aged 5–49 years. In 2007, the LAIV license was revised to include healthy children aged 2–4 years (CDC, MMWR, 2007).

Item	Question	Background
	young children or persons with history of wheezing?	• During clinical trials wheezing was identified as a potential safety concern in young children and persons with history of wheezing. In a study that supported a label change, Belshe identified increased risk for wheezing after LAIV in children aged 6–23 months but not children aged 24–59 months (Belshe, NEJM, 2007). • A CISA study on the genomics of wheezing and variable immune response after influenza vaccination in children 6–59 months of age is in progress. • Plans to develop a VSD study to assess risk for wheezing in young children are under discussion. • MedImmune, the manufacturer of FluMist, is conducting post-licensure studies in children aged 24–59 months to assess safety (including wheezing) and rates of off label use in children for whom LAIV is not indicated (FDA, approval letter, 2007). • VSD's influenza rapid cycle analysis study is evaluating potential adverse events following influenza vaccination, including wheezing and asthma after LAIV.
A-III	**Is exposure to thimerosal associated with increased risk for clinically important tics or Tourette syndrome?**	• In response to IOM recommendations, CDC conducted a cohort study of children to examine the hypothesis that early exposure to thimerosal, a mercury-containing preservative used in vaccines and immune globulin preparations, is associated with neuropsychological deficits (IOM, 2001; Thompson, NEJM, 2007). • The study included children aged 7–10 years; children who had a history of premature birth were not included. The study was not designed to assess possible association between thimerosal and autism (Thompson, NEJM, 2007) (see background, bullet D-IV). • The study's conclusions stated, "Our study does not support a causal association between early exposure to mercury from thimerosal-containing vaccines and immune globulins and deficits in neuropsychological functioning at the age of 7–10 years" (Thompson, NEJM, 2007). • However, the study found that increasing exposure to mercury from birth to age 7 months was associated with motor and phonic tics in boys. The study did not distinguish between minor, transient tics and Tourette syndrome (Thompson, NEJM, 2007). • An association between exposure to thimerosol and tics was found in two earlier studies (Andrews, Pediatrics, 2004; Verstraeten, Pediatrics, 2003). The Thompson study stated, "The replication of the findings regarding tics suggests the potential need for further studies" (Thompson, NEJM, 2007). • Public use dataset from the above study is available. http://pediatrics.aappublications.org/cgi/content/full/125/6/1134
A-IV	**Are aceullar pertussis vaccines associated with increased risk for acute neurological events, particularly hypotonic-hyporesponsive episodes (HHE)?**	• Concern about neurological events following pertussis vaccines is long-standing. IOM concluded that evidence "is consistent with a causal relation" between DTP vaccine and shock and "unusual shock-like state" and "evidence indicates a causal relation" between DTP vaccine and persistent crying (IOM, 1991). • Studies suggest that rates of HHE are lower after DTaP than after DTP vaccines (Heijbel, Dev. Biol. Stand., 1997; Saux Pediatrics, 2003); there are no published comparative post-licensure studies on risk of HHE after DTaP vaccines. • The Advisory Committee on Immunization Practices (ACIP) considers HHE and certain other

Item	Question	Background
		neurological events to be precautions for DTaP vaccine (CDC, ACIP General Recommendations, 2006). • A VSD study assessed the risk for seizures after DTaP vaccine and found no association between DTaP vaccine and seizures (Huang W-T et al 2010). Brighton case definition for HHE, aseptic meningitis, as well as encephalitis, myelitis, and acute demyelinating encephalomyelitis (ADEM) have been published (Buettcher M et al, 2007; Tapiainen T et al 2007; Sejvar J et al 2007).
A-V	**Is immunization associated with increased risk for neurological deterioration in children with mitochondrial disorders?** **High priority**	• Mitochondrial disorders are a heterogeneous group of disorders characterized by impaired energy production. "Mitochondrial studies" are a sub-set of inborn errors of metabolism that include other studies done by CISA. • They are usually progressive and multisystemic; the incidence is estimated to be 1 in 5,000 live births (Haas, Pediatrics, 2007). • Children with mitochondrial disorders commonly present with a range of central nervous system findings. In a chart review study of 36 children with mitochondrial disorders presenting to a neurology clinic in Israel, the nervous system was involved in all children. Six of the 36 children had acute encephalopathy followed by mental deterioration and 2 had autistic features (Nissenkorn, Arch Dis Child, 1999). • In an epidemiological study of Portuguese children with autistic spectrum disorder, 7% had a definitive mitochondrial disease (Olivera, Developmental Medicine and Child Neurology, 2005). • Studies suggest that children with metabolic disorders, including mitochondrial disorders, may experience neurological deterioration during the time of physiologic stress. Children with mitochondrial disorders are at higher risk of complications from vaccine-preventable diseases. Metabolic crisis after vaccination has been reported (Yang, Pediatric Neurology, 2006; Brady, Pediatrics, 2006; Kingsley, Pediatrics, 2006, CDC, Fact Sheet, 2008). • CISA has formed a working group, in collaboration with partners from FDA, NIH, NVPO, HRSA, academic institutions, vaccine health clinics, experts on mitochondrial disorders, and the National Office of Public Health Genomics, and has a number of studies in progress or completed. • CISA is currently conducting retrospective vaccine safety studies of children with mitochondrial disorders at all six CISA sites. • Evaluation of immunization rates and AEFIs among children with mitochondrial disorders at Northern California Kaiser (NCK) and other sites are conducting similar studies. • CISA will develop guidelines for clinical investigations of individual adverse events following immunizations that might occur in children with underlying mitochondrial disorders.
A-VI	**Is combination measles, mumps, rubella, and varicella (MMRV) vaccine associated with increased risk for febrile seizure, and if so are there sequelae?**	• The Brighton case definition for seizure was completed (Bonhoeffer J et al, 2004). • In February 2008, ACIP voted to remove the preference for MMRV over MMR and varicella vaccines, and formed a Working Group (CDC, MMWR, 2008). Final recommendations for MMRV use were published in 2010 (http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5903a1.htm). • A VSD study was completed that examines febrile convulsions associated with MMR and varicella vaccines. Among 12- to 23-month-olds who received their first dose of measles-containing vaccine,

Item	Question	Background
		fever and seizure were elevated 7 to 10 days after vaccination. Vaccination with MMRV results in 1 additional febrile seizure for every 2,300 doses given instead of separate MMR varicella vaccines (Klein NP et al, 2010). A Merck postmarketing study to assess risk of febrile seizures 5–12 days after MMRV vaccine was also published (REF Jacobsen Vaccine 2010).
A-VII	**Are varicella vaccines (i.e., varicella and MMRV and zoster vaccine) associated with increased risk for clinically important events related to reactivation of varicella vaccine virus?**	• Varicella vaccine reports to VAERS during 1995–2005 were reviewed. Identified adverse events associated with evidence of vaccine-strain VZV included herpes zoster requiring hospitalization and meningitis in patients with concurrent herpes zoster (Chaves, JID, 2008). • In the Chaves study, two patients with confirmed vaccine-strain-associated meningitis had sufficient neurological symptoms and signs to warrant diagnostic evaluation of Cerebrospinal Fluid CSF (Chaves, JID, 2008).

Table 3B: ISO 5-Year Research Needs: Vaccines and Vaccination Practices

Item	Thematic Area	Background
B-I	**Bivalent human papillomavirus (bivalent HPV) vaccine (Cervarix™)**	• In March 2007, GlaxoSmithKline submitted a biologics license application for a bivalent HPV vaccine (Cervarix® that was approved by FDA October 16, 2007, which can be found at http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm186959.htm. • Bivalent HPV vaccine contains a novel adjuvant called ASO4 (aluminum hydroxide and 3-deacylated monophosphoryl lipid A). ASO4 is an agonist of Toll-like receptors; it induces an enhanced antibody response to HPV virus-like particles. (Alderson, Journal of Endotoxin Research, 2006). • In pre-licensure studies, bivalent HPV was safe and well-tolerated. No specific safety concerns were identified, but the long-term safety is unstudied (Pederson, Journal of Adolescent Health, 2007). • VSD is planning on conducting a study if uptake in the VSD sites is sufficient.
B-II	**Zoster vaccine (Zostavax®)**	• In 2006, a zoster vaccine, (Zostavax®), which is a live vaccine, has been recommended for adults aged ≥60 years. It is the first live vaccine in the United States routinely recommended for older adults (CDC, ACIP provisional recommendations, 2006). • In a pre-licensure study, the rate of serious adverse events, including cardiovascular events, was higher in persons receiving Zoster vaccinethan with placebo recipients during the 42 days after vaccination (FDA, Product Approval Information and Package Insert, 2006). • VSD has completed a study assessing risk for selected outcomes requiring medical attention following vaccination, including stroke and other cerebrovascular diseases, severe neurological outcomes, severe cardiac outcomes, including myopericarditits, and serious local reaction (manuscript in development). • Merck is conducting studies to assess the general safety profile, serious adverse events, and adverse events in subjects receiving low-to-moderate doses of maintenance steroids (FDA, approval letter, 2006).
B-III	**Annual influenza vaccination in children and adolescents (trivalent inactivated influenza vaccine [TIV] and LAIV)**	• Assuming full coverage, approximately 74 million children and adolescents aged 6 months–18 years would receive at least one dose of TIV or LAIV annually (US Census, 2006). • Available data does not suggest specific safety concerns; however, there are gaps in knowledge. VSD is conducting a rapid cycle study to assess 14 outcomes after TIV and/or LAIV. • VSD is conducting a study of TIV in children aged 24–59 months. One goal of the study is to examine the risk of selected adverse events in children who receive multiple TIV doses. • VSD is conducting a study assessing risk for fever or pain crisis in children with sickle cell disease who receive influenza vaccination. • In 2010–2011, ACIP expanded recommends to include all persons aged 6 months or older. More people are likely to receive seasonal vaccine in the next several years (MMWR, 2010).
B-IV	**Non-antigen components of vaccines (other than thimerosal or ASO4 in bivalent HPV vaccine)**	• Proceeding licensure, as part of FDA's review, FDA takes all the ingredients into account, including the active ingredients and other substances. After FDA approves a vaccine, FDA and CDC continuously monitor its safety (http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/VaccineSafety/ucm187810.htm). • In 2006, more than 50 excipients were present in US-licensed vaccines (CDC, Pink Book, 2008). • US-licensed vaccines also contain conjugate proteins, such as diphtheria and tetanus toxoids.

Item	Thematic Area	Background
		• The patterns of exposure to non-antigen components after licensure may differ from patterns studied before licensure. • A VSD study assessed occurrence of severe local VAEs in adolescents and young adults with varying patterns of diphtheria toxoid-containing vaccines (Jackson JL et al, 2009). Local reactions were the most commonly reported adverse events following tetanus and diphtheria toxoid (Td) vaccine, and the risk of local reactions may increase with the number of prior Td vaccinations. It was concluded that medically attended local reactions were uncommon following Td vaccination. The risk of those reactions varied by age and by prior receipt of tetanus and diphtheria toxoid containing vaccine. These findings provide a point of reference for future evaluations of the safety profile of newer vaccines. • Brighton has developed six case definitions for local reactions (a local reaction, cellulitis, abscess, swelling, induration, and nodule) (Gidudu J et al, 2008; Halperin S et al, 2007; Kohl K S et al, 2007; Kohl KS et al, 2007; Kohl KS et al 2007; Rothstein E et al, 2004) for use in identification of various local reactions following administration of vaccines including non-antigen components. Injection site pain had been associated with some adjuvanted vaccines and a definition for injection site is being developed. • CISA is conducting a case control study to look at people who have had an adverse event to a gelatin containing vaccine.
B-V	**Simultaneous vaccination**	• Under current infrastructure, pre-licensure studies do not assess safety of two unlicensed vaccines administered simultaneously (i.e., Tdap and MCV4 simultaneous administration was not studied before licensure). • ACIP recommends simultaneous vaccination, unless contraindications are present (CDC, ACIP General Recommendations, 2006). • VSD studies attempt to assess risks of simultaneous vaccination when feasible, as part of the rapid cycle studies. • The VAU, jointly managed by CDC and DOD, has conducted a study that found no evidence that the receipt of multiple concurrent vaccinations is related to risk of hospitalization among DoD personnel (Payne et al, 2007). • A VSD manuscript has been published concerning multiple vaccinations and the risk for medically attended fever. The study stated that, “these findings offer reassurance that the multiple vaccinations introduced during the decade studied were not associated with increases in medically attended fever.” (Lin ND et al. Vaccine 2010).
B-VI	**Safety of different products within the same vaccine category**	• Within the same vaccine category, certain vaccines are available from different manufacturers; these vaccines have different antigen and non-antigen compositions. • Some examples of vaccines with more than one formulation on the US market are trivalent inactivated influenza vaccines (TIV), diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccines, and rotavirus vaccines. A quadrivalent human papillomavirus (HPV) vaccine is routinely recommended; a bivalent HPV vaccine has been licensed by FDA and recommended by the ACIP. • The ACIP recommends that “for vaccines in general, vaccination should not be deferred because the brand used for previous doses is not available or is unknown” (CDC, ACIP, 2006).

Item	Thematic Area	Background
		• Information about the interchangeable use of vaccine of the same category from different manufacturers is generally limited. • See also A-VI on febrile seizure risk after MMRV.
B-VII	**Off label use of vaccines**	• Off label use is defined as use of a product other than the indication for which it was approved by FDA. • Off label use may be inadvertent or intentional. Examples of off label use might include use of a product in an age group outside the recommended age group or use in a population for whom the vaccine is contraindicated. For example, administering live, attenuated influenza vaccine (LAIV) to a person with asthma would be an off label use. • Safety data about the off label use is generally not available at the time of licensure. • An example of a study being planned to assess the safety of off label use of a vaccine is underway. VSD plans to study Tdap in persons aged ≥65 years. (Tdap is not licensed for this age group.)
B-VIII	**Vaccine-drug interactions**	• From the standpoint of safety, few vaccine-drug interactions have been systematically studied. • Jackson et al. conducted a cohort study in adults on warfarin therapy. The results of the study do not suggest that vaccinations lead to clinically significant alterations in coagulation measures among adults on chronic warfarin therapy (Jackson, Pharmacoepimemiology and Drug Safety, 2007)." • The Vaccine Adverse Event Report System (VAERS) has received reports of thromboembolic events in women who were vaccinated with human papillomavirus (HPV) vaccine who were taking oral contraceptives (CDC, ACIP presentation, 2007). Oral contraceptive use is a known risk factor for venous thromboembolic events (VTE) (Petitti, NEJM, 2007). In 2002, 31% of US women aged 15–44 years used oral contraceptives (CDC, National Center of Health Statistics, 2007).

Table 3C: ISO 5-Year Research Needs: Special Populations

Item	Thematic Area	Background
C-I	**Premature and low birth weight infants**	• The number of premature (delivered <37 weeks gestation) and low birth weight (LBW: (<2,500 grams) infants is increasing in the United States. In 2005, 12.7% of all US births were premature and 8.2% of births were LBW (CDC, Vital report data, 2005). • ACIP recommends a normal immunization schedule for premature and LBW babies, except for hepatitis B vaccine (CDC, ACIP General Recommendations, 2006). • Apnea and bradycardia are potential clinical outcomes of concern in premature babies. Klein et al. reported that "for infants in the neonatal intensive care unit (NICU) without apnea during the 24 hours immediately before immunization, younger age, smaller size, and more severe illness at birth are important predictors of post-immunization apnea." (Klein, Pediatrics, 2007). • Faldella et al reported that Hexavalent DTaP–IPV–HIb–HBV immunization is not associated with cardiac electric activity and cerebral blood flow variations in both stable and unstable very premature infants. However, it can cause apnea/bradycardia/desaturation in premature babies with chronic disease. Therefore, if the baby is in the NICU for chronic diseases at 2 months post-birth, it should be monitored for apnea, bradycardia and desaturation in association with vaccination (Faldella et al, vaccine 07). • CISA is evaluating the immune response and patterns of vaccine adverse events after polio vaccine in premature and term infants. • CISA is conducting a pilot study to demonstrate the feasibility of measuring rotavirus shedding after administration of rotavirus vaccine to premature infants. • VSD has completed studying wheezing and lower respiratory disease in premature infants following vaccination (a publication is underway).
C-II	**Pregnant women**	• Pregnant women are usually excluded from pre-licensure vaccine trials and data on vaccine safety during pregnancy are limited. • Because of high influenza morbidity during pregnancy, ACIP recommends trivalent inactivated influenza vaccine (TIV) routinely for pregnant women in all trimesters (CDC, ACIP Influenza statement, 2007). • VSD studies are under development or in progress to assess the safety of influenza vaccines, including the 2009 H1N1 monovalent vaccine, in pregnant women, including the risk for spontaneous abortion. • VAERS is monitoring the safety of the 2009 H1N1 monovalent vaccine in pregnant women. • Manufacturers have established pregnancy registries for new adolescent vaccines, including quadrivalent HPV vaccine (FDA, approval letter, 2006). • The Vaccines and Medications in Pregnancy Surveillance System (VAMPSS) is a collaboration of the Organization of Teratology Information Specialists (OTIS), and Slone Epidemiology Center (SEC) at Boston University, and the American Academy of Allergy, Asthma, and Immunology (AAAAI). VAMPSS is conducting prospective cohort studies and retrospective case-control studies

Item	Thematic Area	Background
		of vaccine, influenza antiviral, natural influenza exposure, and maternal and fetal outcomes.
C-III	**Adults aged ≥60 years**	• In 2006, approximately 37 million US persons were aged ≥65 years (~11 million were ≥80 years) (US Census, 2006). • ACIP recommends pneumococcal vaccine and routine tetanus and diphtheria toxoids (Td) vaccination for persons ≥65 years (ACIP recommendations zoster vaccine for people aged ≥60 years (CDC, Adult Immunization Schedule 2010 http://www.cdc.gov/vaccines/recs/schedules/adult-schedule.htm). • ISO typically uses age cut-offs similar to those recommended by ACIP in the immunization schedule of older adults, such as age 65 and older, for some vaccines such as influenza and pneumococcal vaccines (http://www.cdc.gov/mmwr/PDF/wk/mm5901-Immunization.pdf). • Deaths in older persons may occur in temporal association with vaccination. In 2006, in Israel, four deaths occurred shortly after influenza vaccine (three in persons aged ≥65 years); the findings of an investigation suggested that influenza vaccination is not associated with increased risk of death in the short-term (CDC provided assistance) (Kokia, Vaccine, 2007). • Immune function wanes in older populations (Kovaiou, Expert Review Molecular Medicine, 2007); there are limited data on the effects of immunosenescence on vaccine safety. • A VSD study will estimate 1) background age- and functional status-specific rates of mortality and hospitalization of elderly immediately after vaccination (i.e., 2 weeks) when immunity is not expected, and 2) excess risk of mortality and hospitalization of elderly within 2 weeks after influenza vaccination. • Several VSD adult studies are currently underway that include populations 65 years of age or older. These include: Survey to determine the accuracy of administrative data on influenza immunization. Study evaluating influenza vaccine's impact on diabetes complications. An investigation of whether receipt of influenza vaccine increases the risk for Bell's Palsy. Study examining the risk of carditis-type events and cardiomyopathy after live viral vaccinations. Study to assess the independent effects of chronic conditions and functional status on influenza vaccination of the elderly. Study looking at patterns of pneumococcal vaccination and revaccination in seniors. • All ISO influenza studies involve older adults, including the influenza RCA studies.
C-IV	**Persons with primary immunodeficiency**	• ACIP has general recommendations for use of vaccines in people with immunocompromising conditions. Persons with most (but not all) forms of immunodeficiency should not receive live vaccines; certain inactivated vaccines are specifically recommended for these populations. In most situations, household contacts of immunocompromised persons should receive live vaccines (CDC, ACIP General Recommendations, 2006). • A CISA study is assessing VAE and vaccine-preventable disease patterns in patients with DiGeorge

Item	Thematic Area	Background
		syndrome. • Another CISA study is investigating whether there is a risk for horizontal transmission of vaccine virus from infants immunized with Rotateq® to immunocompromised household contacts.
C-V	**Persons with secondary immunodeficiency**	• ACIP has general recommendations for use of vaccines in persons with immunocompromising conditions (CDC, MMWR, 2006a). • See the B-III study in children with sickle cell disease. • See C-IV.
C-VI	**Persons with autoimmune disorders**	• Autoimmune diseases affect 3%–5% of the population (IOM, 2002). • IOM concluded that the evidence "favors rejection of a causal relationship" between influenza vaccines or hepatitis B vaccines and relapse of multiple sclerosis in adults (IOM, 2002 and 2004). A study showed influenza vaccination is not associated with clinical exacerbation of rheumatoid arthritis (Elkayam, Clin Dev Immunol, 2006).
C-VII	**Children with inborn errors of metabolism**	• Inborn errors of metabolism affect an estimated 1 in 2,500 live births (Applegarth, Pediatrics, 2000). • Inflammatory responses, including those associated with minor infections, have been reported to cause clinical decompensation in children with metabolic disorders (Brady, Pediatrics, 2006). Children with metabolic diseases are at higher risk for complications from vaccine-preventable diseases (Brady, Pediatrics, 2006; Kinsely, Pediatrics, 2006). • CISA is conducting a study to describe patterns and prevalence of vaccine adverse events (VAEs) in children with inborn errors of metabolism and to assess risk factors for these events. • Another CISA study is underway to evaluate adverse events following vaccination of patients with underlying urea cycle disorders.
C-VIII	**Race/Ethnicity minorities and gender**	• ISO studies have not adequately examined these factors. The VAERS form lacks race/ethnicity variables and VSD computerized databases have incomplete data on race/ethnicity. These key components would have to be revised on the VAERS form and routinely included in managed care organization databases; feasibility of this effort is not certain. The DMSS database accessed by VAU does include data on race and ethnicity. Gender is described in demographics obtained from both VAERS and VSD surveillance systems.

Table 3D: ISO 5-Year Research Needs: Clinical Outcomes

Item	Thematic Area	Background
D-I	**Autoimmune diseases**	• VSD data contributed to an IOM review that concluded that "the epidemiological and clinical evidence favors rejection of a causal relationship between multiple immunizations and an increased risk of Type 1 diabetes (IOM, 2002b)." • Completed VSD studies have found no associations between vaccination and risk for developing multiple sclerosis, optic neuritis, or autoimmune thyroid disease. • VSD is currently conducting a study to examine whether Hepatitis B vaccine increases the risk of rheumatoid arthritis in adults, and whether there is a genetic predisposition to developing rheumatoid arthritis in persons receiving Hepatitis B vaccine. • VAU has completed a database study that found no increased risk for diagnosed Type 1 diabetes and Anthrax Vaccine Adsorbed (AVA), smallpox, typhoid, hepatitis B, MMR or yellow fever vaccines. • VAU also has an ongoing study to evaluate the risk for diffuse connective tissue diseases (rheumatoid arthritis, Systemic Lupus Erythematosus) and is planning a study of autoimmune thyroid disease following vaccination.
D-II	**Central nervous system demyelinating disorders**	• Regarding influenza vaccine, IOM concluded that "the evidence is inadequate to accept or reject a causal relationship" for incident MS in adults following vacccination; is inadequate "to accept or reject a causal relationship" for optic neuritis in adults or other demyelinating neurological disorders; and there is "no evidence bearing on a causal relationship for demyelinating neurological disorders in children aged 6–23 months (IOM, 2004). • Regarding hepatitis B vaccine, IOM concluded that the evidence "favors rejection" of a causal relationship for incident multiple sclerosis; the evidence is "inadequate to accept or reject a causal relationship" between hepatitis B vaccination and the first episode of a central nervous system demyelinating disorder or acute demyelinating encephalomyelitis (ADEM) (IOM, 2002a). • CISA is assessing if vaccination is associated with an increased risk for transverse myelitis. • The VSD RCA influenza study will assess risk for CNS demyelinating disorders. • VAU conducted a study that found no association between optic neuritis and receipt of anthrax, smallpox, hepatitis B, or influenza vaccines. See also A-I for information about GBS studies. • VAU is planning a study to evaluate medically attended adverse events following Td and Tdap vaccines given at shorter (less than 5 years) time intervals after prior tetanus and diphtheria toxoid containing vaccines.
D-III	**Encephalitis/ encephalopathy**	• IOM concluded that evidence is "consistent with a causal relation" between DTP vaccine and encephalopathy (IOM, 2001). • ACIP recommends that encephalopathy after pertussis vaccines is a contraindication for subsequent pertussis vaccination (CDC, ACIP General Recommendations, 2006). • Encephalopathy and encephalitis are on the Vaccine Injury Table for the vaccines that contain the

Item	Thematic Area	Background
		following antigens: pertussis, measles, mumps, and rubella, (HRSA, Vaccine Injury Table, 2007). • A recent study identified mutations in a sodium channel gene in children with encephalopathy following pertussis vaccines, suggesting that genetic factors may influence the risk for encephalopathy after vaccination (Berkovic, Lancet Neurology, 2006). • CISA is conducting a study to estimate the relative incidence of encephalitis following vaccination. This is a self-controlled case series analysis of the pediatric cases within the California Encephalitis Project. • A VSD study was published that examined the association between Tdap vaccine and adverse events such as encephalitis-meningitis, seizures, and cranial neuropathies; no increased risk was observed for these events after Tdap compared with Td (Yih, Vaccine 2009) • VSD has a study underway assessing recently licensed diphtheria-tetanus-acellular pertussis-inactivated poliovirus (DTaP-IPV) vaccine in a large cohort of children between 4 and 6 years of age. Eight major groups of adverse events are being evaluated, among them meningitis and encephalitis. • VSD published a study that assessed risk for encephalitis after varicella vaccination; no increased risk was observed (Donahue JG et al, 2009). • Brighton case definitions for acute encephalitis, myelitis, and ADEM have been completed (Sejvar JJ et al, 2007). • VAU has proposed a database study on the topics of syncope and unintentional injuries following vaccinations.
D-IV	**Neurodevelopmental disorders, including autism spectrum disorder (ASD)**	• In 2004, the IOM concluded that the evidence "favors rejection of a causal relationship" between MMR vaccine and autism and thimerosal-containing vaccines and autism (IOM, 2004). • VSD has completed a thimerosal and autism case-control study. The chief goal was to determine if exposure to thimerosal in infancy (through 7 months of age) or in-utero is related to development of autism. A secondary objective was to evaluate whether exposure to thimerosal in infancy is related to a subclass of autism predominately associated with regression. The manuscript *Prenatal and Infant Exposure to Thimerosal From Vaccines and Immunoglobulins and Risk of Autism* (Pediatrics) by Price CS et al. showed that prenatal and early-life exposure to ethylmercury from thimerosal-containing vaccines and immunoglobulin preparations was not related to increased risk for Autistic Spectrum Disorders (Price CS et al, Pediatrics 2010). • CDC funded a study in Italy comparing children who previously received thimerosal-containing or non-thimerosal-containing DTaP vaccines (Tozzi AE, 2009). • A VSD study was completed on early thimerosal exposure and neuropsychological outcomes at 7 to 10 years (Thompson WW et al, 2007). Another study using the public dataset was published (Smith MJ, WoodsCR. Pediatrics 2010).
D-V	**Vasculitis syndromes**	• Vasculitis following vaccination has been rarely reported in the literature (Saadoun, Rev Med Interne, 2001).

Item	Thematic Area	Background
		• Kawasaki disease was reported to VAERS after Rotateq® vaccine (FDA, 2007). • Two VSD studies are assessing 1) a possible link between vaccine administration and Kawasaki disease, and 2) risk for Henoch-Schönlein Purpura (HSP) following meningococcal vaccine (manuscript in preparation).
D-VI	**Myopericarditis (not associated with smallpox vaccine)**	• Smallpox vaccine has been associated with increased risk for myopericarditits (Halsell, JAMA, 2003). • VSD is studying the rate of cardiac events following live viral vaccinations in children and adolescents (see also Zoster section B-II). • VAU has proposed a study of risk for myopericarditis following live viral vaccines (including the new smallpox vaccine). • CISA is conducting a study to determine the rate of symptomatic or asymptomatic myopericarditis within 30 days following smallpox vaccination and to assess genetic, immune, or inflammatory markers in people who experience myopericarditis, so that vaccination guidelines for smallpox can be refined.
D-VII	**Clinically important outcomes related to post-immunization fever**	• Fever after vaccination is common and generally self-limited; however, fever may result in medical visits, induce seizures in susceptible children, and exacerbate chronic medical conditions (Kohl, CID, 2004; Dale, ACIP Medicine, 2008; Brady, Pediatrics, 2006). • The pathophysiology and clinical consequences of fever after immunization have not been systematically studied. • A VSD study was assessing the efficacy of acetaminophen prophylaxis for prevention of postvaccination fever following routine childhood immunizations recommended at 2, 4, and 6 months of age. This study was halted after results from another study indicated that such prophylaxis decreases the immune response to vaccination. • Brighton case definition for fever has been completed (Marcy SM et al, 2004). • See B-VI on the risk for medically attended fever following administration of Pediarix® compared to component vaccines. • See also A-VI on the risk for febrile seizure following MMRV.
D-VIII	**Postvaccination syncope and sequeale**	• Postvaccination syncope can be associated with serious injuries. ACIP states, “Vaccine providers should strongly consider observing patients for 15 minutes after they are vaccinated.” • In October 2007, information was presented to ACIP on increased reports to VAERS of postvaccination syncope. This increase in reports was observed following introduction of new adolescent vaccines, particularly HPV vaccine (CDC, ACIP presentation, 2007). • A VSD study will assess risk of syncope associated with vaccination in adolescents and young adults. • VSD’s HPV RCA study is monitoring syncope following vaccination with Gardasil®. • VAU has an ongoing database study on the topics of syncope and unintentional injuries following vaccinations.

Item	Thematic Area	Background
		• A collaborative study with CDC and the University of Colorado is assessing providers' adherence to ACIP guidance on preventing syncope and sequelae.

Table 3E. Methods for Identifying the Immunization Safety Office 5-Year Research Needs

The table below outlines the methods used for identifying the Immunization Safety Office's research needs. A detailed process has previously been described in the draft 2008 Scientific Agenda and is provided at the link provided: http://www.cdc.gov/vaccinesafety/Activities/agenda.html.

Step	Activity and Description
1	**Initial External Input:** • During May 2007 through November 2007, CDC and the National Vaccine Program Office (NVPO) convened three meetings to obtain input from the following groups: external expert scientists, vaccine safety representatives from HHS and DoD agencies and programs, and US vaccine manufacturers' representatives. • Details are available in a companion background document (http://www.cdc.gov/od/science/iso/00_pdf/agenda_background_080321.doc) and in individual meeting reports.
2	**ISO Synthesis of External Inputs:** • ISO staff reviewed and considered suggestions from these meetings and from unsolicited sources (e.g., ACIP statements, IOM reports, and the literature). • ISO staff then created a master list of ideas and reviewed each idea to determine if it met inclusion criteria for the 5-year research needs list. • Inclusion criteria were as follows: ISO routinely leads the topic, ISO could implement a study during the next 5 years with infrastructure generally available to CDC, and routine use of the vaccine(s) in question in the civilian population is likely to happen during the next 5 years. • The first list (March 10, 2008) contained 19 vaccine questions, 42 scientific thematic areas, and 9 items for adjudication.
3	**Internal Reviews:** • At ISO's request, three separate groups conducted internal reviews of the March 10, 2008 list: the Clinical Immunization Safety Assessment (CISA) Network, the Vaccine Safety Datalink (VSD) Project, and the National Center for Immunization and Respiratory Diseases (NCIRD) scientists. • ISO staff asked a liaison to synthesize input from each review and also accepted individual input directly. During the reviews, the scientists suggested additions, deletions, and modifications, and provided rationale for their recommendations.
4	**ISO Synthesis and Adjudication of Inputs from Internal Reviews:** • On the basis of feedback from the internal reviews and additional consultation with vaccine experts and input during the annual VSD meeting, ISO developed a new list of 7 specific questions and 24 scientific thematic areas (April 4, 2008).

Section 4. Postscript: Additions Following NVAC Review

Background:

Following the NVAC review, CDC's Immunization Safety Office (ISO) added new sections that were not part of the initial Scientific Agenda that was reviewed by NVAC. The added sections include a description of the NVAC review process; input from public and stakeholder engagement; a feasibility study of Vaccinated/Unvaccinated/Multiple vaccines; lessons learned from previous vaccine safety experiences; and Vaccine Safety Risk Communications.

NVAC Review Process:

- NVAC convened a Vaccine Safety Working Group from April 2008 through May 2009 that reviewed the ISO draft Scientific Agenda and made 32 recommendations in three general categories: general, capacity, and research needs. The Vaccine Safety Working Group made four assumptions. The Working Group focused primarily on items in the draft ISO Scientific Agenda directly related to research. (The infrastructure needs will be addressed in a second charge of the working group.)
- The Working Group acknowledged that not all of their recommendations to ISO can be carried out without including other disciplines and experts that are not part of ISO's current infrastructure and mission.
- The Working Group reviewed the ISO without any funding or resource considerations. The NVAC Vaccine Safety Working Group met in person three times; results of the three public meetings were presented to the working Group to engage stakeholders in a discussion of gaps and prioritization of the ISO Scientific Agenda.
- The Working Group met monthly by teleconference as well. The entire process is described in the NVAC report on pages 25–32 (NVAC 2009).

Engagement of the Public and Stakeholders:

ISO plans to update the Agenda and present progress to the NVAC periodically. Priority studies and other research activities will also be regularly updated on the CDC Web site (http://www.cdc.gov/vaccinesafety/index.html) to inform stakeholders and the public of ongoing and planned research. ISO plans to continue working with NPVO to engage stakeholders and the public in future updates to the ISO Scientific Agenda as part of efforts related to the National Vaccine Plan. The Agenda benefitted from input from public engagements to identify the safety concerns.

Engaging the public and stakeholders is an important component of federal government vaccine safety activities (http://www.hhs.gov/nvpo/vacc_plan/). ISO plans to work with NVPO and other partners to continue engaging stakeholders and the public in future updates to the Agenda as part of efforts related to the National Vaccine Plan.

Feasibility Study of Vaccinated/Unvaccinated/ Multiple Vaccines:

Members of the public, stakeholders, and the Interagency Autism Coordinating Committee (IACC), as well as the Writing Group convened by Keystone in the *Writing Group Draft Document on Gaps in Research Agenda* (Keystone, 2009) suggested several studies including: vaccinated versus unvaccinated children to determine if there are differences in health outcomes

between groups with varying exposures to vaccines; studies in special populations (e.g., children who had a previous adverse event who are scheduled for revaccination); persons or families who have specified previous illnesses that may be related to vaccination more broadly that could be contraindications; children with concurrent illness with or without fever; children with a personal or family history of allergy or auto immune disease; family history of adverse events (e.g., siblings); simultaneous vaccinations; and vaccines and vaccination practices. NVAC endorsed the Writing Group's recommendation for an external expert committee to offer guidance on the feasibility of conducting such studies and additional studies related to the immunization schedule, including studies that may indicate if multiple vaccinations increase risk for immune system disorders. Although this was not part of its initial draft research agenda, ISO will work with NVPO to convene such an expert external committee.

Lessons Learned from Previous Vaccine Experiences:

In its review of ISO's draft Scientific Agenda, NVAC recommended that ISO attempt to draw lessons learned from past vaccine safety episodes. ISO plans to develop lessons learned from previous studies, including the recent monitoring of the safety of 2009 H1N1 vaccine and the use of scientific data in decision making.

VSD has evaluated its lessons learned in monitoring safety in a report entitled *Active Surveillance of Adverse Events: The Experience of the Vaccine Safety Datalink Project*, soon to be published. Other vaccine safety episodes that could provide valuable lessons on conducting vaccine safety research, including assessment of the 2009 H1N1 vaccine safety monitoring experience, will be considered.

Vaccine Safety Risk Communication

Background and Public Health Importance:

Risk communication is designed to empower the public in making the best health decisions they can in uncertain circumstances. This involves recognizing and using various models of risk communication research to understand public perception of risk.

CDC's Immunization Safety Office's Role and Contribution:

ISO's communication goal is to accurately communicate science-based messages in a timely and consistent manner to the public, clinicians, public health officials, policymakers, stakeholders, and partners on the safety of vaccines. This includes developing messages and materials using accepted risk communication theory and principles; rapidly providing the public, the media, clinicians, policymakers, and other stakeholders with timely, accurate, clear, consistent, credible and easily accessible information; and addressing, as quickly as possible, rumors, inaccuracies, and misperceptions, when appropriate. Experts in health communication in the Division of Healthcare Quality Promotion (DHQP) at CDC lead ISO communication activities. ISO and DHQP work collaboratively with other CDC communications programs and staff at the National Vaccine Program Office (NVPO), FDA, and the National Institutes of Health (NIH) to

accomplish these goals. This includes applying basic risk communication theory, strategy, research, and evaluation to develop appropriate communications methods and tools.

Priority Scientific Areas:

In concert with CDC's Scientific Agenda, ISO communications also involve determining behavioral, social, and other factors affecting the communication of safety information. It includes identifying and evaluating methods of effectively communicating vaccine risks to different audiences (e.g., the public, healthcare providers) and disseminating clear and transparent information, and using science-based methods to foster information processing and informed decision-making.

The following are priority communication research areas:

- Explore perceptions of clinicians and the public on conditions they perceive to be causally associated with a vaccine.
- Assess knowledge, attitudes, and practices of clinicians on reporting of adverse events (e.g., what triggers a clinician to report, what are the barriers to reporting).
- Assess current knowledge, attitudes, and practices of the general public on the adverse events they perceive to be associated with a vaccine.
- Evaluate vaccine safety messaging with a variety of target populations (e.g., African Americans, pregnant women, and mothers).
- Identify messaging gaps in communications on vaccine safety, adverse events, and adverse event reporting.

Implementation:

Periodic updating of the Agenda has the potential to affect the priority scientific areas. Additionally, responding to public health emergencies and unexpected or unanticipated events may affect availability of resources and also cause ISO to establish new priority scientific areas or reprioritize existing ones. Some priority scientific areas and proposed activities in the Agenda may be out of the scope of ISO's mission and responsibilities. For these areas, ISO will work with sister agencies and offices in HHS to identify and clarify roles and responsibilities, and determine ownership or shared responsibility.

As previously stated, actual implementation of the Agenda will largely depend on resource availability, feasibility advances in science, and alignment with CDC's and ISO's missions. The implementation process is dynamic and activities may be added, discontinued, modified or reprioritized as HHS and CDC priorities evolve or scientific knowledge in specific vaccine safety related areas improves.

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REFERENCES

Alderson MR, McGowan P, Baldridge JR, Probst P. TLR4 agonists as immunomodulating agents. J Endotoxin Res. 2006;12(5):313–19.

American Academy of Pediatrics [Internet]. Red Book® Online; c2010 [cited 2010 Oct 26]. Available from: http://aapredbook.aappublications.org/news/vaccstatus.shtml.

Andrews N, Miller E, Grant A. Thimerosal exposure in infants and developmental disorders: a retrospective cohort study in the United Kingdom does not support a causal association. Pediatrics. 2004;114:584–91.

Applegarth DA, Toone JR and Lowry RB. Incidence of inborn errors of metabolism in British Columbia, 1969–1996. Pediatrics. 2000;105(1):e10.

Ball R, Halsey N, Braun MM, Moulton LH, Gale AD, VAERS Working Group, et al. Development of case definitions for acute encephalopathy, encephalitis, and multiple sclerosis reports to the Vaccine Adverse Event Reporting System. J Clin Epidemiol. 2002;55:819–24.

Beigel J, Kohl KS, Khuri-Bulos, Bravo L, Nell P, Marcy SM, et al. Rash including mucosal involvement: Case definition and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine. 2007;25:5697–706.

Belshe RB, Edwards KM, Vesikari T, Black SV, Walker RE, Hultquist M, et al. Live attenuated versus inactivated influenza vaccines in infants and young children. N Engl J Med. 2007; 356(7):685–96.

Berkovic SF, Harkin L, McMahon JM, Peleltanos JT, Zuberi SM, Wirrell EC, et al. De-novo mutations of the sodium channel gene SCN1A in alleged vaccine encephalopathy: a retrospective study. Lancet Neurology. 2006;5:488–92.

Bines KS, Forster J, Zanardi LR, Davis RL, Hansen J, Murphy TM, et al; Brighton Collaboration Intussusception Working Group. Acute intussusception in infants and children as an adverse event following immunization: case definition and guidelines of data collection, analysis, and presentation. Vaccine. 2004;22:569–74.

Bohlke K, Davis RL, Marcy SM, Braun MM, DeStefano F, Black SB, et al.; Vaccine Safety Datalink Team. Risk of anaphylaxis after vaccination of children and adolescents. Pediatrics. 2003 Oct;112(4):815–20.

Bonhoeffer J, Kohl K, Chen R, Duclos P, Heijbel H, Heininger U, et al; Brighton Collaboration. The Brighton Collaboration-enhancing vaccine safety. Vaccine. 2004;22(15–16):2046. (A)

Bonhoeffer J, Heininger U, Kohl K, Chen RT, Duclos P, Heininger H, et al. Standardized case definitions of adverse events following immunization (AEFI). Vaccine. 2004;22(5–6):547–50. (B)

Bonhoeffer J, Kohl K, Chen R, Duclos P, Heijbel H, Heininger U, et al.; Brighton Collaboration. Addressing the need for standardized case definitions of adverse events following immunization (AEFI).Vaccine. 2002 Dec 13;21(3–4):298–302.

Bonhoeffer J, Menkes J, Gold MS, de Souza-Brito G, Fisher MC, Halsey N, et al.; Brighton Collaboration Seizure Working Group. Generalized convulsive seizure as an adverse event following immunization: case definition and guidelines for data collection, analysis, and presentation. Vaccine. 2004;22:557–62.

Brady MT. Immunization recommendations for children with metabolic disorders: more data would help. Pediatrics. 2006;118(2):810–13.

Braun MM, Terracciano G, Salive ME, Blumberg DA, Vermeer-d Bondt PE, Heijbel H, et al. Report of a US public health service workshop on hypotonic-hyporesponsive episode (HHE) after pertussis immunization. Pediatrics. 1998;102(5):E52.

Brightman HJ. Problem solving: a logical and creative approach. Atlanta: Georgia State University Business Press; 1980. 189 p.

Broder K. Synthesis of evidence for febrile seizure risk after MMRV vaccination. Proceedings of the Advisory Committee on Immunization Practices Meeting; 2009 June 24–26; Atlanta: ACIP; 2009.

Buettcher, M, Heininger U, Braun M, Blumberg DA, Vermeer-de Bondt PE, Heijbel H, et al. Hypotonic-hyporesponsive episode (HHE) as an adverse event following immunization in early childhood: Case definition and guidelines for data collection, analysis, and presentation of immunization safety data .Vaccine. 2007;25:5875-81

Carlson CS, Heagerty PJ, Nord AS, Pritchard DK, Ranchalis J, Boguch JM, et al. TagSNP evaluation for the association of 42 inflammation loci and vascular disease: evidence of IL6, FGB, ALOX5, NFKBIA, and IL4R loci effects. Hum Genet. 2007 Mar;121(1):65–75. PubMed PMID: 17115186.

Carty CL, Heagerty P, Nakayama K, McClung EC, Lewis J, Lum D, et al. Inflammatory response after influenza vaccination in men with and without carotid artery disease. Arterioscler Thromb Vasc Biol. 2006;26(12):2738–44. PubMed PMID: 17023683.

Centers for Disease Control and Prevention. Active surveillance for adverse events: the experience of the Vaccine Safety Datalink project. Forthcoming 2010.

Centers for Disease Control and Prevention [Internet]. Adult Immunization Schedule, 2007–2008. [updated 2010 Aug 30; cited 2010 Oct 24]. Available from: http://www.cdc.gov/vaccines/recs/schedules/adult-schedule.htm.

Centers for Disease Control and Prevention [Internet]. Advisory Committee on Immunization Practices (ACIP) presentation, quadrivalent HPV vaccine safety update. 2007 Jun 28. [cited 2010 Oct 26]. Available from: http://www.cdc.gov/vaccines/recs/acip/downloads/min-archive/min-jun07.pdf.

Centers for Disease Control and Prevention [Internet]. Advisory Committee on Immunization Practices meeting presentation: Post-licensure safety summary: quadrivalent meningococcal conjugate vaccine (MCV4, Menactra®) 2007 June. [cited 2010 Oct 23]. Available from: http://www.cdc.gov/vaccines/recs/acip/meetings.htm#slides.

Centers for Disease Control and Prevention [Internet]. Advisory Committee on Immunization Practices meeting presentation: Summary of syncope reports to Vaccine Adverse Event Reporting System (VAERS) January 1, 2005–July 31, 2007. 2007 Oct 25. [cited 2010 Oct 26]. Available from: http://www.cdc.gov/vaccines/recs/acip/meetings.htm#slides.

Centers for Disease Control and Prevention [Internet]. Advisory Committee on Immunization Practices (ACIP) Recommendations. 2010 Sep 30. [cited 2010 Oct 23]. Available from: http://www.cdc.gov/vaccines/pubs/ACIP-list.htm.

Centers for Disease Control and Prevention [Internet]. Advisory Committee on Immunization Practices Provisional Recommendations. [updated 2010 Oct 1; cited 2010 Oct 24]. Available from: http://www.cdc.gov/vaccines/recs/provisional/default.htm.

Centers for Disease Control and Prevention [Internet]. Advisory Committee on Immunization Practices. [updated 2010 Oct 21; cited 2010 Oct 24]. Available from: http://www.cdc.gov/vaccines/recs/ACIP/default.htm.

Centers for Disease Control and Prevention [Internet]. Epidemiology and prevention of vaccine-preventable diseases (the Pink Book), March 2008, appendices. [updated 2010 Feb 8; cited Oct 23]. Available from: http://www.cdc.gov/vaccines/pubs/pinkbook/default.htm.

Centers for Disease Control and Prevention [Internet]. Frequently asked questions: mitochondrial disease. [cited 2010 Oct 26]. Available from: http://www.cdc.gov/ncbddd/autism/mitochondrial_faqs.htm.

Centers for Disease Control and Prevention. General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep. 2006;55(RR15):1–48.

Centers for Disease Control and Prevention. National Center for Health Statistics, United States, 2007 with chartbook on trends in the health of Americans. Hyattsville, MD: US Government Printing Office; 2007.

Centers for Disease Control and Prevention [Internet]. National vital statistics reports. births: final data for 2005. 2007 Dec 5 [cited 2010 Oct 27]. Available from: http://www.cdc.gov/nchs/data/nvsr/nvsr56/nvsr56_06.pdf.

Centers for Disease Control and Prevention. Use of Combination Measles, Mumps, Rubella, and Varicella. Morb Mort Wkly Rep MMWR. 2010 May 7;59(03):1–12.

Centers for Disease Control and Prevention. Notice to readers: expansion of use of live attenuated influenza vaccine (FluMist®) to children aged 2–4 years and other FluMist changes for the 2007–08 influenza season. MMWR Morb Mort Wkly Rep. 2007a;56(46):1217–9.

Centers for Disease Control and Prevention. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices. MMWR Morb Mort Wkly Rep. 2007b;56(RR06):1–54.

Centers for Disease Control and Prevention. Public Health Information Network—improving early detection by using a standards-based approach to connecting public health and clinical medicine. MMWR Morb Mort Wkly Rep. 2004a;(53)Supp:199–202.

Centers for Disease Control and Prevention [Internet]. Questions and answers about Hib recall. 2010 Feb 19 [cited 2010 Oct 27]. Available from: http://www.cdc.gov/vaccines/vpd-vac/hib/faqs-hcp.htm.

Centers for Disease Control and Prevention. Safety of influenza A (H1N1) 2009 monovalent vaccines—United States, October 1–November 24, 2009. MMWR Morb Mort Wkly Rep. 2009 Dec 11;58(48):1351–6.

Centers for Disease Control and Prevention [Internet]. Sexually transmitted diseases treatment guidelines. [updated 2010 Aug 19; cited 2010 Oct 27]. Available from: http://www.cdc.gov/std/treatment/.

Centers for Disease Control and Prevention. Surveillance for safety after immunization: Vaccine Adverse Event Reporting System (VAERS)—United States, 1991–2001. MMWR Morb Mortal Wkly Rep. 2003;52(SS-1):1–24.

Centers for Disease Control and Prevention. Suspension of rotavirus vaccine after reports of intussusception—United States, 1999. MMWR Morb Mortal Wkly Rep.. 2004b;53(34):786–89.

Centers for Disease Control and Prevention. Update: Guillain-Barré syndrome among recipients of Menactra® meningococcal conjugate vaccine—United States, June 2005–September 2006b. MMWR Morb Mortal Wkly Rep. 2006;55(41);1120–4.

Centers for Disease Control and Prevention. Update: recommendations from the advisory committee on immunization practices (ACIP) regarding administration of combination MMRV vaccine. MMWR Morb Mortal Wkly Rep. 2008;57(10):258–60.

Centers for Disease Control and Prevention. Vaccine Adverse Event Reporting System (VAERS) Master Search Tool, v 3.2. [unpublished] Accessed April 2, 2008.

Centers for Disease Control and Prevention [Internet]. Vaccine information statements. [updated 2010 Jul 14; cited 2010 Oct 23]. Available from: http://www.immunize.org/vis/vis_pcv7.asp.

Centers for Disease Control and Prevention. Safety of influenza A (H1N1) 2009 monovalent vaccines—United States, October 1–November 24, 2009. MMWR Morb Mort Wkly Rep. 2009 Dec 11;58(48):1351–6.

Centers for Disease Control and Prevention. Recommendations of the Advisory Committee on Immunization Practices (ACIP), prevention and control of influenza with vaccines. MMWR Morb Mort Wkly Rep. 2010 July 29; 59(Early Release);1–62.

Chaves SS, Haber P, Walton K, Wise RP, Izurieta HS, Scott-Schmid D, et al. Safety of varicella vaccine after licensure in the United States: experience from reports to the Vaccine Adverse Event Reporting System, 1995–2005. J Inf Dis. 2008;197:S170–S177.

Chen RT, DeStefano F, Pless R, Mootrey G, Kramarz P, Hibbs B. Challenges and controversies in immunization safety. Infect Dis Clin North Am. 2001;15(1):21–39, viii. Pubmed PMID: 11301817.

Chen RT, Rastogi SC, Mullen JR, Hayes SW, Cochi SL, Donlon JA, et al. The Vaccine Adverse Event Reporting System (VAERS). Vaccine. 1994 May 12;2(6):542–550. PubMed PMID: 8036829.

CIOMS Working Group. Suspect Adverse Reaction Form. 1993. [cited 2010 Oct 26]. Available from: http://www.cioms.ch/form/frame_form.htm.

Dale DC, Federman DD. ACP medicine. Dale DC, Federman DD, editors. Danbury, CT: WebMD Inc.; 2008.

Donahue JG, Kieke BA, Yih KW, Berger NR, McCauley JS, Baggs J, et al.; the Vaccine Safety DataLink Team. Varicella vaccination and ischemic stroke in children: is there an association? Pediatrics. 2009;123:e228–e234.

Duclos P, Hofman CA. Immunization safety: a priority of the World Health Organization's Department of Vaccines and Biologicals. Drug Saf. 2001;24:1105–12.

Elkayam O. Safety and efficacy of vaccination against influenza in patients with rheumatoid arthritis. Clin Dev Immunol. 2006;13(2–4):349–51.

European Medicines Agency (EMEA) [Internet]. Note for guidance on the clinical evaluation of vaccines. Committee for Human Medicinal Products (CHMP). 2005 May 17. [cited 2010 Oct 26]. Available from: http://www.emea.europa.eu/pdfs/human/vwp/16465305en.pdf; p. 20–23.

Faldella G, Galletti S, Corvaglia L, Ancora G, Alessandroni R. Safety of DTaP–IPV–HIb–HBV hexavalent vaccine in very premature infants. Vaccine. 2007;25:1036–42. PubMed PMID: 17088013.

Fink A, Kosecoff J, Chassin M, Brook R. Consensus methods: characteristics and guidelines for use. Am J Public Health. 1984;74:979–83.

Gelder CM, Lambkin R, Hart KW, Fleming D, Williams OM, Bunce M, et al. Associations between human leukocyte antigens and unresponsiveness to influenza vaccine. J Infect Dis. 2002;185:114–7.

Gidudu J, Kohl KS, Halperin S, Hammer SJ, Heath PT, Hennig R, et al. A local reaction at or near injection site: Case definition and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine. 2008;26:6800–13. PubMed PMID: 18950670.

Glanz JM, McClure DL, Xu S, Hambidge SJ, Lee M, Kolczak MS, et al. Four different study designs to evaluate vaccine safety were equally validated with contrasting limitations. J Clin Epidemiol. 2006;59(8):808–8.

Godkin A, Davenport M, Hill AV. Molecular analysis of HLA class II associations with hepatitis B virus clearance and vaccine nonresponsiveness. Hepatology. 2005 41(6):1383–90. PubMed PMID: 15915462.

Haas RH, Parikh S, Falk MJ, Saneto RP, Wolf NI, Darin N, et al. Mitochondrial disease a practical approach for primary care physicians. Pediatrics. 2007;120(6):1326–33.

Haber P, DeStefano F, Angulo FJ, Iskander J, Shadomy SV, Weintraub E, et al. Guillain-Barré syndrome following influenza vaccination. JAMA. 2004;292(20):2478–81. PubMed PMID: 15562126.

Halperin S, Kohl KS, Gidudu, Ball, L, Hammer SJ, Heath P, et al. Cellulitis at injection site: case definition and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine. 2007;25:5803–20.

Halsell JS, Riddle JR, Atwood E et al. Myopericarditis following smallpox vaccination among vaccinia-naive US military personnel. JAMA. 2003;289:2383–9.

Heijbel H, Ciofi degli atti MC, Harzer E. Hypotonic hyporesponsive episodes in eight pertussis vaccine studies. Dev Biol Stand. 1997;89:101–3.

Huang WT, Chang S, Miller ER, Jane Woo E, Hoffmaster AR, Gee JE, et al. Safety assessment of recalled Haemophilus influenzae type b (Hib) conjugate vaccines—United States, 2007–2008. Pharmacoepidemiol Drug Saf. 2010;19:306–10.

Huang WT, Gargiullo PM, Broder KR, Weintraub ES, Iskander JK, Klein NP, et al. Lack of association between acellular pertussis vaccine and seizures in early childhood. Pediatrics. 2010;126(2):263–269.

Institute of Medicine [Internet]. Immunization safety review: multiple immunizations and immune dysfunction, 2002b. [updated 2010 Feb 24; cited 2010 Oct 23]. Available from: http://www.iom.edu/Reports/2002/Immunization-Safety-Review-Multiple-Immunizations-and-Immune-Dysfunction.aspx.

Institute of Medicine [Internet]. Immunization safety review committee, immunization safety review: vaccines and autism. [updated 2010 Feb 1; cited 2010 Oct 26]. Available from: http://www.iom.edu/Reports/2004/Immunization-Safety-Review-Vaccines-and-Autism.aspx.

Institute of Medicine [Internet]. Immunization safety review: Influenza vaccines and neurological complications. [updated 2010 Oct 26; cited 2010 Oct 26]. Available from: http://www.iom.edu/?ID=4705.

Institute of Medicine [Internet]. Immunization safety review: thimerosal-containing vaccines and neurodevelopmental disorders. [updated 2010 Oct 26; cited 2010 Oct 26]. Available from: http://www.iom.edu/?ID=4705.

Institute of Medicine [Internet]. Immunization safety review: hepatitis B vaccine and demyelinating neurological disorders. [updated 2010 Feb 24; cited 2010 Oct 26].

Available from: http://www.iom.edu/CMS/3793/4705/4435.aspx.

Institute of Medicine [Internet]. Vaccine safety research, data access, and public trust. [updated 2010 Feb 22; cited 2010 Oct 26]. Available from: http://www.iom.edu/CMS/3793/21144/25184.aspx.

Institute of Medicine. Howson CP, Howe CJ, Fineberg HV, editors. Adverse effects of pertussis and rubella vaccines. Washington, DC: National Academy Press; 1991.

International conference on harmonization of technical requirements for registration of pharmaceuticals for human use (ICH). [cited 2010 Oct 26]. Available from: http://www.ich.org/cache/compo/276-254-1.html.

Iskander J, Miller E, Chen, RT. The role of the vaccine adverse event reporting system (VAERS) in monitoring vaccine safety. Pediatr Ann. 2004 33(9):599–606.

Iskander J, Pool V, Zhou W, English-Bullard R; the VAERS Team. Data mining in the US using the Vaccine Adverse Event Reporting System. Drug Safety. 2006;29(5):375–4.

Jackson LA, Yu O, Nelson J, Belongia EA, Hambidge SJ, Baxter R, et al. Risk of medically attended local reactions following diphtheria toxoid containing vaccines in adolescents and young adults: A Vaccine Safety Datalink study. Vaccine. 2009;27(36):4912–6.

Jackson ML, Nelson JC, Chen RT, Davis RL, Jackson LA. Vaccines and changes in coagulation parameters in adults on chronic warfarin therapy: a cohort study. Pharmacoepidemiol and Drug Safety. 2007;16(7):790–6.

Johns J, Hunter D. Consensus methods for medical and health services research. BMJ. 1995;311:376–80.

Kingsley JD, Varman M, Chatterjee A, Kingsley RA, Roth KS. Immunization for patients with metabolic disorders. Pediatrics. 2006 June 30:e1–e11.

Klein NP, Massolo ML,Greene J, Dekker CL, Black S, Escobar GJ; Vaccine Safety Datalink. Risk factors for developing apnea after immunization in the neonatal intensive care unit. Pediatrics. 2008;121(3):463–9. PubMed PMID: 18310193.

Klein NP, Fireman B, Yih WK, Lewis E, Kulldorff M, Ray P, et al. Measles-Mumps-Rubella-Varicella combination vaccine and the risk of febrile seizures. Pediatrics. 2010;126(1):e1–8. Pubmed PMID: 20587679.

Kohl KS, Marcy SM, Blum M, Connell Jones M, Dagan R, Hansen J, et al. Fever after immunization: current concepts and improved future scientific understanding. Clin Infect Dis. 2004;39:389–94.

Kohl KS, Bonhoeffer J, Chen R, Duclos P, Heijbel H, Heininger U, et al.
The Brighton Collaboration: enhancing comparability of vaccine safety data. ISPE commentary. Pharmacoepidemiol Drug Saf. 2003 June;12(4):335–40. Pubmed PMID: 12812014.

Kohl KS, Bonhoeffer J, Braun MM, Chen RT, Duclos P, Heijbel H, et al.; the Brighton Collaboration. The Brighton Collaboration: creating a global standard for case definitions (and guidelines) for adverse events following immunization. AHRQ in advances in patient safety. Vol 2. concepts and methodology; 2005. [cited 2010 Oct 26]. Available from: http://www.ahrq.gov/downloads/pub/advances/vol2/kohl.pdf.

Kohl KS, Gidudu J, Bonhoeffer J, Braun MM, Buettcher M, Chen RT, et al. The development of standardized case definitions and guidelines for adverse events following immunization. Vaccine. 2007;25(31):567–14.

Kohl KS, Ball L, Gidudu J, Hammer SJ, Halperin S, Heath P, et al. Abscess at injection site: case definition and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine. 2007;25(31):5821–38.

Kohl KS, Walop W, Gidudu J, Ball L, Halperin S, Hammer SJ, et al. Induration at or near injection site: case definition and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine. 2007;25(31):5839–57.

Kokia ES, Silverman BG, Green M, Kedem H, Guindy M, Shemer J. Deaths following influenza vaccination—background mortality or causal connection? Vaccine. 2007;25(51):8557–61. PubMed PMID: 18006121.

Kovaiou RD, Herndler-Brandstetter D, Grubeck-Loebenstein B. Age-related changes in immunity: implications for vaccination in the elderly. Exp Rev Mol Med. 2007;9:1–17.

Lahdenpera A, Lennart J, Regnstrom. Kinetics of asthma- and allergy-associated immune response gene expression in peripheral blood mononuclear cells from vaccinated infants after in vitro re-stimulation with vaccine antigen. Vaccine. 2008;26:1725–30.

Le Saux N, Barrowman NJ, Moore DL, Whiting S, Scheifele D, Halperin S. Decrease in hospital admissions for febrile seizures and reports of hypotonic-hyporesponsive episodes presenting to hospital emergency departments since switching to acellular pertussis vaccine in Canada: a report from IMPACT. Pediatrics. 2003;112(5):e348–e348.

Lieu TA, Kulldorff M, Davis RL, Lewis EM, Weintraub E, Yih K, et al. Real-time vaccine safety surveillance for the early detection of adverse events. Med Care. 2007;45(10 Supl 2):S89–95. PubMed PMID: 17909389.

Lin ND, Kleinman K, Chan KA, Soumerai S, Mehta J, Mullooly JP,et al. Multiple vaccinations and the risk of medically attended fever. Vaccine. 2010;28(25):4169–74.

Michael MS, Kohl KS, Dagan R, Nalin D, Blum M, Jones MC, et al.; the Brighton Collaboration Fever Working Group. Fever as an adverse event following immunization: case definition and guidelines of data collection, analysis, and presentation. Vaccine. 2004;22(5–6):551–6.

Mitchell LA, Tingle AJ, MacWilliam L, Horne C, Keown P, Gaur LK, et al. HLA-DR class II associations with rubella vaccine-induced joint manifestations. J Infect Dis. 1998;177(1):5–12. PubMed PMID: 9419163.

National Vaccine Advisory Committee (NVAC) [Internet]. Recommendations on the Centers for Disease Control and Prevention Immunization Safety Office draft 5-year scientific agenda, June 2009. [cited 2010 Oct 26]. Available from: http://www.hhs.gov/nvpo/nvac/NVACRecommendationsISOScientificAgendaFinal.pdf

Nissenkorn A, Zeharia A, Lev D, Fatal-Valevski A, Barash V, Gutman A,et al. Multiple presentation of mitochondrial disorders. Arch Dis Child. 1999;81:209–15.

Oliveira G, Diogo L, Grazina M, Garcia P, Ataíde A, Marques C,et al. Mitochondrial dysfunction in autism spectrum disorders: a population-based study. Dev Med Child Neurol. 2005; Mar 47(3):185–9. PubMed PMID: 15739723.

Payne DC, Franzke LH, Stehr-Green PA, Schwartz B, McNeil MM. Development of the Vaccine Analytic Unit's research agenda for investigating potential adverse events associated with anthrax vaccine adsorbed Pharmacoepidemiol Drug Saf. 2007;16:46–54.

Pedersen C, Petaja T, Strauss G, Rumke HC, Poder A, Richardus JH,et al. Immunization of early adolescent females with human papillomavirus type 16 and 18 L1 virus-like particle vaccine containing ASO4 adjuvant. J Adolesc Health. 2007;40:564–71. PubMed PMID: 17531764.

Petitti DB. Combination Estrogen–Progestin Oral Contraceptives. N Engl J Med. 2003;349:1443–50. PubMed PMID: 14534338.

Piyasirisilp S, Schmeckpeper BJ, Chandanayingyong D, Hemachudha T, Griffin DE. Association of HLA and T-cell receptor gene polymorphisms with Semple rabies vaccine-induced autoimmune encephalomyelitis. Ann Neurol. 1999;45(5):595–600.

Price CS, Thompson WW, Goodson B, Weintraub ES, Croen LA, Hinrichsen VL, et al. Prenatal and infant exposure to thimerosal from vaccines and immunoglobulins and risk of autism. Pediatrics. 2010;126:656–64

Proceedings of a workshop on standardization of definitions of post-marketing surveillance of adverse reactions, Ottawa, Canada, October 30–31, 1991. Ottawa, Canada: Laboratory Center for Disease Control; 1992.

Regnstrom K, Ragnarsson EGE, Rydell N, Sj¨oholm I, Artursson P. Tetanus antigen modulates the gene expression profile of aluminum phosphate adjuvant in spleen lymphocytes in vivo. Pharmacogenomics J. 2002;2:57–64.

Reveille JD. Genetic studies in the rheumatic diseases: present status and implications for the future. J Rheumatol. 2005;72(suppl 1):10–3.

Rock MT, Yoder SM, Talbot TR, Edwards KM, Crowe JE Jr. Adverse events after smallpox immunizations are associated with alterations in systemic cytokine levels. J Infect Dis. 2004;189(8):1401–10.

Rosenthal S, Chen R, Hadler S. The safety of acellular pertussis vaccine vs whole-cell pertussis vaccine. a postmarketing assessment. Arch Pediatr Adolesc Med. 1996;150(5):457–60.

Rothstein E, Kohl KS, Ball L, Halperin SA, Halsey N, Hammer SJ, et al.; the Brighton Collaboration Local Reaction Working Group. Nodule at injection site as an adverse event following immunization: case definition and guidelines for data collection, analysis, and presentation. Vaccine. 2004;22(5–6):575–85.

Saadoun D, Cacoub P, Mahoux D, et al. Postvaccine vasculitis: a report of three cases. Rev Med Interne. 2001;22(2):172–6. French.

Schonberger LB, Bregman DJ, Sullivan-Bolyai JZ, Keenlyside RA, Ziegler DW, Retailliau HF, et al. Guillain-Barré syndrome following vaccination in the National Influenza Immunization Program, United States, 1976–1977. Am J Epidemiol. 1979;110(2):105–23.

Sejvar JJ, Kohl KS, Bilynsky R, Blumberg D, Cvetkovich T, Galama J, et al. Encephalitis, myelitis, and acute disseminated encephalomyelitis (ADEM): case definitions and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine. 2007;25(31):577–92.

Sejvar JJ, Kohl KS, Gidudu J, Amato A, Bakshi N, Baxter R,et al. Guillain-Barré syndrome and Fisher syndrome: case definitions and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine. Epub 2010 June 17. PMID: 20600491.

Smith MJ, Woods CR. On-time vaccine receipt in the first year does not adversely affect neuropsychological outcomes. Pediatrics. 2010;125(6):1134–41.

Stratton KR, Howe CJ, Johnston RB Jr. Adverse events associated with childhood vaccines other than pertussis and rubella. Summary of a report from the Institute of Medicine. JAMA. 1994;271:1602–5.

Tapiainen T, Prevots R, Izurieta HS, Abramson J, Bilynsky R, Bonhoeffer J, et al. Aseptic meningitis: Case definition and guidelines for collection, analysis and presentation of immunization safety data. Vaccine. 2007;25:5793–802.

The Keystone Center [Internet]. DRAFT Gaps in the ISO research agenda identified by the writing group, February 20–21, 2009. [cited 2010 Oct 26]. Available from: http://www.hhs.gov/nvpo/nvac/WritingGroupGaps.doc.

The Uppsala Monitoring Center [Internet]. WHO adverse reaction terminology (WHO-ART). December 2005. [cited 2010 Oct 26]. Available from: http://www.umc-products.com/graphics/3149.pdf.

Thompson WW, Price CS , Goodson B , Shay DK , Benson P, Hinrichsen VL, et al. Early thimerosal exposure and neuropsychological outcomes at 7 to 10 years. N Engl J Med. 2007;357(13):1281–92.

Tozzi AE, Bisiacchi P, Tarantino V, De Mei B, D'Elia L, Chiarotti F, et al. Neuropsychological performance 10 years after immunization in infancy with thimerosal-containing vaccines. Pediatrics. 2009;123(2):475–82).

US Census Bureau [Internet]. National population estimates—characteristics. [cited 2010 Oct 26]. Available from: http://www.census.gov/popest/national/asrh/NC-EST2006-sa.html.

US Department of Health and Human Services [Internet]. Advisory Commission on Childhood Vaccines (ACCV). 2010 Jul [cited 2010 Oct 26]. Available from: http://www.hrsa.gov/vaccinecompensation/accv.htm.

US Department of Health and Human Services [Internet]. Agency for Healthcare Research and Quality National Guideline Clearinghouse. [cited 2010 Oct 26]. Available from: http://www.guideline.gov/.

US Department of Health and Human Services [Internet]. Health Resources and Services Administration vaccine injury table. [cited 2010 Oct 23]. Available from: http://www.hrsa.gov/vaccinecompensation/table.htm.

US Department of Health and Human Services [Internet]. HHS strategic plan, fiscal years 2007–2012. [cited 2010 Oct 23]. Available from: http://aspe.hhs.gov/hhsplan/2007/HHSStrategicPlan0712.htm#zzee_link_2_119134309.

US Department of Health and Human Services [Internet]. National Vaccine Advisory Committee. [cited 2010 Oct 26]. Available from: http://www.hhs.gov/nvpo/nvac/index.html.

US Food and Drug Administration (FDA) [Internet]. Guidance for industry. toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials. [updated 2009 Apr 30; cited 2010 Oct 23]. Available from: http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm074775.htm.

US Food and Drug Administration [Internet]. Product approval information—licensing action: influenza virus vaccine, live, intranasal, September 2007. [updated 2009 May 1; cited 2010 Oct 23]. Available from: http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm123746.htm.

US Food and Drug Administration [Internet]. Product approval information and package insert: zoster vaccine, live, May 2006. [updated 2010 Feb 22; cited 2010 Oct 23]. Available from: http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm094075.htm.

US Food and Drug Administration [Internet]. Product approval information: human papillomavirus quadrivalent vaccine. June 8, 2006 recombinant product approval letter. [updated 2010 Jul 9; cited 2010 Oct 23]. Available from: http://www.fda.gov/cber/products/gardasil.htm.

Vaccine Healthcare Center Network [Internet]. [cited 2010 Oct 26]. Available from: http://www.vhcinfo.org/.

Vaccine Safety Datalink Publications [Internet]. [updated 2010 Feb 11; cited 2010 Oct 26]. Available from: http://www.cdc.gov/vaccinesafety/library/vsd_pubs.html.

VanGundy A B. Techniques of structured problem solving: Arthur B. VanGundy, Ph.D. 4th ed. New York: Van Nostrand Reinhold; 1988.

van Sorge NM, van der Pol WL, Jansen MD, Geleijns KP, Kalmijn S, Hughes RA, et al. Severity of Guillain-Barré syndrome is associated with Fc gamma receptor III polymorphisms. J Neuroimmunol. 2005;162:157–64.

Varricchio F, Iskander J, DeStefano F, Ball R, Pless R, Braun MM, et al. Understanding vaccine safety: information from the Vaccine Adverse Event Reporting System (VAERS). Pediatr Infect Dis J. 2004;23:287–94.

Vellozzi C, Broder KR, Haber P, Guh A, Nguyen M, Cano M, et al. Adverse events following influenza A (H1N1) 2009 monovalent vaccines reported to the Vaccine Adverse Event Reporting System, United States, October 1, 2009–January 31, 2010. Vaccine. 2010;28(45):7248–55.

Verstraeten T, Davis RL, DeStefano F, Lieu TA, Rhodes PH, Black SB, et al.
Safety of thimerosal-containing vaccines: a two-phased study of computerized health maintenance organization databases. Pediatrics. 2003;112(5):1039–48.

Wilke RA, Lin DW, Roden DM, Watkins PB, Flockhart D, Zineh I, et al. Identifying genetic risk factors for serious adverse drug reactions: current progress and challenges. Nat Rev Drug Discov. 2007;6(11):904–16.

Wilson C. Genetic risk factors for smallpox vaccine associated myopericarditis. Proceedings of the vaccine safety evaluation: post-marketing surveillance conference; 2007 Apr 10–11; New York: Springer; 2007.

Wood RA, Berger M, Dreskin SC, Setse R, Engler RJM, Dekker CL, et al. An algorithm for treatment of patients with hypersensitivity reactions after vaccines. Pediatrics. 2008;122(3):e77–e777.

Wood RA, Berger M, Dreskin SC, Setse R, Engler RJ, Dekker CL, et al. Hypersensitivity working group of the Clinical Immunization Safety Assessment (CISA) Network. An algorithm for treatment of patients with hypersensitivity reactions after vaccines. Pediatrics. 2008 Sep;122(3):e771–7.

World Health Organization [Internet]. WHO surveillance of adverse events following immunization. Field guide for managers of immunization programmes. Global programme for vaccines and immunization. Expanded programme on immunisation. Geneva, Switzerland: World Health Organization, Geneva 1997. [cited 2010 Oct 23]. Available from:
http://who.int/vaccines-documents/DocsPDF/www9541.pdf.

World Health Organization [Internet]. WHO Weekly epidemiological record (WER). 2006 July 7; vol. 81, 27: p 261–72. [cited 2010 Oct 26]. Available from:
http://www.who.int/wer/2006/wer8127/en/index.html.

World Health Organization. WHO consultation on global monitoring of adverse events following immunization, 9–10 January 2006. Wkly Epidemiol Rec. 2006 Jul 7;81(27)261–5). PubMed PMID: 16826644.

Yih WK, Nordin JD, Kulldorff M, Lewis E, Lieu TA, Shi P, et al. An assessment of the safety of adolescent and adult tetanus–diphtheria–acellular pertussis (Tdap) vaccine, using active surveillance for adverse events in the Vaccine Safety Datalink. Vaccine. 2009;27(32):4257–62.

Yang Y, Sujan S, Sun F. Acute metabolic crisis induced by vaccination in seven Chinese patients. Pediatr Neurol. 2006;35(2):114–8.

Zent O, Arras-Reiter C, Broeker M, Hennig R. Immediate allergic reactions after vaccinations—a post-marketing surveillance review. Eur J Pediatr. 2002;161(1):21–5.

Appendix A. List of Acronyms

Acronym	Term / Description
ACIP	Advisory Committee on Immunization Practices
ACCV	Advisory Commission on Childhood Vaccines
ADEM	acute disseminated encephalomyelitis
AE	adverse events
AEFI	adverse events following immunization
ASD	autism spectrum disorder
ASO4	aluminum hydroxide and 3-deacylated monophosphoryl lipid A
AVA	Anthrax Vaccine Adsorbed
BC	Brighton Collaboration
CDC	Centers for Disease Control and Prevention
CISA	Clinical Immunization Safety Assessment
CRS	congenital rubella syndrome
CSF	cerebrospinal fluid
DDF	dynamic data file
DDM	distributed data model
DNA	Deoxyribonucleic acid
DTaP	diphtheria, tetanus and pertussis
ECDC	European Centers for Disease Control and Prevention
EMEA	European Agency for the Evaluation of Medicinal Product
Epi-X	Epidemic Information Exchange
eSub	Electronic report submission
FDA	Food and Drug Administration
GBS	Guillain-Barré syndrome
HBV	hepatitis B virus
HL7	Health Level 7
HLA	human leukocyte antigens
HHE	hypnotic-hyporesponsive episodes
HHS	US Department of Health and Human Services
Hib	*Haemophilus influenza type b*
HIPAA	Health Insurance Portability and Accountability Act of 1996
HPV2	Bivalent Human Papillomavirus vaccine (Cervarix™)
HSP	Henoch-Schonlein Purpura
ICD-9	International Classification of Diseases, Ninth Revision
IOM	Institute of Medicine
IRB	Institutional Review Boards
ISO	Immunization Safety Office
JAMA	Journal Of the American Medical Association
LAIV	live, attenuated influenza vaccine
MCO	managed care organization
MCV4	meningococcal conjugate vaccine
MedDRA	Medical Dictionary for Regulatory Activities
MMR	measles, mumps, rubella
MMRV	measles, mumps, rubella, varicella, vaccine
NCIRD	National Center for Infectious and Respiratory Diseases
NCK	Northern California Kaiser
NCVIA	National Childhood Vaccine Injury Act
NOPHG	National Office of Public Health Genomics
NVAC	National Vaccine Advisory Committee
NVPO	National Vaccine Program Office
PBMC	Peripheral blood mononuclear cells
PHINMS	Public Health Information Network Messaging System

Acronym	Term / Description
RA	rheumatoid arthritis
RCA	rapid cycle analysis
RNA	Ribonucleic acid (RNA)
SCCS	self-controlled case series
SNPs	single nucleotide polymorphisms
SPRT	sequential probability ratio test
TIV	trivalent inactivated vaccine
VAE	vaccine adverse event
VAERS	Vaccine Adverse Event Reporting System
VAU	Vaccine Analytic Unit
VHC	Department of Defense Vaccine Healthcare
VSD	Vaccine Safety Datalink
WBC	white blood cell
WHO	World Health Organization

Appendix B. Glossary of Terms

Term	Definition
acute disseminated encephalomyeltitis (ADEM)	A medical condition characterized by a brief but intense attack of inflammation in the brain and spinal cord that damages myelin—the protective covering of nerve fibers.
Acellular	A vaccine containing no cells; not made up of cells
Adjuvant	A substance (e.g., aluminum, salt) that is added to a vaccine during production to increase the body's immune response to a vaccine.
agonist	A chemical that binds to a receptor of a cell and triggers a response by that cell.
aluminum hydroxide and 3-deacylated monophosphoryl lipid A (ASO4)	Arsenate can replace inorganic phosphate in the step of glycolysis that produces1,3-bisphosphoglycerate to produce 1-arseno-3-phosphoglycerate instead. This molecule is unstable and quickly hydrolyzes, forming the next intermediate in the pathway, 3-phosphoglycerate. Therefore, glycolysis proceeds, but the ATP molecule that would be generated from 1,3-bisphosphoglycerate is lost; arsenate is an uncoupler of glycolysis.
anaphylaxis	An induced systemic or generalized sensitivity. The term is commonly used to denote the immediate, transient kind of immunologic (allergic) reaction characterized by contraction of smooth muscle and dilation of capillaries from release of pharmacologically active substances (histamine, bradykinin, serotonin, and slow-reacting substance).
Angelman syndrome	A genetic disorder that causes developmental delay and neurological problems. Infants with Angelman syndrome appear normal at birth, but often have feeding problems in the first months of life and exhibit noticeable developmental delays by 6 to 12 months. Seizures often begin between 2 and 3 years of age. Speech impairment is pronounced, with little to no use of words. Patients with this syndrome often display hyperactivity, small head size, sleep disorders, and movement and balance disorders that can cause severe functional deficits. Angelman syndrome results from absence of a functional copy of the *UBE3A* gene inherited from the mother.
antibody	An immunoglobulin molecule produced by B lymphoid cells with a specific amino acid sequence evoked in humans or other animals by an antigen (immunogen). These molecules help the body fight bacteria.
anti-ganglioside antibodies	Antibodies that are found in autoimmune neuropathies and that react to self-gangliosides. These antibodies were first found to react with cerebellar cells. These antibodies show highest association with certain forms of Guillain-Barré syndrome.
athralgia	Neuralgic pain in a joint or joints.
autism spectrum disorder (ADS)	A spectrum of psychological conditions characterized by widespread abnormalities of social interactions and communication, as well as severely restricted interests and highly repetitive behavior. Also called spectrum disorders (ASD) or autism spectrum conditions (ASC).
autoimmune disorders	A condition that occurs when the immune system mistakenly attacks and destroys healthy body tissue. There are more than 80 different types of autoimmune disorders.
bivalent human papillomavirus (HPV2) vaccine (Cervarix™)	A vaccine indicated for the prevention of the following diseases caused by oncogenic human papillomavirus (HPV) types 16 and 18.

Term	Definition
confidence interval	A confidence interval is an interval in which a measurement or trial falls corresponding to a given probability.
confounder	Also referred to as a confounding variable, confounding factor, lurking variable, or confounder), is an extraneous variable in a statistical model that correlates (positively or negatively) with both the dependent variable and the independent variable.
congenital rubella syndrome (CRS)	An infection that can occur in a developing fetus of a pregnant woman who has contracted rubella during her first trimester.
contraindication	A condition in a recipient which is likely to result in a life-threatening problem if a vaccine were given.
covariate	An independent variable not manipulated by the experimenter but still affecting the response.
cytokine	A small protein released by cells that has a specific effect on the interactions between cells, on communications between cells or on the behavior of cells.
demyelinating neurologic disorders	A medical condition wherein the myelin sheath is damaged. The myelin sheath surrounds nerves and is responsible for the transmission of impulses to the brain. Damage to the myelin sheath results in muscle weakness, poor coordination and possible paralysis. Examples of demyelinating disorders include Multiple Sclerosis (MS), optic neuritis, transverse neuritis and Guillain-Barre syndrome (GBS).
DiGeorge syndrome	A genetic disorder characterized by hypocalcemia, immunodeficiency, and congenital heart disease: Hypocalcemia (low calcium levels in the blood) due to hypoplasia (underdevelopment) of the parathyroid glands that are needed to control calcium; Immunodeficiency due to hypoplasia (underdevelopment) of the thymus (an organ behind the breastbone needed for the maturation of lymphocytes into T cells); and Congenital heart disease with defects of the outflow tracts (the pulmonary artery and aorta) from the heart.
encephalitis	An acute inflammation of the brain, commonly caused by a viral infection. It can be caused by a bacterial infection such as bacterial meningitis, or may be a complication of other infectious diseases like rabies (viral) or syphilis (bacterial). Encephalitis can result in permanent brain damage or death.
encephalomyelitis	Inflammation of both the brain and the spinal cord. Encephalomyelitis can be caused by a variety of conditions that lead to inflammation of the brain and spinal cord. Among the common causes of encephalomyelitis are viruses which infect the nervous system.
excipients	Inactive ingredients of a drug product necessary for production, including adjuvants.
fragile X syndrome	The most common inherited form of mental retardation. It results from a change, or mutation, in a single gene, which can be passed from one generation to the next (also called Fragile X).
gene expression profiles	Measures the activity of thousands of genes at once, creating a global picture of cellular function. These profiles can distinguish between cells that are actively dividing, or show how the cells react to a particular treatment.
gene polymorphisms	The occurrence together in the same locality of two or more discontinuous forms of a species in such proportions that the rarest of them cannot be maintained just by recurrent mutation.

Term	Definition
General Practice Research Database	The world's largest computerized database of anonymised longitudinal medical records from primary care.. It is the largest and most comprehensive source of data of its kind and is used worldwide for research by the pharmaceutical industry, clinical research organizations, regulators, government departments and leading academic institutions (also known as GPRD).
genetic variation	Refers to the total number of genetic characteristics.
geocode data	Data that assigns geographic identifiers (e.g., codes or geographic coordinates expressed as latitude-longitude) to map features and other data records, such as street addresses.
Guillain-Barré syndrome	An acute, immune-mediated disorder of peripheral nerves, spinal roots, and cranial nerves, commonly presenting as a rapidly progressive, areflexive, relatively symmetric ascending weakness of the limb, truncal, respiratory, pharyngeal, and facial musculature, with variable sensory and autonomic dysfunction; typically reaches its nadir within 2–3 weeks, followed initially by a plateau period of similar duration, and then subsequently by gradual but complete recovery in the majority of cases.
Henoch-Schonlein Purpura (HSP)	A systemic vasculitis (inflammation of blood vessels) characterized by deposition of immune complexes containing the antibody IgA, especially in the skin and kidney. It occurs mainly in children. (HSP, also known as allergic purpura).
hepatitis B	A virus that infects the liver of hominoidae, including humans, and causes an inflammation called hepatitis.
humoral	Relating to or being the part of immunity or the immune response that involves antibodies secreted by B cells and circulating in bodily fluids.
hypersensitivity	Abnormal sensitivity, a condition in which there is an exaggerated response by the body to the stimulus of a foreign agent.
inborn errors of metabolism	Comprise a large class of genetic diseases involving disorders of metabolism. The majority are due to defects of single genes that code for enzymes that facilitate conversion of various substances (substrates) into others (products). Inborn errors of metabolism are also called congenital metabolic diseases or inherited metabolic diseases, and these terms are considered synonymous.
intussusception	The telescoping of one segment of intestine into another adjacent distal ("downstream") segment of the intestine. Intussusception is the most common cause of intestinal obstruction in children between 3 months and 6 years of age.
Kawasaki disease (protocol approved)	A condition that causes inflammation in the walls of small- and medium-sized arteries throughout the body, including the coronary arteries, which supply blood to the heart muscle. Kawasaki disease is also called mucocutaneous lymph node syndrome because it also affects lymph nodes, skin, and the mucous membranes inside the mouth, nose and throat. Kawasaki disease, named after the physician that first identified and described it in 1967.
measles	An infectious disease caused by a virus. It spreads easily from person to person. The main symptom of measles is an itchy skin rash. The rash often starts on the head and moves down the body.
microarray	Consist of large numbers of molecules (often, but not always, DNA) distributed in rows in a very small space. Microarrays permit scientists to study gene expression by providing a snapshot of all the genes that are active in a cell at a particular time. Microarray is also called a gene chip or a DNA chip.
mitochondria	A membrane-enclosed organelle found in most eukaryotic cells. Mitochondria is described as "cellular power plants" because they generate most of the cell's supply of adenosine triphosphate (ATP), used as a source of chemical energy.

Term	Definition
mumps	An acute contagious viral illness marked by swelling, especially of the parotid (salivary) glands.
myalgia	Pain in a muscle; or pain in multiple muscles.
myopericarditis	Inflammation of the muscular wall of the heart and of the enveloping pericardium; also, perimyocarditis-choice of term determined by whether the principal involvement is pericardial or myocardial.
neurodevelopmental disorder	An impairment of the growth and development of the brain or central nervous system. These disorders are recognized to be the result of abnormalities in brain development due to both genetic and environmental/biological causes. These conditions affect approximately 1-3% of the population.
neuroimmunology	A growing branch of biomedical science that studies of all aspects of the interactions between the immune system and nervous system
Personalized Health Care Initiative	Using "genomics," or the identification of genes and how they relate to drug treatment, personalized health care will enable medicine to be tailored to each person's needs.
pertussis	Also known as whooping cough, is a highly contagious disease caused by the bacterium Bordetella pertussis; it derived its name from the characteristic severe hacking cough followed by intake of breath that sounds like 'whoop'; a similar, milder disease is caused by B. parapertussis
pharmacoepidemiology	The study of the use and effects of drugs in large numbers of people.
primary immunodeficiencies	Generally are inherited and include conditions defined by an absence or quantitative deficiency of cellular and/or humoral components that provide immunity.
proteomics	A branch of molecular biology concerning protein sets in organisms
rabies	Highly fatal infectious disease that may affect all species of warm-blooded animals, including humans; transmitted by the bite of infected animals including dogs, cats, skunks, wolves, foxes, raccoons, and bats, and caused by a neurotropic species of Lyssavirus, a member of the family *Rhabdoviridae*, in the central nervous system and the salivary glands. The symptoms are characteristic of a profound disturbance of the nervous system, *e.g.,* excitement, aggressiveness, and madness, followed by paralysis and death.
Rett syndrome	A neurological and developmental disorder that mostly occurs in females. Most cases of Rett syndrome are caused by a mutation on the MECP2 gene, which is found on the X chromosome.
rheumatoid arthritis	A generalized disease, occurring more often in women, which primarily affects connective tissue; arthritis is the dominant clinical manifestation, involving many joints, especially those of the hands and feet, accompanied by thickening of articular soft tissue, with extension of synovial tissue over articular cartilages, which become eroded; the course is variable but often is chronic and progressive, leading to deformities and disability.
rubella	An acute but mild exanthematous disease caused by rubella virus (Rubivirus family *Togaviridae*), with enlargement of lymph nodes, but usually with little fever or constitutional reaction; a high incidence of birth defects in children results from maternal infection during the first trimester of fetal life (congenital rubella syndrome).
secondary immunodeficiency	Generally is acquired and is defined by loss or qualitative deficiency in cellular and humoral immune components that occurs as a result of a disease process or its therapy.

Term	Definition
smallpox	An acute eruptive contagious disease caused by a poxvirus (Orthopoxvirus, a member of the family *Poxviridae*) and marked at the onset by chills, high fever, backache, and headache; in 2–5 days the constitutional symptoms subside and an eruption appears as papules, which become umbilicated vesicles, develop into pustules, dry, and form scabs that, on falling off, leave a permanent marking of the skin (pock marks); average incubation period is 8–14 days. As a result of increasingly aggressive vaccination programs carried out over a period of about 200 years, smallpox is now eradicated.
SNP	Genetic variation in a DNA sequence that occurs when a single nucleotide in a genome is altered; SNPs are usually considered to be point mutations that have been evolutionarily successful enough to recur in a significant proportion of the population of a species.
tetanus toxoid	A substance that is derived from the toxin released by the bacterium that causes the disease tetanus. It is used as a vaccine to prevent tetanus or to help boost the immune response to other vaccines.
thimerosal	A mercury-containing organic compound (an organomercurial). Thimerosal has been widely used as a preservative in a number of biological and drug products, including many vaccines, to help prevent potentially life threatening contamination with harmful microbes. Thimerosal has been removed from or reduced to trace amounts in all vaccines routinely recommended for children 6 years of age and younger, with the exception of inactivated influenza vaccine.
thrombocytopenia	A decrease in the number of platelets in the blood that may result in easy bruising and excessive bleeding from wounds or bleeding in mucous membranes and other tissues.
thymus	A glandular structure of largely lymphoid tissue that functions in cell-mediated immunity by being the site where T cells develop, that is present in the young of most vertebrates typically in the upper anterior chest or at the base of the neck, that arises from the epithelium of one or more embryonic branchial clefts, and that tends to disappear or become rudimentary in the adult - also called *thymus gland.*
toll-like receptors	A class of single membrane-spanning non-catalytic receptors that recognize structurally conserved molecules derived from microbes once they have breached physical barriers such as the skin or intestinal tract mucosa, and activate immune cell responses. They are believed to play a key role in the innate immune system (also known as TLRs).
Tourette syndrome	A disorderwith symptoms including involuntary facial tics, motor tics, and vocal tics. The diagnosis of Tourette syndrome is by clinical observation. There is no laboratory test for the disorder.
transverse myelitis	A neurological disorder caused by inflammation across both sides of one level, or segment, of the spinal cord.
tuberous sclerosis	Phacomatosis characterized by the formation of multisystem hamartomas producing seizures, mental retardation, and angiofibromas of the face; the cerebral and retinal lesions are glial nodules; other skin lesions are hypopigmented macules, shagreen patches, and periungual fibromas.
varicella	An acute contagious disease, usually occurring in children, caused by the varicella-zoster virus genus, Varicellovirus, a member of the family *Herpesviridae*, and marked by a sparse eruption of papules. Varicella is also called “chickenpox”.

Term	Definition
vasculitis syndromes	An inflammation of the vascular system, which includes the veins, arteries, and capillaries. Vasculitis can cause problems in any organ system, including the central (CNS) and peripheral (PNS) nervous systems.
yellow fever	An acute viral hemorrhagic disease. The virus is transmitted by the bite of female mosquitoes.

Definitions were obtained from the following sources: HHS (CDC, NIH, and FDA), MedlinePlus, Stedman's Medical Dictionary, Wikipedia, Mayo Clinic, Merriam Webster, and other reference, academic, and medical Web sites.

Appendix C: Summary of NVAC Recommendations

Recommendation	CDC/ISO Response	Page in Scientific Agenda
General Recommendations and Capacity Recommendations		
Recommendation #1: NVAC recommends that ISO develop the research topic sections of Vaccines and Vaccination Practices, Special Populations, and Clinical Outcomes to consist of testable research questions that can be prioritized.	• ISO supports implementing this recommendation. • Other agencies may also have a role in implementing this recommendation. Conclusions from an IOM review of adverse events following vaccination may be useful.	*Pages 3–7, 25–27,36-38*
Recommendation #2: NVAC recommends periodic external review of VSD and CISA research and the ISO Scientific Agenda more broadly.	• ISO supports implementation of this recommendation.	*Pages 3-44-46*
Recommendation #3: NVAC recommends that ISO regularly engage the public and stakeholders as ISO conducts research, interprets the findings from their studies, and revises their research agenda.	• This recommendation has been partially implemented. ISO will coordinate with NVPO on implementing this recommendation.	*Pages 3-4,44-46*
Recommendation #4: NVAC recommends that CDC perform case studies of past decision making processes related to vaccine safety issues to identify lessons learned on the use of scientific data in decision making.	• This recommendation has been partially implemented.	*Page 45*
Recommendation #5: To prepare for mass use of vaccines not traditionally given to the civilian population, NVAC recommends that ISO research in advance approaches to safety monitoring, including the extent to which they would be used off label or in new populations.	• This recommendation has been partially implemented.	*Pages 5-7,35-38*

Recommendation	CDC/ISO Response	Page in Scientific Agenda
Recommendation #6: To better understand the biological mechanisms of action responsible for adverse events following immunization, NVAC recommends that ISO coordinate with other agencies to support basic research into such mechanisms and that CISA conduct clinical research on the pathophysiologic basis of adverse events.	• ISO supports the need for research in this area.	*Page 17–22*
Recommendation #7: NVAC endorses the CDC Writing Group's recommendation for an external expert committee, such as IOM, with broad methodological, design, and ethical expertise to consider "strengths and weaknesses, ethical issues and feasibility including timelines and cost of various study designs to examine outcomes in unvaccinated, vaccine delayed and vaccinated children and report back to the NVAC."	• CDC/ISO and NVPO are working on implementing this recommendation.	*Pages 3-4, 44-46*
Recommendation #8: NVAC recommends that ISO studies are designed and adequately powered to assess the role of differences in race/ ethnicity and gender, when appropriate.	• Ongoing efforts are underway to include these variables in studies.	*Pages 11,38*
Recommendation #9: NVAC recommends that ISO have an active role in risk communications research.	• This is an agency-wide priority in which CDC/ISO is actively engaged.	*Pages 45, 46*
Recommendation #10: NVAC recommends that ISO identify and evaluate ways to 1) increase the number of serious events that are reported to VAERS; and 2) improve the quality and completeness of the reports received.	• This recommendation has been partially implemented during the recent 2009 H1N1 response.	*Pages 9–11*
Recommendation #11: NVAC recommends that ISO evaluate approaches to follow up with people reported to VAERS with rare or unusual adverse events for further study, including the collection of biological specimens, when appropriate.	• Activities regarding this recommendation are ongoing.	*Pages 9-11,17–22*

Recommendation	CDC/ISO Response	Page in Scientific Agenda
Recommendation #12: NVAC recommends that the ISO Scientific Agenda specify the laboratory capacity needed for vaccine safety research and identify potential collaborations with other federal agencies or private entities for those areas where ISO lacks capacity. For the laboratory capacity that ISO currently possesses, ISO should request input from external experts to advise on the ongoing work and development of new laboratory methodologies.	• CDC/ISO supports the need for research in this area.	*Pages 3-4, 17–22,44–46*
Recommendation #13: NVAC recommends that ISO study molecular immune responses to vaccinations, including common adverse events such as fever or rash, as subclinical correlates that might predict severe adverse events.	• CDC/ISO supports the need for research in this area.	*Pages 17–22,44-46*
Recommendation #14: NVAC recommends that ISO create an expert advisory group on genomics and vaccine safety to assist with developing a focused genomics research agenda and protocol development.	• This recommendation has been partially implemented. CDC/ISO will actively engage with NVPO and other agencies in furthering this recommendation.	*Pages 3-4, 20–22,44–46*
Recommendation #15: NVAC recommends ISO focus Brighton Collaboration research efforts on the adequacy of the case definitions and their usefulness in ongoing safety research conducted by VSD and other groups.	• CDC/ISO no longer leads secretariat activities of the Brighton Collaboration.	*Pages 23–24*
Recommendation #16: NVAC recommends that ISO create a single written guide dedicated to comprehensive clinical guidance, including identification, reporting, and treatment, for vaccine adverse events.	• This recommendation is partially implemented; CDC/ISO favors inclusion of such guidance in the ACIP General Recommendations and in focused materials for healthcare providers.	*Pages 25–26*

Recommendation	CDC/ISO Response	Page in Scientific Agenda
Recommendation #17: NVAC recommends that ISO include the vaccination of children with mitochondrial disease, mitochondrial dysfunction, and other metabolic diseases as a priority scientific area for research to develop clinical guidance.	• Activities regarding this recommendation are ongoing.	*Pages 17–22, 31*
Research Needs Recommendations 18–32		
Three priority questions have been addressed (Rec #18, 22 and an unnumbered recommendation)		
Item A-I Recommendation # 18: Suggested rewording. Are influenza vaccines or meningococcal conjugate vaccine [MCV4]) associated with increased risk for Guillain-Barré syndrome (GBS)?	• CDC/ISO prefers including all vaccines based on questions raised in the literature and the IOM.	*Page 29*
Item A-III Recommendation # 19: Suggested modification. Is exposure to thimerosal associated with increased risk for clinically important tics, Tourette syndrome, or speech and language delays?	• ISO sponsored a reanalysis of its neurodevelopmental study with a focus on tics. • A public use dataset is available from the neurodevelopmental study for other researchers to further address these questions.	*Page 30*
Item A-III Recommendation #20: Suggested expansion. ISO should sponsor external and multidisciplinary additional analysis of data published in 2007 by Thompson et al.[2] ISO should formulate and issue an RFP pursuant to awarding a contract to an independent organization to analyze the data on thimerosal exposure and neurodevelopmental outcomes. Additionally, ISO should work with VSD sites involved in this study to use information in the available medical records (thimerosal exposure and appropriate health outcomes) of children selected for the study, and examine who did and did not agree to participate to assess the potential for selection bias.	• This recommendation has been partially implemented. • See above. • The characteristics of participants are fully explored in the technical document that accompanies the neurodevelopmental study.	*Page 30*

Recommendation	**CDC/ISO Response**	**Page in Scientific Agenda**
Item A-VII Recommendation # 21: NVAC suggested expansion to include zoster vaccine. Are varicella vaccines (varicella, MMRV, and Zoster) associated with increased risk for clinically important events related to varicella vaccine virus reactivation?	• CDC/ISO will implement this recommendation	*Page 36*
Recommendation # 22: **Added during NVAC review.** Do multiple vaccinations increase risk for immune system disorders?	• CDC/ISO and NVPO are working on implementing this recommendation (see recommendation 7).	*Pages 3-4, 44-46*
Item B-I Recommendation # 23: NVAC suggested removal of Bivalent human papillomavirus (bivalent HPV) vaccine (Cervarix™).	• CDC/ISO disagrees with the suggestion because Cervarix is now licensed in the United States. This recommendation is already partially implemented.	*Page 33*
Item B-II: Recommendation # 23: NVAC suggested removal of Zoster vaccine.	• CDC/ISO disagrees with this suggestion because studies are underway.	*Page 33*
Item B-III: Recommendation # 25: NVAC suggested that ISO publish a regular summary report on the safety profile of the expanded influenza vaccination program that would be made publicly available.	• This recommendation is partially implemented.	*Pages 33,44*
Item B-IV: Recommendation # 26: NVAC suggested modification: ISO should evaluate cumulative levels of non-antigen component exposure possible through the scheduling of recommended vaccinations.	• CDC/ISO, NVPO and FDA are working on implementing this recommendation along with other related recommendations.	*Page 3–7, 33-34, 44–46*
Item B-IV: Recommendation # 27: NVAC suggested modification to remove the parenthetical statement “other than thimerosal or ASO4 in bivalent HPV vaccine.”	• ISO agrees with this suggestion.	*Page 33*

Recommendation	CDC/ISO Response	Page in Scientific Agenda
Item B-VII: Recommendation # 28: NVAC suggested expansion: Off label vaccination practices should be characterized and quantified. Off-label use recommendations sometimes included in ACIP statements that are not indicated on the label should be considered as research agenda topics for ISO.	• CDC/ISO has partially implemented this recommendation.	*Pages 9–11, 35*
Item C-III: Recommendation # 29: Expand to include adults aged ≥ 60 years of age.	• ISO agrees with this recommendation.	*Page 37*
Item C-VI: Recommendation # 30: NVAC suggested expanding to include persons with autoimmune disorders or a well-documented family history of autoimmune disorders.	• CDC/ISO and NVPO are working on implementing this recommendation along with other recommendations and will incorporate it in future studies to the extent feasible.	*Pages 3–7,38, 44–46*
Recommendation # 31: Added during NVAC review. Children with siblings or parents who experienced an adverse event following immunization.	• CDC/ISO and NVPO are working on implementing this recommendation to the extent feasible.	*Pages 44–46*
Recommendation # 32: Added during NVAC review On Special Populations Children who have previously suffered an adverse event following immunization who are recommended to receive additional doses in a booster regimen.	• This recommendation is partially implemented. CDC/ISO and NVPO are exploring the feasibility of additional studies to address this recommendation.	*Pages 3–4,25-26, 44-46*