# DRAFT

## Centers for Disease Control and Prevention's Immunization Safety Office Scientific Agenda: Draft Recommendations

**EMBARGOED UNTIL 9AM EST ON APRIL 11, 2008**

This draft document was prepared for the National Vaccine Advisory Committee (NVAC) Vaccine Safety Working Group for its scientific review on April 11, 2008. It does not represent Centers for Disease Control and Prevention (CDC) or Department of Health and Human Services policy, nor does it necessarily reflect which ideas will be incorporated into CDC's final Immunization Safety Offices Scientific Agenda.[1]

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**ISO Scientific Agenda: Draft Recommendations**

## Overview

In response to a 2005 Institute of Medicine (IOM) recommendation (IOM, 2005) and to guide CDC's Immunization Safety Office's (ISO) scientific direction, ISO developed a draft ISO Scientific Agenda (referred to as the Agenda) for the next 5 years. ISO obtained input from expert scientists through three planned meetings with external expert scientists, federal scientists, and vaccine manufacturers' representatives. ISO also gathered input from day-to-day partners and CDC experts in vaccine safety. A companion background document provides additional information on ISO research and surveillance infrastructure, the Agenda's rationale and scope, and the approach used (http://www.cdc.gov/od/science/iso/00_pdf/agenda_background_080321.doc).

At the request of CDC, the National Vaccine Advisory Committee (NVAC) Vaccine Safety Working Group will advise on the content and priorities of the Agenda. CDC will finalize the Agenda and respond to NVAC feedback. The Agenda makes recommendations for the next 5 years in three scientific areas: vaccine safety research, selected surveillance, and selected clinical guidance activities. It covers topics that are part of ISO's mission, are in ISO's realm to lead, and could be implemented during the next 5 years with infrastructure generally accessible to CDC.

The Agenda recommendations are summarized in Box 1. This document also provides information about the process the NVAC Vaccine Safety Working Group might use to establish priorities. Scientific suggestions that were outside the scope of the Agenda are summarized in the Appendix.

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

1. **Respond to emerging issues and conduct core, required scientific activities**
2. **Enhance vaccine safety public health and clinical guidance capacity in 7 areas:**
    - **A. Infrastructure for Vaccine Safety Surveillance: Vaccine Adverse Event Reporting System (VAERS)**
    - **B. Infrastructure for Vaccine Safety Surveillance and Research: Vaccine Safety Datalink (VSD) Project**
    - **C. Epidemiologic and Statistical Methods for Vaccine Safety**
    - **D. Laboratory Methods**
    - **E. Genomics and Vaccine Safety**
    - **F. Case Definitions, Data Collection, and Data Presentation for Adverse Events Following Immunization**
    - **G. Vaccine Safety Clinical Practice Guidance**
3. **Address 5-Year Research Needs**
    - **A. Specific Vaccine Safety Questions**
    - **B. Vaccines and Vaccination Practices**
    - **C. Special Populations**
    - **D. Clinical Outcomes**

**Section 1: Emerging Issues and Core, Required Scientific Activities**

The Center for Disease Control'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 has four integrated research and surveillance components that conduct vaccine safety science activities. These include the Vaccine Adverse Event Reporting System (VAERS), the Vaccine Safety Datalink (VSD) Project, the Clinical Immunization Safety Assessment (CISA) Network, and the Brighton Collaboration. 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 http://www.cdc.gov/od/science/iso/about_iso.htm.

To ensure optimal vaccine safety, during the next 5 years ISO will continue to respond to emerging issues and conduct core scientific activities. CDC is not asking the NVAC Vaccine Safety Working Group to prioritize these activities. Rather, priorities will be set by ISO and CDC, after considering public health needs and programmatic factors which may evolve during the 5-year time period.

The emerging issues and core activities include:

- **Monitoring the safety of all newly licensed and Advisory Committee on Immunization Practices (ACIP) recommended vaccines and previously licensed vaccines with new recommendations (Table 1, Case Example 1):** The general monitoring approach includes reviewing existing vaccine safety data to identify potential areas of concern and developing VAERS and VSD monitoring plans. When indicated, key case definitions or other special studies may be developed.
- **Respond to new vaccine safety concerns and hypotheses, which are not always predictable (Table 1, Case Example 1)**: Some vaccine safety concerns are apparent at the time of licensure but it is common for new concerns to emerge 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., the Institute of Medicine [IOM]), reports to VAERS, clinical consultation calls to investigators in the CISA network, the media, and the general public. When a hypothesis arises, the teams work together to investigate it and determine if it needs further study. The VSD Project historically has conducted most of the office's hypothesis testing research (Table 1, Example 1).
- **Provide 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 expertise for numerous scientific activities, including those related to immunization services, risk perception, economic analyses, or risk-benefit analyses. ISO also directly participates in three of the four federal advisory committees related to vaccines: the Advisory Committee on Immunization Practices (ACIP), the National Vaccine Advisory Committee (NVAC), and the Advisory Commission on Childhood Vaccines (ACCV) (ACIP, NVAC, and ACCV charters).
- **Prepare to monitor vaccine safety in the event of a mass vaccination campaign or other vaccine safety emergency (Table 1, Case example 2):** Preparing for and rapidly responding to vaccine safety emergencies is a core ISO public health function (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).

**Table 1 Examples of Emerging Issues and Core, Required Scientific Activities**

**Example 1: Measles, Mumps, Rubella, and Varicella (MMRV) Vaccine and Febrile Seizures[2]**

| 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 MMRV vaccine administration in children aged 12–23 months.<br>▪ A possible risk for seizures was identified in the computerized data. |
| Respond to new vaccine safety signals and hypotheses, which are not always predictable. | ▪ On the basis of this signal, VSD rapidly implemented an epidemiologic study to assess risk for febrile seizures, using chart data.<br>▪ The preliminary results found that risk for febrile seizures was about 2 times higher during the 7–10 days after vaccination in children receiving MMRV vaccine, compared with MMR and varicella vaccine at the same visit. |
| Provide technical consultation to CDC immunization experts and other stakeholders | ▪ ISO informed FDA and Merck scientists and presented this information during the ACIP meeting in 2/2008.<br>▪ 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 varicella vaccines administered separately.<br>▪ ACIP also is forming an MMRV Vaccine Safety Working Group to evaluate the data more thoroughly and develop policy options. ISO will co-lead this Working Group with CDC's National Center for Immunization and Respiratory Diseases (NCIRD). |

**Example 2: Response to a Vaccine Recall Safety Concern[3]**

| Ongoing Activity | Event |
|---|---|
| Prepare to monitor vaccine safety in the event of a mass vaccination campaign or other vaccine safety emergency (Table 1, Case Example 2): | ▪ In December 2007, ISO responded to a potential safety concern after 1.2 million doses of *Haemophilus influenzae* type b (Hib) conjugate vaccine were recalled, because *Bacillus cereus* was isolated from the manufacturing equipment (no contamination of the vaccine was found).<br>▪ VAERS conducted a rapid review of reports from recalled Hib lots.<br>▪ ISO used CDC's Epidemic Information Exchange (*Epi-X*) to call for vaccine-associated *B. cereus* infections with onset since 4/1/2007 in recipients aged <6 years.<br>▪ CDC found no evidence of vaccine-associated *B. cereus* infection in recipients of recalled Hib vaccine.<br>▪ The *Epi-X* posting stimulated one report of vaccine-associated *B. cereus* infection in a subject who received a non-recalled Hib vaccine. CDC conducted molecular typing of the isolate and it differed from the isolate from the manufacturing equipment. |

[2] CDC, MMWR, 2008.
[3] 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, surveillance, and clinical translation activities. ISO could conduct initial work in these areas using infrastructure generally accessible to CDC; however, to carry out these activities, the Office may need to forge new collaborations and tap into federal infrastructure beyond ISO. 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 7 areas:**

**A. Infrastructure for Vaccine Safety Surveillance: Vaccine Adverse Event Reporting System (VAERS)**
- **Enhance VAERS reporting**
- **Improve VAERS surge capacity infrastructure and analytical capabilities**
- **Improve surveillance and evaluation of VAERS data**

**B. 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**

**C. Epidemiologic and Statistical Methods for Vaccine Safety**
- **Improve near real-time surveillance methods**
- **Overcome limitations of conventional epidemiologic designs**

**D. Laboratory Methods**
- **Collect biological specimens**
- **Assess lab testing methods for hypersensitivity to vaccines**
- **Conduct cytokine analyses**
- **Measure single nucleotide polymorphisms (SNPs)**

**E. 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.**

**F. Case Definitions, Data Collection, and Data Presentation for Adverse Events Following Immunization**
- **Development of case definitions**
- **Evaluation of case definitions**
- **Translation case definitions into practice**

**G. Vaccine Safety Clinical Practice Guidance**
- **Use evidence-based methods, including expert clinical opinion, to develop and widely disseminate clinical guidance that will assist clinicians assess, reporting, and manage 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 the US Department of Health and Human Services specific adverse events that occur after the administration of routinely recommended vaccines. In response to NCVIA, CDC and the Food and Drug Administration (FDA) established the Vaccine Adverse Event Reporting System (VAERS) in 1990 (Chen, Vaccine, 1994). VAERS is a national passive reporting system co-managed by the CDC and FDA. In 2007, VAERS received 30,000 primary reports annually, with 13% classified as serious (e.g., associated with disability, hospitalization, life-threatening illness or death) (CDC VAERS Master Search Tool, April 2, 2008). Anyone can file a VAERS report, including health care 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)[4]; 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; 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. CDC/ISO and FDA review adverse reports; VAERS has identified important signals that after further research resulted in changes to vaccine recommendations. VAERS demonstrated its public health importance when the system detected multiple reports for intussusception after RotaShield® rotavirus vaccine 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).[5]

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

VAERS is a critical component of vaccine safety surveillance as the most broad-based system to detect adverse events. 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, Clinical Immunization Safety Assessment (CISA) Network, and the Brighton Collaboration. Because of CDC's important role in partnering with the state departments of health, ISO generally leads major activities that involve close collaboration with state epidemiologists or require special laboratory analysis of clinical specimens. Because CDC manages the VAERS contract, ISO/CDC often leads projects to evaluate and further develop VAERS infrastructure in order to optimize infrastructure for vaccine safety scientific activities. In addition, CDC commonly assists the FDA in its surveillance and evaluation efforts related to vaccine lot safety.

[4] 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.
[5] A different rotavirus vaccine, Rotateq®, is currently licensed and recommended for use in the United States.

**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 health care providers about reporting to VAERS.
- Identify ways to facilitate reporting to VAERS by primary health care providers and specialists (e.g., neurologists, 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, compared with about 16,000 reports received in 2002 (CDC VAERS Master Search Tool, April 2, 2008). In addition to handling increased amount of reports under routine conditions, VAERS needs to have surge capacity for emergency response and preparedness (e.g., pandemic influenza preparedness). Developing and implementing new VAERS electronic reporting mechanisms is crucial to meet these public health needs. Currently VAERS accepts reports through mail, facsimile, and internet/web-based (eSub) 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 Michigan 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 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 a 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 (i.e., 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 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 such as detailed immunization and medical histories and total cohort population, provided through direct linkage with registries and electronic medical records.

**3) Improve surveillance and evaluation of VAERS data**

Specific activities include:

- Evaluate the effectiveness of 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 evaluation of 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 and ISO activities, (e.g., CISA Network).
- Enhance capabilities to identify and evaluate reports of specific AE that are more common for one product than another, for example through advanced signal detection or data mining (Iskander, Drug Safety, 2006).

## 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, testing 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 infrastructure includes 8 managed care organizations (MCOs) with a beneficiary population that represents 3.2% of the US population aged <18 years of age, 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 but 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, where data were sent to CDC annually, to a distributed data model (DDM), where anonymous patient data reside at sites and CDC is provided access through computer programs. While the change to the distributed data model (DDM) enhanced data confidentiality, there have been some challenges. Programming through the DDM is more difficult. In addition, the VSD sites must monitor submitted programs to ensure data quality and compliance with the Health Insurance Portability & Accountability Act of 1996 (HIPAA).

In addition to creating data files annually, in 2006, the VSD began to create files which 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 as well as 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 understand 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 the dynamic data files 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 since a major concern is that these data may not capture immunizations that occur outside the medical home, particularly among adults.
- Studies to monitor the uptake and use patterns of new vaccines as they enter the U.S. market and are administered at a participating MCO.
- Studies to understand patterns of vaccine administration, including the patterns of simultaneous vaccination.
- Establishing both background rates of diseases and outcomes for selected potential vaccine adverse events as well as immunization coverage rates. To quantify the occurrence of an event and its relationship with 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 our ability to collect socioeconomic and demographic information. Using geocode data collected in the VSD cycle files and appended data from the U.S. census, one proposed project would characterize VSD participants based on area-level sociodemographics and compare the distribution of these characteristics across participating MCOs; evaluate VSD representation by comparing prevalent sociodemographic distributions within the VSD participants' area of residence with residents of the MCO service areas and with the entire U.S. population; and explore the quality of collected geocode data and the potential for bias due to poor quality address matches.

## Item C: Epidemiologic and Statistical Methods for Vaccine Safety

**Background and Public Health Importance:**

Ensuring the availability of high quality risk assessment data for vaccines in a timely manner is important for a variety of purposes including clinician and patient education, guideline and policy development, and regulatory action. Postlicensure investigations of vaccine safety based on automated immunization and diagnosis data have generally employed 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 the time 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. The VSD Project is collaboration among CDC's Immunization Safety Office and eight large managed care organizations (MCOs). VSD scientists 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 address the problem of timeliness for vaccine adverse event (VAE) detection, 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 now ranges from surveillance to analytical investigations.

RCA has advantages over passive surveillance programs: it is based on systematically collected data from patients' medical records and it includes denominator data. As with other epidemiologic designs used in VSD, RCA studies use the electronic data to identify a presumptive association between a vaccine and pre-specified outcomes. Additional investigations further elucidate the relationship between the exposure and the outcome. The basic structure for the RCA facilitates follow-up investigations, including the review of 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.

Because the data for an RCA project are being analyzed weekly (or perhaps monthly), 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 specific hypothesis (Lieu, Med Care, 2007). A further refinement has been termed 'flex-maxSPRT.'

**Goals:**

Because the RCA is a new and critical VSD activity, substantial research in multiple areas is both ongoing and planned that will more fully elucidate 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 length of study influences RCA results and finding the right balance between timely data acquisition versus 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.

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.

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 Methods

**Background and Public Health Importance:**

A variety of laboratory methods are useful for assessing adverse events following vaccination (AEFIs)[6]. Understanding the association between the immune response to vaccination and AEFI is particularly important. 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 utility 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 the adverse events in an attempt to better understand and perhaps modulate 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 subjects experiencing AEFI and to perform laboratory assessments on these samples. The network has a 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, and to collaborate with specialty laboratories throughout the country in the performance of additional immunologic and microbiologic studies.

**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 patient population. The range of possible specimens which 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-Barre Syndrome, etc.) the network sites also have IRB approval for collection and storage of samples from individuals with VAEs that are not pre-specified.

**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

[6] 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.

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), 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 (type IV hypersensitivity reactions) occur hours to days after exposure and do not involve IgE mediation. Most delayed reactions are rather due to formation of immune complexes with complement activation.

**Goals:**

CISA is developing an immediate hypersensitivity algorithm as well as 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, laboratory testing recommendations include skin (prick or scratch) tests, measurement of total IgE and specific IgE antibodies against the suspected allergens. Since 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) Conducting cytokine analysis**

Although cytokines are important secreted messenger molecules that coordinate the normal immune response, they can cause disease if their activity is not tightly regulated. Recent work at Vanderbilt University showed significantly different cytokine patterns in subjects who reported an AE after smallpox vaccination, compared with subjects who did not (Rock et al. JID 2004). Subjects with 1 of 4 AEFIs (fever, lymphadenopathy, and localized or generalized rash) exhibited significantly increased levels of IFN-γ, TNF-α, IL-2, IL-5, and IL-10 compared with subjects who did not experience an AEFI.

**Goals:**

Broad scale cytokine analysis provides one of the most powerful measurements for assessing systematic alternations of the inflammatory state following vaccination and during a subsequent adverse event. CISA proposes to characterize the cytokine patterns that accompany the immune responses to a wide range of vaccine and to any associated VAEs. A broad range of systemic cytokine expression can be studied for each patient before and after immunization and during any adverse event. Protein microarray techniques allow the simultaneous quantitation of hundreds of cytokines and chemokines. Such studies will require collaboration with physicians to collect real-time samples from their patients that can be sent to the Columbia CISA specimen repository for storage so that samples can be tested in batch mode to maximize testing economics.

**4) 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 in skin and hair color, height, creativity, and intelligence. At the same time, SNPs also 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:**

CISA proposes to perform vaccine studies in which correlations can be made between SNPs associated with cytokines, mRNA levels for cytokines in blood cells, and protein levels of those same cytokines in the serum. The Vanderbilt genetics center is developing techniques for simultaneously analyzing patterns in these three types of data, with the hypothesis that the strongest associations with adverse events will match in the trend of DNA, mRNA and protein associations. Complete technologies for determination of mRNA levels exist at several of the CISA sites.

**5) Conducting assays to profile immune response gene expression**

Little is known about the immune gene expression changes that occur after vaccination; even less is know about immune genes expressed during an AEFI. Quantitative gene expression analysis can be used to determine which immune response genes are up- or down-regulated during an AEFI and help to elucidate the associated pathophysiological changes (See also Section 2 Genomics and Vaccine Safety).

Microarray technology (see glossary) is ideally suited to study the involved cellular responses, since the expression of thousands of genes can be assessed simultaneously**.** Previous studies have shown that peripheral blood mononuclear cells (PBMCs) are a good source to analyze gene expression profiles and identify genes relevant to immune responses (Lahdenpera et al., Vaccine, 2008). Gene markers for the adaptive as well as the innate immune responses can be evaluated, as well as genes involved in toxicity, inflammation, apoptosis and stress. Cytokine markers measured on the gene expression level by microarray technology show good correlation with the corresponding cytokine levels measured by

conventional technology using serum (Regnstrom et al., Pharmacogenomics, 2002). The Vanderbilt University CISA site has had extensive experience in these methods.

**Goals:**

CISA proposed 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:**

Why do only a small number of individuals develop serious AEFIs? Are genetically determined differences in immune responses to vaccination 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 and AEFI (Wilke, Nat Rev Drug Discov, 2007). While 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, there are a number of unique aspects of vaccine safety that 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 (1) Mitchel reported higher frequencies of HLA-DR2 and DR5 in women who developed joint symptoms after rubella vaccination (Mitchel, J Infect Dis, 1998); (2) 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 vaccine (Piyasirisilp, Ann Neurol, 1999); (3) Wilson et al reported four loci preliminarily linked to myopericarditis after smallpox vaccine including interleukin associated genes and HLA genes (Wilson, Vaccine Safety Evaluation: Post Marketing Surveillance Conference, 2007); and (4) 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 the Food and Drug Administration (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 objective of the genomics research initiative within the Immunization Safety Office (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 will be a CDC leader in implementing the U.S. Department of Health and Human Services (HHS) goal of personalized healthcare. The Personalized Health Care Initiative will improve the safety, quality and effectiveness of healthcare for every patient in the US. By identifying genes and how they may relate to risks associated with vaccination, personalized health care will enable medicine to be more individualized (http://www.hhs.gov/myhealthcare/). The resources of ISO, including the Clinical Immunization Safety Assessment (CISA) Network, and the presence of the National Office of Public Health Genomics (NOPHG) create a unique opportunity for CDC to lead research into understanding the genetic basis of vaccine safety. In January 2008, CISA hosted the first interdisciplinary US workshop on understanding the genetic basis of VAEs.

**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/CISA has developed an IRB-approved protocol for a registry of clinically significant VAE. This registry complies with the HIPAA regulations to maintain patient privacy. The registry will include persons who have experienced serious VAEs along with related clinical data and a code-linked repository of biological specimens from these patients. Because serious VAEs are relatively rare, such studies will require surveillance and tracking of a large number of VAE patient cases and creating centralized databases of post-vaccination AE clinical data and specimens. 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 in order to maintain privacy. These specimens include serum, whole blood, biopsies, urine, cerebrospinal fluid (CSF), white blood cell (WBC) pellets and/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). Since GBS is rare, it has been suggested that a genetic predisposition may be an important contributing factor. Enrollment in case-control studies using cases 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. **Assessing genetic predisposition to developing rheumatoid arthritis (RA) in persons receiving HBV vaccine.** This ongoing study will examine the hypothesis that an interaction between receipt of HBV vaccine and certain HLA genes predisposes to the development of RA. This association will be examined in a case-only study of RA cases from the CDC Vaccine Safety Datalink (VSD) project. The family of immune response HLA genes that are associated with increased RA susceptibility also controls immune responsiveness to HBV vaccine (Godkin, Hepatology, 2005; Reveille, J. Rheumatol, 2005). The genetic markers being examined include HLA type DRB1*04 as well as several dozen polymorphisms that have been pre-screened for potential associations with autoimmune diseases.
4. **The genomics of wheezing and variable immune response after influenza vaccination in children 6-59 months of age.** There is recent evidence 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 aim of this study is 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 will be a retrospective study to collect DNA samples from 80 children ages 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 will be made between (1) children who wheezed following vaccination with 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.

5. **The genomics of yellow fever vaccine associated viscerotropic syndrome and neurologic disease.** In approximately 1 in every 100,000 to one million recipients of yellow fever vaccine, a disseminated illness associated with viral replication in multiple body organs occurs causing a disease resembling wild-type yellow fever. Risk factors for disseminated disease after vaccination include underlying thymus disease and age over 60. A unique genetic predisposition, perhaps associated with the innate immune system, is the most logical explanation for this rare adverse event. This study will collect samples from all patients with suspect or documented serious adverse events associated with yellow fever vaccine and comparing these results with larger populations of normal healthy individuals. Similarly, specimens would be collected from all patients with neurologic disorders following yellow fever vaccine including GBS and acute disseminated encephalomyelitis (ADEM). Since there are only a small number of new cases every year, the specimens would be collected prospectively with the intent of analyzing after obtaining sufficient numbers in the repository, which could take three to six years.

**Goals:**

ISO is developing a genomics initiative with the following intent:

- To develop a scientific approach to understanding the genetic basis for AEFI and their 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

**Benchmarks:**

- Increase the number of samples/patients in the specimen repository
- Develop ongoing collaborations with clinical specialist groups (e.g., neurology, allergists) to provide cases and samples
- Include a requirement for collection of specimens to be placed in specimen repository for future genomic studies within all CISA protocols
- Implement up to 3 new genomic protocols within the next 5 years

## Item F: Case Definitions, Data Collection, and Data Presentation for Adverse Events Following Immunization

**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 can not 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 were composed of 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 to develop case definitions for use in immunization safety had occurred (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, 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 November 2007, Brighton had completed a total of 24 case definitions; these include definitions on anaphylaxis, intussusception, thrombocytopenia, and unexplained sudden death in the first and second years of life (Kohl, Vaccine, 2007). In addition, several case definitions are under development including one for Guillain-Barré Syndrome (GBS). A complete list of case definitions is available and can be downloaded via a quick registration process at our 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:**

ISO manages the Brighton Collaboration, a consortium of more than 1,600 voluntary professional participants from over 90 countries. As a global leader in immunization safety science, ISO serves a critical role in helping the BC achieve its mission and engaging international stakeholders. Today, the use of BC case definitions is recommended by key organizations in vaccine safety including: WHO, the Institute of Medicine (IOM), the US Food and Drug Administration (FDA), and European Agency for the Evaluation of Medicinal Product (EMEA) (WHO, Wkly Epi Record, 2006; IOM, 2002a; FDA Draft Guidance, 2007; EMEA, 2005). The Brighton Collaboration is unique: 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 develop new case definitions, disseminate completed BC case definitions, and translate them into practice.

Key goals during the next 5 years are:

- Development of case definitions to contribute to priority research and surveillance needs in vaccine safety
- Evaluation of case definitions to be used in research and surveillance
- 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 technique, 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). The CDC sexually transmitted disease treatment guidelines (CDC, Sexually Transmitted Diseases Treatment Guidelines, 2008) and the Advisory Committee on Immunization Practices (ACIP) recommendations (CDC, Advisory Committee on Immunization Practices, 2008) for vaccine use are two prominent examples of clinical guidance. Availability of vaccine safety clinical practice guidance will help clinicians investigate, diagnose, and manage patients with VAEs. While all clinicians, from primary care providers to sub-specialists, 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 regarding clinical problems that are potentially attributable to vaccines. These sub-specialists could be a particular focus for vaccine safety clinical practice guidance.

Although severe VAEs are rare, they are of concern to clinician, their patients, and their patients' caregivers. The healthcare provider needs to manage the adverse event, 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 adverse events management for targeted military service members and their beneficiaries. However, a broader evidence base is needed because of the diversity of vaccines, adverse events, and vaccinated populations.

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 may have limited understanding of VAEs, how to characterize them, their differential diagnoses, and how to manage 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 the 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 and the agency disseminates guidance in a number of health areas.

**Priority Scientific Areas:**

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

- 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

**Goals:**

Using evidence-based methods, including expert clinical expert, to develop and widely disseminate clinical guidance that will to assist clinicians assess, report, and manage VAEs. Specific deliverables in the next 5 years are:

- Guidelines for investigating and assessing the causality of individual adverse events
- Guidelines for assessment and management of hypersensitivity reactions that occur after immunization
- Guidelines for revaccination after adverse reactions, including hypersensitivity reactions
- Guidelines for the clinical investigation of GBS after immunization and demyelinating central nervous system disorders, including acute disseminated encephalomyelitis (ADEM) and transverse myelitis after immunization
- Guidelines for minimizing risk of VAEs in immunocompromised persons.

## Section 3: 5-Year Research Needs

The draft ISO Scientific Agenda recommendations propose **30 research needs** for the next 5 years. Seven are specific vaccine safety questions and 23 are scientific thematic areas (Table 2 and Tables 3A–D). The scientific thematic areas fall into in three categories: vaccines and vaccination practices (8 topics), special populations (7 topics), and 3) clinical outcomes (8 topics). Two clinical categories stand out across the lists: pediatrics (8 topics) and neurology (8 topics). ISO developed these lists in collaboration with numerous internal and external experts through a multi-step process described in Table 4. 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 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).

We developed the technical tables to assist the NVAC Vaccine Safety Working Group review and prioritize the topics (Tables 3A–D) (see section 4: Approaches for Prioritizing CDC's Immunization Safety Office Vaccine Safety Scientific Activities). This background material is not a comprehensive review of all potentially relevant information. Rather, it includes selected summary background information form the literature, Institute of Medicine (IOM) reports, and Advisory Committee on Immunization Practices (ACIP) recommendations. In addition, we present information about ongoing and planned ISO research studies to help the Working Group assess the priority of developing new research initiatives in these areas; we are not asking the Working Group to assess the priority of these studies or whether or not to continue them. In addition, we present information on selected manufacturer post marketing studies of vaccine safety. The technical tables include numbers and letters to facilitate review and discussion of the items, rather than to indicate a priority level.

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 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; and other experts across CDC, other federal agencies and academia. Clinical expertise in subspecialty areas may be needed.
5. The feasibility and level of resources needed to conduct studies in these areas vary. All could be carried out using infrastructure generally accessible to CDC, including ISO's Vaccine Safety Datalink (VSD) Project and Clinical Immunization Safety Assessment (CISA) Network (see Section 2: **Vaccine Safety Public Health and Clinical Guidance Capacity**) and Background Document [http://www.cdc.gov/od/science/iso/00_pdf/agenda_background_080321.doc]).

**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 and/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 and/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 (varicella and MMRV) 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 ≥65 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** |
| | |
| **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 postimmunization fever** |
| **D-VIII** | **Postvaccination 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)?** | ▪ The Institute of Medicine (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 relation between tetanus toxoid--containing vaccines and GBS (Stratton, JAMA, 1994).<br>▪ Data suggest a small increased risk for GBS after MCV4 vaccination; however, uncertainty exists regarding this risk estimate (CDC, MMWR, 2006; Haber, JAMA, 2004).<br>▪ The Clinical Immunization Safety Assessment (CISA) Network is conducting a study on genetics of GBS and one on the relapse of GBS following vaccination.<br>▪ The Vaccine Safety Datalink (VSD) near real-time surveillance studies specifies GBS as an outcome for several vaccines.<br>▪ 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.<br>▪ CDC's Vaccine Analytic Unit (VAU) is planning studies to evaluate the risk of GBS associated with influenza, anthrax and meningococcal vaccines.<br>▪ Harvard Medical School/ Harvard Pilgrim Health Care is conducting a study assess the relationship between immunization with MCV4 and Guillain-Barré syndrome (GBS) in adolescents (ACIP presentation, 6/2007). |
| **A-II** | **Is live, attenuated influenza vaccine (LAIV) associated with increased risk for asthma and/or wheezing, particularly in young children or persons with history of wheezing?** | ▪ 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).<br>▪ During clinical trials wheezing was identified as potential safety concern in young children and persons with wheezing history. In the study that supported the label change, Belshe identified increased risk for wheeze after LAIV in children aged 6–23 months but not children aged 24–59 months (Belshe, NEJM, 2007).<br>▪ 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.<br>▪ Plans to develop a VSD study to assess risk for wheezing in young children are under discussion.<br>▪ MedImmune is conducting postlicensure 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). |

| Item | Question | Background |
|---|---|---|
| **A-III** | **Is exposure to thimerosal associated with increased risk for clinically important tics and/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).<br>▪ The study included children ages 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).<br>▪ The study found few significant associations with exposure to mercury from vaccines and immune globulins administered parentally or during the first 7 months of life. 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 to 10 years," (Thompson, NEJM, 2007).<br>▪ 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).<br>▪ An association with 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). |
| **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).<br>▪ Studies suggest that rates of HHE are lower after DTaP than DTP vaccines (Heijbel, Dev. Biol. Stand., 1997; Saux Pediatrics, 2003); there are no published comparative postlicensure studies on risk HHE after DTaP vaccines.<br>▪ The Advisory Committee on Immunization Practices (ACIP) considers HHE and certain other neurological events to be precautions for DTaP vaccine (CDC, ACIP General Recommendations, 2006).<br>▪ A VSD study is being developed to assess risk of HHE after DTaP vaccines. |

| Item | Question | Background |
|---|---|---|
| **A-V** | **Is immunization associated with increased risk for neurological deterioration in children with mitochondrial disorders?** | ▪ Mitochondrial disorders are a heterogeneous group of disorders characterized by impaired energy production. They are usually progressive and multisystemic; the incidence is estimated to be 1 in 5000 live births (Haas, Pediatrics, 2007).<br>▪ Children with mitochondrial disorders commonly present with a range 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).<br>▪ In an epidemiological study of Portuguese children with autistic spectrum disorder, 7% had a definitive mitochondrial disease (Olivera, Developmental Medicine and Child Neurology, 2005).<br>▪ Studies suggest that children with metabolic disorders, including mitochondrial disorders, may experience neurological deterioration during 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).<br>▪ CISA has formed a working group to identify key research questions and consider study methods related to mitochondrial disorders and immunization, in collaboration with partners. |
| **A-VI** | **Is combination measles, mumps, rubella, and varicella (MMRV) vaccine associated with increased risk for febrile seizure and if so are there sequelae?** | ▪ Preliminary results from a VSD study underway found that children aged 12–23 who received MMRV vaccine were about 2 times more likely to have febrile seizures during the 7–10 days after vaccination than children who received MMR and varicella vaccines at the same visit (CDC, MMWR, 2008).<br>▪ A Merck postmarketing study is underway to assess risk of febrile seizures 5–12 days after MMRV vaccine; interim results were consistent with the VSD study findings but were not statistically significant (CDC MMWR, 2008).<br>▪ Limited data are available on the risk of febrile seizures after the second dose of MMRV vaccine.<br>▪ In February 2008, ACIP voted to remove the preference for MMRV over MMR and varicella vaccines and formed a Working Group (CDC, MMWR, 2008).<br>▪ US availability of MMRV vaccine currently is limited because of manufacturing constraints unrelated to vaccine safety or efficacy. MMRV vaccine is not expected to be widely available before 2009 (CDC, MMWR, 2008). |

| Item | Question | Background |
|---|---|---|
| **A-VII** | **Are varicella vaccines (varicella and MMRV) associated with increased risk for clinically important events related to varicella vaccine virus reactivation?** | ▪ Varicella vaccine reports to the Vaccine Adverse Event Reporting System (VAERS) reports during 1995–2005 were reviewed. This study 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)<br>▪ In the Chaves study 2 patients with confirmed vaccine-strain–associated meningitis had sufficient neurological symptoms and signs to warrant diagnostic evaluation of 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™) (AAP Redbook Online, 2007); the BLA is under FDA review.<br>▪ 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).<br>▪ If licensed, this bivalent HPV vaccine would be the first US vaccine with ASO4.<br>▪ In a clinical trial, 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). |
| **B-II** | **Zoster vaccine (Zostavax®)** | ▪ Since 2006, zoster vaccine, live (Zostavax®) is 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).<br>▪ In a prelicensure study the rate of serious adverse events, including cardiovascular events, was higher in person receiving Zoster vaccine, compared with placebo recipients during the 42 days after vaccination (FDA, Product Approval Information and Package Insert, 2006).<br>▪ A VSD study under development will assess risk for selected outcomes, including herpes zoster, severe neurological outcomes and severe cardiac outcomes, including myopericarditits.<br>▪ 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)** | ▪ In February 2008, ACIP voted to expand annual influenza vaccine recommendations to include children aged 5–18 years (CDC, ACIP Provisional recommendations, 3/2008).<br>▪ 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).<br>▪ Available data does not suggest specific safety concerns; however, there are gaps in knowledge. |

| Item | Thematic Area | Background |
|---|---|---|
| **B-IV** | **Non-antigen components of vaccines (other than thimerosal [see item A-III] and ASO4 adjuvant HPV vaccine [see item B-I])** | ▪ In 2006, there were more than 50 exipients present in US-licensed vaccines (CDC, Pink Book, 2008)<br>▪ US-licensed vaccines also contain conjugate proteins, such as diphtheria and tetanus toxoids.<br>▪ The patterns of exposure to non-antigen components after licensure may differ from patterns studied before licensure.<br>▪ A VSD study is assessing occurrence of severe local VAEs in adolescents and young adults with varying patterns of diphtheria toxoid-containing vaccines. |
| **B-V** | **Simultaneous vaccination** | ▪ Usually simultaneous vaccination is incompletely studied at time of licensure.<br>▪ Under current infrastructure, prelicensure studies do not assess safety of two unlicensed vaccines administered simultaneously (e.g., Tdap and MCV4 simultaneous administration was not studied before licensure).<br>▪ ACIP recommends simultaneous vaccination, unless contraindications are present (CDC, ACIP General Recommendations, 2006).<br>▪ VSD studies try to assess risks of simultaneous vaccination when feasible, as part of the rapid cycle studies.<br>▪ CDC's and DoD's Vaccine Analytic Unit (VAU) has conducted a study which found no evidence that the receipt of multiple concurrent vaccinations is related to hospitalization risk among DoD personnel. |
| **B-VI** | **Safety of different products within the same vaccine category** | ▪ Pending[7] |
| **B-VII** | **Off label use of vaccines** | ▪ Pending[5] |
| **B-VIII** | **Vaccine-drug interactions** | ▪ Pending[5] |

[7] These topics were suggested during the Vaccine Safety Datalink annual meeting, April 3, 2008. Background information is under development.

**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: (<2500 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).<br>▪ ACIP recommends a usual immunization schedule for premature and LBW babies, except for hepatitis B vaccine (CDC, ACIP General Recommendations, 2006).<br>▪ 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 postimmunization apnea." (Klein, Pediatrics, 2007).<br>▪ CISA is evaluating the immune response and patterns of vaccine adverse events after polio vaccine in premature and term infants.<br>▪ VSD is studying wheezing and lower respiratory disease in premature infants following vaccination. |
| **C-II** | **Pregnant women** | ▪ Pregnant women are usually excluded from prelicensure vaccine trials and data on vaccine safety during pregnancy are limited.<br>▪ 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).<br>▪ VSD studies are under development to assess the safety of TIV in pregnant women, including the risk for spontaneous abortion.<br>▪ Manufacturers have established pregnancy registries for new adolescent vaccines, including quadrivalent HPV vaccine (FDA, approval letter, 2006). |

| Item | Thematic Area | Background |
|---|---|---|
| **C-III** | **Adults aged ≥65 years** | ▪ In 2006, approximately 37 million US persons were aged ≥ 65 years (~11 million were ≥ 80 years) (US Census, 2006).<br>▪ ACIP recommends annual TIV and pneumococcal vaccine and tetanus and diphtheria toxoids (Td) vaccine routinely for persons ≥ 65 years (CDC, Adult Immunization Schedule, 2007–2008).<br>▪ Deaths in older persons may occur in temporal association with vaccination. In 2006, in Israel 4 deaths occurred shortly after influenza vaccine (3 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).<br>▪ Immune function wanes in older populations (Kovaiou, Expert Review Molecular Medicine, 2007); there are limited data on the effects of immunosenescence on vaccine safety.<br>▪ 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. |
| **C-IV** | **Persons with primary immunodeficiency** | ▪ ACIP has general recommendations for use of vaccines in person with immunocompromising conditions. Persons with most (but not all) forms of immunodeficiency should not receive live vaccines; certain inactivated vaccines are specifically recommended. In most situations, household contacts of immuncompromised persons should receive live vaccines (CDC, ACIP General Recommendations, 2006).<br>▪ A CISA study is assessing VAE and vaccine-preventable disease patterns in patients with DiGeorge syndrome.<br>▪ 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 person with immunocompromising conditions (CDC, MMWR, 2006a)<br>▪ See bullets in C-IV. |

| Item | Thematic Area | Background |
|---|---|---|
| **C-VI** | **Persons with autoimmune disorders** | ▪ Autoimmune diseases affect about 3–5% of the population (IOM, 2002).<br>▪ IOM concluded that 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** | ▪ It is estimated that inborn errors of metabolism affect 1 in 2500 live births (Applegarth, Pediatrics, 2000).<br>▪ 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 of complications from vaccine-preventable diseases (Brady, Pediatrics, 2006; Kinsely, Pediatrics, 2006).<br>▪ A CISA protocol aims to describe patterns and prevalence vaccine adverse events (VAEs) in children with inborn errors of metabolism and assess risk factors for these events (under development). |

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

| Item | Thematic Area | Background |
|---|---|---|
| **D-I** | **Autoimmune diseases** | ▪ The IOM 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).<br>▪ VSD is conducting a study assessing if there is a genetic predisposition to developing rheumatoid arthritis after hepatitis B vaccination.<br>▪ The VAU is completing a study evaluating the risk of type 1 diabetes as an outcome following vaccination. Also, a chart validation study on the same topic is under development by VAU. The VAU has a planned study to evaluate the risk of diffuse connective tissue diseases 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; 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).<br>▪ 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" for hepatitis B vaccine and the first episode of a central nervous system demyelinating disorder or acute demyelinating encephalomyelitis (ADEM) (IOM, 2002a).<br>▪ CISA is assessing if vaccination is associated with increase risk for transverse myelitis.<br>▪ The VSD RCA influenza study will assess risk for CNS demyelinating disorders.<br>▪ The VAU conducted a study which found no association between optic neuritis and receipt of anthrax, smallpox, hepatitis B, or influenza vaccines. |

| Item | Thematic Area | Background |
|---|---|---|
| **D-III** | **Encephalitis/ encephalopathy** | ▪ The IOM concluded that evidence is "consistent with a causal relation" between DTP vaccine and encephalopathy (IOM, 2001)<br>▪ ACIP recommendations that encephalopathy after pertussis vaccines is a contraindication for subsequent pertussis vaccination (CDC, ACIP General Recommendations, 2006)<br>▪ Encephalopathy and encephalitis are on the Vaccine Injury Table for the vaccines that contain the following antigens: pertussis, measles, mumps, and rubella, (HRSA, Vaccine Injury Table, 2007).<br>▪ A recent study identified mutations in a sodium channel gene in children with encephalopathy after pertussis vaccines, suggesting that genetic factors may influence the risk for encephalopathy after vaccination (Berkovic, Lancet Neurology, 2006). |
| **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).<br>▪ VSD is conducting a thimerosal and autism case-control study (in progress). The chief aim is 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 is to evaluate whether exposure to thimerosal in infancy is related to a subclass of autism predominately associated with regression.<br>▪ CDC has funded a study in Italy comparing children who previously received thimerosal-containing or non-thimerosal-containing DTaP vaccines; the authors submitted a manuscript for publication. |
| **D-V** | **Vasculitis syndromes** | ▪ Vasculitis after vaccination has been rarely reported in the literature (Saadoun, Rev Med Interne, 2001)<br>▪ Kawasaki disease was reported to VAERS after Rotateq® vaccine (FDA, 2007).<br>▪ Two VSD studies are assessing: 1) a possible link between vaccine administration and Kawasaki disease and 2) risk for Henoch-Schönlein Purpura (HSP) after meningococcal vaccine (manuscript in preparation). |

| Item | Thematic Area | Background |
|---|---|---|
| **D-VI** | **Myopericarditis (not associated with smallpox vaccine)** | ▪ Smallpox vaccine has been associated with increased risk for myopericarditits (Halsell, JAMA, 2003).<br>▪ VSD is studying the rate of cardiac events following live viral vaccinations in children and adolescents (see also Zoster section B-II).<br>▪ The VAU will study risk of myopericarditis following live viral vaccines (including the new smallpox vaccine). |
| **D-VII** | **Clinically important outcomes related to postimmunization 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).<br>▪ The pathophysiology and clinical consequences of fever after immunization have not been systematically studied.<br>▪ A VSD study is assessing the efficacy of acetaminophen prophylaxis for prevention of postvaccination fever following routine childhood immunizations recommended at 2, 4, and 6 months of age. |
| **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."<br>▪ In 10/2007 information was presented to ACIP about increased reports to the Vaccine Adverse Event Reporting System (VAERS) of postvaccination syncope. This increase in reports was observed following introduction of new adolescent vaccines, particularly HPV vaccine (CDC, ACIP presentation, 2007).<br>▪ VSD study will assess risk of syncope associated with vaccination in adolescents and young adults.<br>▪ A collaborative study with NCIRD will assess providers' adherence to ACIP guidance to prevent syncope and sequelae.<br>▪ The topic of unintentional injuries following vaccinations is also the focus of a planned VAU research study. |

## Table 4: Methods for Identifying the Immunization Safety Office 5-Year Research Needs

| Step | Activity and Description |
|---|---|
| 1 | **External Input:**<br>▪ During May 2007 through November 2007 CDC and National Vaccine Program Office (NVPO) convened three meetings to obtain input from the following groups: external expert scientists, vaccine safety representatives from HHS and Department of Defense agencies and programs, and US vaccine manufacturers' representatives<br>▪ 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:**<br>▪ ISO staff reviewed and considered suggestions from these meetings and from unsolicited sources (e.g., ACIP statements, Institute of Medicine reports, and the literature).<br>▪ ISO staff then created a master list of ideas, reviewed each input idea to determine if it met inclusion criteria for the 5-year research needs list.<br>▪ Inclusion criteria were: ISO routinely leads the topic, ISO could implement a study during 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.<br>▪ The first list (3-10-08) contained 19 vaccine questions, 42 scientific thematic areas, and 9 items for adjudication. |
| 3 | **Internal Reviews:**<br>▪ At ISO's request, 3 separate groups conducted internal reviews of the 3-10-08 list: the Clinical Immunization Safety Assessment (CISA) Network, Vaccine Safety Datalink (VSD) Project, and National Center for Immunization and Respiratory Diseases (NCIRD) scientists.<br>▪ ISO staff asked a liaison to synthesize input from each review, but also accepted individual input directly. During the reviews, the scientists suggested additions, deletions, modifications, and provided rationale for decisions. |
| 4 | **ISO Synthesis and Adjudication of Inputs from Internal Reviews:**<br>▪ 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 23 scientific thematic areas (4-4-08). |

## Section 4: Approaches for Prioritizing CDC's Immunization Safety Office Vaccine Safety Scientific Activities

### Background

CDC's Immunization Safety Office (CDC/ISO) has developed a scientific agenda with four components: 1) emerging issues and core scientific activities, 2) vaccine safety public health capacity building/infrastructure areas in need of strengthening, and 3) a list of 5-year research needs. The 5-year research needs include a list of vaccine safety questions and a list of scientific thematic areas of concern and interest.

One of the major reasons for engaging the NVAC working group is to obtain external opinions about the priority of the various activities proposed in the draft agenda. There are already more activities listed on the Agenda than can be accomplished with existing resources within the next five years, so it is important to CDC/ISO to obtain the insights of the working group about what activities are most important to undertake.

For the reasons given below, CDC/ISO recommends that the Working Group use either a nominal group technique or interacting group technique for establishing priorities.

### Approaches to Prioritization and Rationale for Recommendation

We considered quantitative approaches to prioritization. An example quantitative approach might involve developing criteria, weighting each criterion, and asking each member of the group to apply these criteria and weights to each item on the agenda. However, quantitative approaches work best when everything to be prioritized is in a similar format, has a similar level of specificity, and the data are available to use the prioritization criteria in a meaningful way. These characteristics are, of necessity, not present in the current draft Agenda. Quantitative approaches can also be very time-consuming and resource intensive. Therefore, we do not recommend a quantitative approach to prioritization.

"Consensus" approaches to group decision-making have been used for many years (Fink, 1984). Three commonly used approaches are: 1) the interacting group technique (Brightsman, 1980), 2) the nominal group technique (Johns and Hunter, 1995) and 3) the Delphi group technique (Van Gundy 1981). Because the Delphi approach requires that members not interact with one another, we do not recommend that approach.

The interacting group technique is the simplest approach. It involves having the group discuss each area of the Agenda and then, through some open voting process, identify the most important activities. Further discussion may follow and some adjustments made based upon that discussion. The nominal group technique involves allowing each member of the group to rank priorities privately and then presenting their views to the group in a "round robin" manner (the idea behind this technique is that members are not initially influenced by the opinions of others in the group). Following the "round robin" presentations, an open discussion occurs. This is followed by a silent and private voting process. The nominal group approach can involve multiple iterations. ISO/CDC recommends that the NVAC working group use either of the latter two techniques. However, we are open to modifications and/or other ideas.

### Prioritization Criteria

CDC/ISO has reviewed a number of previous research agenda prioritization approaches and discussed prioritization criteria with a several experienced individuals. Based upon the literature review and these discussions, we are proposing some draft prioritization criteria to the

working group for discussion. Because the working group is being asked to prioritize three dissimilar parts of the ISO scientific agenda, we have developed three different sets of criteria, one for each of the three "sections."

For the section of the Agenda that articulates specific hypotheses to be tested (Section 3, Table 3A), we propose that the following criteria be discussed:

1. Clinical severity of the adverse event. This refers to both the seriousness of the event e.g., from a sore injection site to death) and the duration of the event (e.g., hours of discomfort to life-long disability).
2. Biological plausibility. This means that a cause and effect relationship between vaccination and an adverse event seems possible based on existing scientific and medical knowledge.
3. Population exposure to the vaccine. This is meant to ask you to consider not only that a vaccine is administered but also to consider how many times and how frequently it is administered.
4. Level of public concern. Please consider not only reports that appear in the media and the concerns of advocacy groups, but the broader concerns of parents and patients about the vaccines and/or adverse events.
5. Feasibility of designing and implementing a study. Simply put, is it likely that the study will successfully address the issue of concern? For purposes of this discussion, studies of rare events and special populations are less feasible to design and implement than studies of more common events and in the general public. In addition, studies which would require new "platforms" or different sources of data are less feasible to implement than are studies conducted using existing data systems. At times, ethical considerations may make a study not feasible or less feasible.
6. Sufficiency of previous or ongoing research/scientific activities. Do we know enough about the question already? Are adequate studies underway to address the question? For this discussion, consider whether the activity should be undertaken based on what is already known, the quality of data and studies currently underway.
7. Potential to influence clinical practice/ vaccination policy. The activity has the potential to yield results which will impact clinical practice and/or vaccination policy, such as ACIP recommendations or the Vaccine Injury Compensation table.

For the section of the Agenda that involves "thematic areas" (where additional discussions will be necessary to determine what specific hypotheses should be formulated), we are proposing the following draft criteria for discussion: (Section 3, Tables 3A–D)

1. Severity of outcome. For those thematic areas where potential adverse outcomes are specified, how severe are those outcomes?
2. Population exposure to vaccine. For those thematic areas where exposures are specified, how much exposure is there, e.g., how many people are vaccinated and how often?
3. Biologic plausibility. For all thematic areas, is there some scientific evidence which suggests that a causal association may be biologically plausible and how strong is that evidence?
4. Public and scientific concern. What is you sense of the level of public (and/or scientific) concern about the thematic area?

5. Sufficiency of existing knowledge. Do you believe this area has been adequately studied or is there an important gap in our knowledge in this thematic area?
6. Projected impact of the work. Do you think successful work in this area would provide a basis for additional studies (lower priority for CDC) or does it have the potential to more immediately influence policy and practice (higher priority for CDC).

For the section of the agenda that involves capacity-building/infrastructure, we are only asking the NVAC committee the rank the relative importance of each area. The following criteria are offered for discussion:

1. How important is strengthening this area for meeting CDC's mandated/required vaccine safety activities?
2. How important is it to build capacity in this area to address the important hypotheses and thematic areas in this agenda?
3. How important is this area to advancing knowledge in vaccine safety science generally?
4. How important is it that CDC take the lead in moving this area forward?
5. How important is strengthening this area to CDC's stakeholders and the public?
6. How feasible is it to strengthen these areas given current resources?

After discussing and ranking activities in each of the three areas listed above and considering that there are also mandated/required activities that are a part of the agenda, CDC/ISO would appreciate the NVAC working groups' opinion on the relative amount of effort that should be put into each area.

**Approach to Prioritization**

We suggest a tiered approach to prioritization of the items on the Agenda. First, the working group could use an interacting group technique or nominal group technique to determine the relative priority of each of the capacity building/infrastructure areas. Second, the group could use one of these techniques to prioritize the vaccine safety questions (hypotheses) and the scientific thematic areas. Lastly, the groups could look at the overall agenda and provide their opinions on how much effort should be but into each of the four areas of the agenda. This input could be expressed as a percentage of effort.

CDC accepts the principle articulated by the IOM that prioritization by an external group in a public venue will enhance the scientific quality of the Agenda and the transparency of the process. NVAC Working Group recommendations will not replace the need for future study planning among scientific investigators nor interfere with scientific innovation and creativity. They also cannot replace the need to respond to urgent and emerging events. At the same time, we believe that the workgroup's guidance will be very useful for guiding the future direction of the ISO scientific activities.

## Appendix: Important Vaccine Safety Scientific Activities Outside the Scope of the ISO Scientific Agenda

a. Part of ISO mission for ISO to lead
    - Clinical consultation to healthcare providers for VAEs
    - Vaccine safety scientific training
    - Certain aspects of evaluation and improvements of ISO surveillance systems
b. Outside the scope of ISO mission for ISO to lead
    - Risk perception research and evaluation
    - Risk-benefit studies
    - Routine monitoring for clusters of lot-specific VAEs after vaccination
    - Basic science research
    - General assessment of baseline rates of clinical outcomes
    - Global etiology of clinical outcomes

## References: Excluding 5-Year Research Needs

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**List of Abbreviations**

| | |
|---|---|
| ACIP | Advisory Committee on Immunization Practices |
| 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 |
| BC | Brighton Collaboration |
| CDC | Centers for Disease Control and Prevention |
| CISA | Clinical Immunization Safety Assessment |
| CSF | cerebrospinal fluid |
| DDF | dynamic data file |
| DDM | distributed data model |
| DTaP | diphtheria, tetanus and pertussis |
| ECDC | European Centers for Disease Control and Prevention |
| EMEA | European Agency for the Evaluation of Medicinal Product |
| eSub | Electronic report submission |
| FDA | Food and Drug Administration |
| GBS | Guillain-Barré Syndrome |
| HBV | hepatitis B virus |
| HLA | human leukocyte antigens |
| HHE | hypnotic-hyporesponsive episodes |
| HHS | U.S. Department of Health and Human Services |
| 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 |
| ISO | Immunization Safety Office |
| LAIV | live, attenuated influenza vaccine |
| MCO | managed care organization |
| MCV4 | meningococcal conjugate vaccine |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MMRV | measles, mumps, rubella vaccine |
| NCIRD | National Center for Infectious and Respiratory Diseases |
| NCVIA | National Childhood Vaccine Injury Act |
| NOPHG | National Office of Public Health Genomics |
| NVAC | National Vaccine Advisory Committee |
| NVPO | National Vaccine Program Office |
| PHINMS | Public Health Information Network Messaging System |
| RA | rheumatoid arthritis |
| RCA | rapid cycle analysis |
| SCCS | self-controlled case series |
| SPRT | sequential probability ratio test |
| TIV | trivalent inactivated vaccine |
| VAE | vaccine adverse event |
| VAERS | Vaccine Adverse Event Reporting System |
| VHC | Department of Defense Vaccine Healthcare |
| VSD | Vaccine Safety Datalink |
| WBC | white blood cell |
| WHO | World Health Organization |

**Glossary of Terms**

| | |
|---|---|
| acute disseminated encephalomyeltitis (ADEM) | Acute disseminated encephalomyelitis (ADEM) is characterized by a brief but intense attack of inflammation in the brain and spinal cord that damages myelin – the protective covering of nerve fibers. It often follows viral infection, or less often, vaccination for measles, mumps, or rubella. The symptoms of ADEM come on quickly, beginning with encephalitis-like symptoms such as fever, fatigue, headache, nausea and vomiting, and in severe cases, seizures and coma. It may also damage white matter (brain tissue that takes its name from the white color of myelin), leading to neurological symptoms such as visual loss (due to inflammation of the optic nerve) in one or both eyes, weakness even to the point of paralysis, and difficulty coordinating voluntary muscle movements (such as those used in walking). ADEM is sometimes misdiagnosed as a severe first attack of multiple sclerosis (MS), since some of the symptoms of the two disorders, particularly those caused by white matter injury, may be similar. However, ADEM usually has symptoms of encephalitis (such as fever or coma), as well as symptoms of myelin damage (visual loss, paralysis), as opposed to MS, which doesn't have encephalitis symptoms. In addition, ADEM usually consists of a single episode or attack, while MS features many attacks over the course of time. Doctors will often use imaging techniques, such as MRI (magnetic resonance imaging), to search for old and new lesions (areas of damage) on the brain. Old "inactive" brain lesions on MRI suggest that the condition may be MS rather than ADEM, since MS often causes brain lesions before symptoms become obvious. In rare situations, brain biopsy may show findings that allow differentiation between ADEM and severe, acute forms of MS. Children are more likely than adults to have ADEM. |
| acellular | Containing no cells; not made up of cells |
| adjuvant | 1. A substance added to a drug product formulation that affects the action of the active ingredient in a predictable way.<br>2. In immunology, a vehicle used to enhance antigenicity; e.g., a suspension of minerals (alum, aluminum hydroxide, or phosphate) on which antigen is adsorbed; or water-in-oil emulsion in which antigen solution is emulsified in mineral oil (Freund incomplete adjuvant), sometimes with the inclusion of killed mycobacteria (Freund's complete adjuvant) to further enhance antigenicity (inhibits degradation of antigen and/or causes influx of macrophages).<br>3. Additional therapy given to enhance or extend primary therapy's effect, as in chemotherapy's addition to a surgical regimen.<br>4. A treatment added to a curative treatment to prevent recurrence of clinical cancer from microscopic residual disease. |
| agonist | 1. Denoting a muscle in a state of contraction, with reference to its opposing muscle, or antagonist.<br>2. A drug capable of combining with receptors to initiate drug actions; it possesses affinity and intrinsic activity |

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| 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 due to release of pharmacologically active substances (histamine, bradykinin, serotonin, and slow-reacting substance). |
| Angelman syndrome | Angelman syndrome is 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. Individuals 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 are characterized by reacting specifically with the antigen in some demonstrable way, antibody and antigen each being defined in terms of the other. Antibodies may also exist naturally, without being present as a result of the stimulus provided by the introduction of an antigen; antibodies are found in the blood and body fluids, although the basic structure of the molecule consists of two light and two heavy chains, antibodies may also be found as dimers, trimers, or pentamers. |
| anti-ganglioside antibodies | Anti-ganglioside antibodies are antibodies that are found in autoimmune neuropathies and react to self-gangliosides.<br>These antibodies were first found to react with cerebellar cells. These antibodies show highest association with certain forms of Guillain-Barré syndrome. |
| athralgia | Joint pain |
| autism spectrum disorder (ADS) | The autism spectrum, also called autism spectrum disorders (ASD) or autism spectrum conditions (ASC), with the word autistic sometimes replacing autism, is a spectrum of psychological conditions characterized by widespread abnormalities of social interactions and communication, as well as severely restricted interests and highly repetitive behavior. |
| autoimmune disorders | An autoimmune disorder is 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 | Genital HPV infection is a sexually transmitted disease (STD) that is |

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|---|---|
| papillomavirus (HPV2) vaccine (Cervarix™) | caused by human papillomavirus (HPV). Human papillomavirus is the name of a group of viruses that includes more than 100 different strains or types. More than 30 of these viruses are sexually transmitted, and they can infect the genital area of men and women including the skin of the penis, vulva (area outside the vagina), or anus, and the linings of the vagina, cervix, or rectum. |
| confidence interval | A confidence interval is an interval in which a measurement or trial falls corresponding to a given probability. |
| confounder | A confounding variable (also confounding factor, lurking variable, a confound, or confounder) is an extraneous variable in a statistical model that correlates (positively or negatively) with both the dependent variable and the independent variable. The methodologies of scientific studies therefore need to control for these factors to avoid what is known as a type 1 error: A 'false positive' conclusion that the dependent variables are in a causal relationship with the independent variable. Such a relation between two observed variables is termed a spurious relationship. Thus, confounding is a major threat to the validity of inferences made about cause and effect, i.e. internal validity, as the observed effects should be attributed to the confounder rather than the independent variable. |
| congenital rubella syndrome | CRS can occur in a developing fetus of a pregnant woman who has contracted rubella during her first trimester. Many organs that develop in the early stages of pregnancy can be affected by rubella infection. Some of the common effects of rubella during pregnancy include impairments to ears, eyes, heart, brain and nervous system. |
| contraindication | Any special symptom or circumstance that renders the use of a remedy or the carrying out of a procedure inadvisable, usually because of risk. |
| covariate | A variable that is possibly predictive of the outcome under study. |
| cytokine | Any of numerous hormone like, low-molecular-weight proteins, secreted by various cell types, that regulate the intensity and duration of immune response and mediate cell-cell communication. |
| demyelinating neurologic disorders | A demyelinating disease is any condition that results in damage to the protective covering (myelin sheath) that surrounds nerves in your brain and spinal cord. When the myelin is damaged, nerve impulses slow or even stop, causing neurological problems. Central nervous system (CNS) demyelinating disorders include: multiple sclerosis, transverse myelitis, optic neuritis, and acute disseminated encephalomyeltitis (ADEM) |
| DiGeorge syndrome | A disorder caused by the deletion of a small piece of chromosome 22. The deletion occurs near the middle of the chromosome at a location designated q11.2.<br>Characteristic signs and symptoms include heart defects that are often present from birth, an opening in the roof of the mouth (a cleft palate or other defect in the palate), autism, other learning disabilities, mild differences in facial features, and recurrent viral or fungal infections are common due to problems with the immune system's T-cell mediated response. DiGeorge syndrome is often first spotted when the affected newborn begins convulsing from hypocalcemia due to an absence of |

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| | parathyroid and parathyroid hormone. Affected individuals may also have kidney abnormalities, significant feeding difficulties, autoimmune disorders such as rheumatoid arthritis, and an increased risk of developing mental illnesses. |
| encephalitis | Encephalitis is 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). Certain parasitic or protozoal infestations, such as toxoplasmosis, malaria, or primary amoebic meningoencephalitis, can also cause encephalitis in people with compromised immune systems. Brain damage occurs as the inflamed brain pushes against the skull, and can lead to death. |
| encephalomyelitis | Inflammation of the brain and spinal cord |
| excipients | excipients are inactive ingredients of a drug product necessary for production, including adjuvants. |
| fragile X syndrome | Fragile X syndrome, or Martin-Bell syndrome, is a syndrome of X-linked mental retardation. Boys with the syndrome may have large testicles (macroorchidism), prognathism, hypotonia and autism, and a characteristic but variable face with large ears, long face, high-arched palate, gynecomastia, and malocclusion. Additional abnormalities may include lordosis, heart defect, pectus excavatum, flat feet, shortening of the tubular bones of the hands, and joint laxity. Females who have one fragile chromosome and one normal X chromosome may range from normal to mild manifestations of the fragile X syndrome. The fragile X syndrome has an estimated incidence of 1 in 3600 males and 1 in 4,000–6,000 females. |
| gene expression profiles | Gene expression profiling 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, for example, or show how the cells react to a particular treatment. |
| gene polymorphisms | Genetic polymorphism is 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. |
| General Practice Research Database | The GPRD is the world's largest computerized database of anonymised longitudinal medical records from primary care. Currently data are being collected on over 3.4 million active patients (approx. 13 million total) from around 450 primary care practices throughout the UK. 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. |
| 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, |

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| | 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) | Henoch-Schönlein purpura (HSP, also known as allergic purpura) is 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. Typical symptoms include palpable purpura (small hemorrhages in the skin), joint pains and abdominal pain. |
| hepatitis B | Hepatitis B virus 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 | 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). In most of the disorders, problems arise due to accumulation of substances which are toxic or interfere with normal function, or to the effects of reduced ability to synthesize essential compounds. Inborn errors of metabolism are now often referred to as congenital metabolic diseases or inherited metabolic diseases, and these terms are considered synonymous. |
| intussusception | The taking up or receiving of one part within another, especially the enfolding of one segment of the intestine within another. Often, specifically, the process of incorporation of new material in the growth of the cell wall. |
| Kawasaki disease (protocol approved) | Kawasaki disease, also known as lymph node syndrome, mucocutaneous node disease, infantile polyarteritis and Kawasaki syndrome, is a poorly understood self-limited vasculitis that affects many organs, including the skin and mucous membranes, lymph nodes, blood vessel walls, and the heart. It does not seem to be contagious. It was first described in 1967 by Dr. Tomisaku Kawasaki in Japan. |
| measles | Measles is 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 | Sometimes called a gene chip or a DNA chip. Microarrays 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. |
| mitochondria | Mitochondria are sometimes 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 |

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| mumps | Mumps is an illness caused by the mumps virus. Mumps causes fever, headache, muscle aches, tiredness, and loss of appetite. Swelling of the salivary glands follows these symptoms. |
| myalgia | Muscle pain |
| 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 disorders | Neurodevelopmental disorders such as fragile X syndrome are severe disabling conditions often associated with life-long impairment. These disorders are now recognized to be the result of abnormalities in brain development due to both genetic and environmental/biological causes. In total, these conditions affect approximately 1-3% of the population. |
| neuroimmunology | Neuroimmunology is 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 | Pertussis, also known as whooping cough, 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 utilization 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 | Rett syndrome is a neurological and developmental disorder that mostly occurs in females. Infants with Rett syndrome seem to grow and develop normally at first, but then stop developing and even lose skills and abilities. For instance, they stop talking even though they used to say certain words. They lose their ability to walk properly. They stop using their hands to do things and often develop stereotyped hand movements, such as wringing, clapping, or patting their hands. Rett syndrome is considered one of the autism spectrum disorders. Most cases of Rett syndrome are caused by a mutation on the MECP2 gene, which is found on the X chromosome. |

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| 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 | 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. An example is HIV infection. |
| 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 extinct. |
| 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 | Thimerosal is a mercury-containing organic compound (an organomercurial). Since the 1930s, it 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. A preservative-free version of the inactivated influenza vaccine (contains trace amounts of thimerosal) is available in limited supply at this time for use in infants, children and pregnant women. |
| 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 |

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| 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 -- called also *thymus gland* |
| toll-like receptors | Toll-like receptors (TLRs) are 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. |
| Tourette syndrome | A tic disorder appearing in childhood, characterized by multiple motor tics and vocal tics present for more than 1 year. Obsessive-compulsive behavior, attention-deficit disorder, and other psychiatric disorders may be associated; coprolalia and echolalia rarely occur; autosomal dominant inheritance. An estimated 200,000 Americans have TS, and perhaps as many as 1 in 100 people show a milder form of the disorder, such as chronic or transient tics in childhood. |
| transverse myelitis | Transverse myelitis is 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; autosomal dominant inheritance with variable expression, caused by mutation in either the tuberous sclerosis gene (TSC1) on chromosome 9q or TSC2 on 16p. |
| 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, which become vesicles and then pustules, like that of smallpox although less severe and varying in stages, usually with mild constitutional symptoms; incubation period is about 14–17 days. |
| vasculitis syndromes | Vasculitis is an inflammation of the vascular system, which includes the veins, arteries, and capillaries. Researchers think that inflammation is due to a faulty immune system response. Vasculitis can cause problems in any organ system, including the central (CNS) and peripheral (PNS) nervous systems. Vasculitis disorders, or syndromes, of the CNS and PNS are characterized by the presence of inflammatory cells in and around blood vessels, and secondary narrowing or blockage of the blood vessels that nourish the brain, spinal cord, or peripheral nerves. A vasculitis syndrome may begin suddenly or develop over time. Symptoms include: headaches, especially a headache that doesn't go away; fever; feeling out-of-sorts; rapid weight loss; confusion or forgetfulness leading to dementia; aches and pains in the joints and muscles; pain while chewing or swallowing; paralysis or numbness, usually in the arms or legs; and visual disturbances, |

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| | such as double vision, blurred vision, or blindness. |
| yellow fever | A tropical mosquito-borne viral hepatitis, due to yellow fever virus, a member of the family *Flaviviridae*, with an urban form transmitted by *Aedes aegypti*, and a rural, jungle, or sylvatic form from tree-dwelling mammals by various mosquitoes of the *Haemagogus* species complex; characterized clinically by fever, slow pulse, albuminuria, jaundice, congestion of the face, and hemorrhages, especially hematemesis. |

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