

NVAC Vaccine Safety Working Group

Draft Report

April 14, 2009

This is a draft paper of the NVAC Vaccine Safety Working Group. The full committee will deliberate on the content of, and the recommendations made in, the working group's final report, and will vote on whether or not to adopt or modify this report as a report of the NVAC.

All recommendations of the NVAC are made to the Department's Assistant Secretary for Health. Thus, any recommendations of the NVAC on these vaccine safety issues will be made to the Assistant Secretary for Health for his consideration in his communications with components of the Department, including the Centers for Disease Control and Prevention.

The NVAC working group recognizes that there may be pending or future litigation concerning some of the issues addressed in its recommendations. The working group's recommendations in no way suggest that any of these scientific issues have been resolved or that they should be resolved in any particular way in the context of litigation. Rather, out of an abundance of caution, and based upon the considerations described in this report, the working group suggests that further exploration of these issues is warranted.

The views represented in this draft paper represent the current thinking of the NVAC Vaccine Safety Working Group. The positions expressed and the recommendations proposed in this draft do not necessarily represent those of the United States Government or of Departmental employees who contributed to, or assisted in the formulation of, this paper.

**NVAC VACCINE SAFETY WORKING GROUP ON THE REVIEW OF THE CDC
IMMUNIZATION SAFETY OFFICE DRAFT SCIENTIFIC AGENDA**

Andrew Pavia, MD* (*Working Group Chair*)

George & Esther Gross Presidential Professor
Department of Pediatrics
University of Utah School of Medicine
Discipline: Pediatric and Adult Infectious Diseases
Group Representation: Academia

Trish Parnell*

Founder & Executive Director
Parents of Kids with Infectious Diseases
Parent of a child with an infectious disease
Group Representation: Public Representative

Mark Feinberg, MD, PhD*

Vice President for Policy, Public Health, & Medical Affairs
Merck Vaccine Division
Merck & Co., Inc.
Discipline: Immunology
Group Representation: Industry

Guthrie S. Birkhead, MD, MPH* (*NVAC Chair*)

Deputy Commissioner, Office of Public Health,
New York State Department of Health
Discipline: Epidemiology
Group Representation: State Health Department

Cornelia L. Dekker, MD*

Professor of Pediatrics & Medical Director
Stanford-LPCH Vaccine Program
Division of Pediatric Infectious Diseases
Stanford University School of Medicine
Discipline: Pediatrics
Group Representation: Academia

James O. Mason, MD, DrPH*

Discipline: Public Health
Group Representation: Former CDC Director and Assistant Secretary for Health

Lance Gordon, PhD*

ImmunoBiologics Corp
Discipline: Immunology
Group Representation: Industry

Marie McCormick, MD, ScD*

Sumner and Esther Felberg Professor of Maternal and Child Health
Harvard School of Public Health
Discipline: Maternal and Child Health
Group Representation: Academia

Lynn R. Goldman, MD, MPH

Professor
Chair, Interdepartmental Program in Applied Public Health
Johns Hopkins Bloomberg School of Public Health
Discipline: Toxicology/Environmental Health
Group Representation: Academia

Steven Goodman, MD, PhD

Professor
Co-director, Epidemiology Doctoral Program
Johns Hopkins Bloomberg School of Public Health
Discipline: Biostatistics/Epidemiology
Group Representation: Academia

Gerald Medoff, MD

Division of Infectious Diseases
Washington University School of Medicine
Discipline: Immunology
Group Representation: Academia

Christopher Carlson, PhD

Fred Hutchinson Cancer Research Center
Discipline: Genomics
Group Representation: Academia

Bennett Shaywitz, MD

Department of Pediatrics
Yale School of Medicine
Discipline: Neurology
Group Representation: Academia

Sean Hennessy, PharmD, PhD

Center for Clinical Epidemiology and Biostatistics
University of Pennsylvania School of Medicine
Discipline: Pharmacoepidemiology
Group Representation: Academia

Tawny Buck

Parent of a child injured by a vaccine

Group Representation: Public Representative

Lawrence Gostin, JD, LL.D (Hon)

Associate Dean, Professor of Global Health
Georgetown University Law Center
Discipline: Ethics/Law
Group Representation: Academia

Paul-Henri Lambert, MD

Center of Vaccinology
Centre Médical Universitaire
Discipline: Global aspects of vaccine safety
Group Representation: Chair, WHO Global Advisory Committee on Vaccine Safety

*Denotes NVAC Member

NVAC MEMBERS NOT ON THE VACCINE SAFETY WORKING GROUP

JON R. ALMQUIST, MD, Federal Way, Washington
RICHARD D. CLOVER, MD, Louisville, Kentucky
JAIME FERGIE, MD, Corpus Christi, Texas
SHARON G. HUMISTON, MD, MPH, Rochester, New York
LISA A. JACKSON, MD, MPH, Seattle, Washington
CHARLES LOVELL JR., MD, Norfolk, Virginia
CHRISTINE NEVIN-WOODS, DO, MPH, Pueblo, Colorado
LAURA E. RILEY, MD, Boston, Massachusetts

STAFF

DANIEL A. SALMON, PhD, MPH, Vaccine Safety Specialist, National Vaccine Program Office, U.S. Department of Health and Human Services
KIRSTEN S. VANNICE, MHS, Policy Analyst Fellow, National Vaccine Program Office, U.S. Department of Health and Human Services
ROBERT BEDNARCZYK, MS, Assistant to the Chair of NVAC, State University of New York, Albany NY

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Executive Summary

In 2005, the Institute of Medicine (IOM) Committee on the Review of the National Immunization Program's (NIP) Research Procedures and Data Sharing Program published the report "Vaccine Safety Research, Data Access, and Public Trust."¹ One of the recommendations of the IOM Committee was that "a subcommittee of the National Vaccine Advisory Committee that includes representatives from a variety of stakeholders (such as advocacy groups, vaccine manufacturers, FDAⁱ, and CDCⁱⁱ) review and provide advice to the NIP on the VSDⁱⁱⁱ research plan annually" (p.12). In response to the IOM review and recommendation, the CDC Immunization Safety Office (ISO) developed a 5-year research agenda for all of their vaccine safety research activities, referred to in this report as the ISO Scientific Agenda.

ISO requested that National Vaccine Advisory Committee (NVAC) address the following charge: undertake and coordinate a scientific review of the draft ISO Scientific Agenda, and advise on (1) the content of draft ISO Scientific Agenda (e.g., are the topics on the Agenda appropriate? Should other topics be included?); (2) the prioritization of scientific topics; and (3) possible scientific barriers to implementing the Scientific Agenda and suggestions for addressing them.

To address this charge, the NVAC formed the Vaccine Safety Working Group, which deliberated on the draft ISO Scientific Agenda from April 2008 through June 2009. The Working Group identified gaps in the ISO Scientific Agenda and developed prioritization criteria for research topics. The Working Group made 32 recommendations in three general categories: general recommendations, capacity recommendations, and research needs recommendations.

ⁱ Food and Drug Administration

ⁱⁱ Centers for Disease Control and Prevention

ⁱⁱⁱ Vaccine Safety Datalink

The proposed prioritization criteria included consideration of the significance of the exposure to a vaccine, burden of the adverse health event following immunization, public concern, scientific concern and degree to which science warrants further study, impact on policy, and feasibility. Specific Vaccine Safety Questions were prioritized using these criteria. Due to the lack of specificity provided in the broad topical categories in draft ISO Scientific Agenda, the Working Group encountered difficulty evaluating the content and prioritizing certain sections of the Agenda.

The Working Group requested broad public engagement, for which community and stakeholder meetings were undertaken to identify public concerns, values, and priorities related to vaccine safety research. Public input was solicited in four ways: (1) community meetings were held in Birmingham AL, Ashland OR, and Indianapolis IN, (2) a Writing Group met in Salt Lake City, UT, (3) a stakeholder meeting was held in Washington, D.C., and (4) written comments were solicited by two notices published in the Federal Register.

The Working Group found it challenging to limit discussion of vaccine safety research to the ISO, acknowledging that many other governmental agencies and departments have important roles in vaccine safety research. There is a strong need for a federal vaccine safety research agenda that encompasses research undertaken by non-ISO CDC offices, FDA, and NIH and requires increased collaboration and coordination between all federal agencies with a stake in vaccine safety. Further discussion of the federal safety system will resume in the second phase of the Working Group's charge, to review the current federal vaccine safety system and develop a White Paper describing the infrastructure needs for a federal vaccine safety system to fully characterize the safety profile of vaccines in a timely manner, reduce adverse events whenever possible, and maintain and improve public confidence in vaccine safety.

Summary of Recommendations

General Recommendations

- (1) The Working Group recommends ISO develop the research topic sections of Vaccines and Vaccination Practices, Special Populations, and Clinical Outcomes to consist of testable research questions that can be prioritized.
- (2) The Working Group recommends periodic external review of VSD and CISA research and the ISO Scientific Agenda more broadly.
- (3) The Working Group recommends ISO regularly engage the public and stakeholders as ISO conducts research, interprets the findings from their studies, and revises their research agenda.
- (4) The Working Group recommends ISO perform case studies of past decision making processes related to vaccine safety issues to identify lessons learned regarding the use of scientific data in decision making.
- (5) To prepare for mass vaccination use of vaccines not traditionally given to the civilian population, the Working Group recommends ISO research in advance approaches to safety monitoring, including the extent to which they would be used off-label or in new populations.
- (6) In order to better understand the biological mechanisms of action responsible for adverse events following immunization, the Working Group recommends that ISO should coordinate with other agencies to support basic research into such mechanisms and that CISA should conduct clinical research on the pathophysiologic basis of adverse events.
- (7) The Working Group endorses the Writing Group’s recommendation for an external expert committee, such as the Institute of Medicine, with broad methodological, design, and ethical expertise to consider “strengths and weaknesses, ethical issues and feasibility including timelines and cost of various study designs to examine outcomes in unvaccinated, vaccine delayed and vaccinated children and report back to the NVAC.”
- (8) The Working Group recommends that ISO studies are designed and adequately powered to assess the role of differences in race/ethnicity and gender when appropriate.
- (9) The Working Group recommends ISO have an active role in risk communications research.

Capacity Recommendations

- (10)** The Working Group recommends ISO identify and evaluate ways to (1) increase the number of severe events that are reported to VAERS; and (2) improve the quality and completeness of the reports received.
- (11)** The Working Group recommends ISO evaluate approaches to follow up individuals reported to VAERS with rare or unusual adverse events for further study, including the collection of biological specimens, when appropriate.
- (12)** The Working Group recommends that the ISO Scientific Agenda specify the laboratory capacity needed for vaccine safety research and identify potential collaborations with other Federal agencies or private entities for those areas where ISO lacks capacity. For the laboratory capacity that CDC/ISO currently possesses, ISO should request input from external experts to advise on the ongoing work and development of new laboratory methodologies.
- (13)** The Working Group recommends ISO study molecular immune responses to vaccinations, including common adverse events such as fever or rash, as subclinical correlates that might predict severe adverse events.
- (14)** The Working Group recommends ISO create an expert advisory group on genomics and vaccine safety to assist with developing a focused genomics research agenda and protocol development.
- (15)** The Working Group recommends ISO focus Brighton Collaboration research efforts on the adequacy of the case definitions and their usefulness in ongoing safety research conducted by VSD and other groups.
- (16)** The Working Group recommends ISO create a single written guide dedicated to comprehensive clinical guidance, including identification, reporting, and treatment, for vaccine adverse events.
- (17)** The Working Group recommends ISO include the vaccination of children with mitochondrial disease, mitochondrial dysfunction, and other metabolic diseases as a priority scientific area for research to develop clinical guidance.

Research Needs Recommendations		
Draft ISO Agenda Item	Recommended Action	Recommended Rewording
A-I: Are vaccines (e.g., influenza vaccines, meningococcal conjugate vaccine [MCV4]) associated with increased risk for Guillain-Barré Syndrome (GBS)?	Modify: Specify influenza and meningococcal conjugate vaccines	(18) Are influenza vaccines or meningococcal conjugate vaccine [MCV4]) associated with increased risk for Guillain-Barré Syndrome (GBS)?
A-III: Is exposure to thimerosal associated with increased risk for clinically important tics and/or Tourette syndrome?	Modify: Expand to include speech and language delays as potential outcomes of interest.	(19) Is exposure to thimerosal associated with increased risk for clinically important tics, Tourette syndrome, and/or speech and language delays?
	Expand	(20) ISO should sponsor an external and multidisciplinary reanalysis of data published in 2007 by Thompson et al. ISO should formulate and issue an RFP pursuant to awarding a contract to an independent organization to reanalyze the data on thimerosal exposure and neurodevelopmental outcomes. Additionally, ISO should work with VSD sites involved in this study to use information in the available medical records (thimerosal exposure and appropriate health outcomes) of children selected for the study and examine who did and did not agree to participate in order to assess the potential for selection bias.
A-VII: Are varicella vaccines (varicella and MMRV) associated with increased risk for clinically important events related to varicella vaccine virus reactivation?	Modify: Expand to include zoster vaccine.	(21) Are varicella vaccines (varicella, MMRV, and Zoster) associated with increased risk for clinically important events related to varicella vaccine virus reactivation?
None	Add Specific Vaccine Safety Questions	(22) Do multiple vaccinations increase risk of immune system disorders?
B-I: Bivalent human papillomavirus (bivalent HPV) vaccine (Cervarix™)	Remove	(23) Remove

Research Needs Recommendations		
Draft ISO Agenda Item	Recommended Action	Recommended Rewording
B-II: Zoster vaccine (Zostavax®)	Remove	(24) Remove
B-III: Annual influenza vaccination in children and adolescents (trivalent inactivated influenza vaccine [TIV] and LAIV)	Expand	(25) ISO should publish a regular summary report on the safety profile of the expanded influenza vaccination program that would be made publicly available.
B-IV: Non-antigen components of vaccines (other than thimerosal and ASO4 adjuvant HPV vaccine)	Expand	(26) ISO should evaluate cumulative levels of non-antigen component exposure possible through the schedule of recommended vaccinations.
	Modify: Remove the parenthetical statement “other than thimerosal or ASO4 in bivalent HPV vaccine.”	(27) B-IV: Non-antigen components of vaccines
B-VII: Off label use of vaccines	Expand	(28) Off-label vaccination practices should be characterized and quantified. Off-label use recommendations sometimes included in ACIP statements that are not indicated on the label should be considered as research agenda topics for the ISO.
C-III: Adults aged ≥ 65 years	Modify: Expand to include adults aged ≥ 60 years of age.	(29) Adults aged ≥ 60 years.
C-VI: Persons with autoimmune disorders	Modify: Expand to include well-documented family history.	(30) Persons with autoimmune disorders or a well-documented family history of autoimmune disorders.
None	Add: New Special Population	(31) Children with siblings or parents who experienced an adverse event following immunization
None	Add: New Special Population	(32) Children who have previously suffered an adverse event following immunization who are recommended to receive additional doses in a booster regime

Background

The development of active immunization has been widely hailed as one of the greatest achievements of medicine and public health. Since the development of smallpox vaccine by Edward Jenner, it was clear that immunization carried a small but quantifiable risk that must be weighed against the benefits that immunization provides individuals and societies. By its nature, research on immunization safety is challenging as it generally deals with many possible outcomes that are often very rare, and identifying adequate control groups can be problematic. Given that vaccines are given to healthy individuals, often children, to prevent disease, expectations for vaccine safety are very high. In recent years, there has been highly visible public concern about the safety of immunization and the adequacy of safety research.

In 2005, the Institute of Medicine (IOM) Committee on the Review of the National Immunization Program’s Research Procedures and Data Sharing Program published the report “Vaccine Safety Research, Data Access, and Public Trust.”¹ The report focused on vaccine safety research conducted by the Centers for Disease Control and Prevention (CDC) using the Vaccine Safety Datalink (VSD), with particular emphasis on data sharing and access, communication of preliminary findings and results, and independent review of VSD activities. One of the recommendations of the IOM Committee was that “a subcommittee of the National Vaccine Advisory Committee that includes representatives from a variety of stakeholders (such as advocacy groups, vaccine manufacturers, FDA^{iv}, and CDC) review and provide advice to the NIP^v on the VSD research plan annually” (p.12).

^{iv} Food and Drug Administration

^v National Immunization Program; In 2006, the CDC underwent an internal reorganization, and the NIP merged with the National Center for Infectious Diseases (NCID) to become the National Center for Immunization and Respiratory Diseases (NCIRD). Research on immunization safety was relocated to the Immunization Safety Office (ISO) which was separated from NCIRD. ISO is now located in the Division of Healthcare Quality Promotion (DHQP), in National Center for Preparedness, Detection, and Control of Infectious Diseases (NCPDCID).

ISO assesses the post-licensure safety of vaccines routinely administered to children, adolescents and adults. ISO “identifies possible vaccine side effects, conducts epidemiological studies to determine whether a particular adverse event is caused by a specific vaccine, helps determine the appropriate public health response to vaccine safety concerns, and communicates the benefits and risks of vaccines to the public, media, and healthcare communities.”² These activities are primarily carried out using infrastructure such as the Vaccine Adverse Event Reporting System (VAERS), the VSD, and the Clinical Immunization Safety Assessment (CISA) Network.

In response to the IOM review and recommendation, ISO developed a 5-year research agenda, referred to in this report as the draft ISO Scientific Agenda.³ The Agenda encompasses all vaccine safety research within ISO’s scope. The rationale for creating a broader long term agenda than that recommended by the IOM included enhancing integration of the ISO research and surveillance components, and promoting scientific excellence and public trust through transparency. At the request of CDC, the National Vaccine Advisory Committee (NVAC) formed a Vaccine Safety Working Group. ISO requested that the NVAC Vaccine Safety Working Group address the following charge:

Undertake and coordinate a scientific review of the draft ISO Scientific Agenda

- a. Advise on:
 - i. Content of draft ISO Scientific Agenda (e.g., are the topics on the Agenda appropriate? Should other topics be included?)
 - ii. Prioritization of scientific topics
 - iii. Possible scientific barriers to implementing the Scientific Agenda and suggestions for addressing them⁴

The Working Group will later complete a second charge, to review the entire federal vaccine safety system and develop a White Paper describing the infrastructure needs for a federal vaccine

safety system for the 21st century. Such a system should be able to fully characterize the safety profile of an increasing number of vaccines in a timely manner, reduce adverse events whenever possible, and maintain and improve public confidence in vaccine safety.⁴ The Working Group will initiate efforts on second charge upon completion of this report.

The Vaccine Safety Working Group was comprised of eight NVAC members and nine external expert consultants. Expertise spanned the disciplines of medicine, academia, state and local health departments, industry, and public representation (see Table 1).

Table 1. NVAC Vaccine Safety Working Group member disciplines.

Pediatric and Adult Infectious Diseases
Neurology
Genomics
Immunology
Epidemiology
Public Health
Ethics/Law
Toxicology/Environmental Health
Maternal and Child Health
Global aspects of vaccine safety
Pharmacoepidemiology
Biostatistics
Parent of a child injured by a vaccine
Parent of a child injured by an infectious disease

Process and Methods

Assumptions

The Vaccine Safety Working Group made three assumptions that guided their review:

1. The Working Group only considered items in the draft ISO Scientific Agenda directly related to research; it did not consider issues related to ISO's infrastructure in carrying out the Scientific Agenda. A full infrastructure review was not seen as informative for the purposes of research content since the draft ISO Scientific Agenda was not organized

in a way that matched research topics to infrastructure, nor should it have been.

Infrastructure needs will be addressed in the second charge of the Working Group.

2. The Working Group acknowledged that not all of their recommendations to ISO can be carried out without including other disciplines and expertise that are not part of the current infrastructure and mission. This assumption acknowledges the necessary collaboration with other federal agencies to maximize expertise and resources in vaccine safety research. The Working Group frequently found areas of important vaccine safety research in which the National Institutes of Health (NIH), for example, should have a role. The Working Group did not distinguish these areas of research from those exclusive to CDC/ISO and will comment further on the additional infrastructure of the federal vaccine safety system in the second charge.

3. The Working Group will assume a Zero-Based budgeting model. This assumption is based on a request from ISO not to consider resources in evaluation of the draft ISO Scientific Agenda. Therefore, the Working Group adopted a zero-based budgeting model, such that the Working Group did not take into consideration what ISO has invested to date: the Working Group did not consider expenditures from last year in reviewing the draft ISO Scientific Agenda nor did the Working Group take into account what the study will cost and whether ISO has the financial resources to undertake it. In the interest of pure scientific scrutiny, this was felt to be the most appropriate approach.

Content Review Methods

The NVAC Vaccine Safety Working Group met in person three times as a full committee: on April 11th 2008, during which ISO presented the draft Scientific Agenda to the Working Group; on February 4th, 2009, during which the results of the three public meetings were presented to the Working Group; and March 16th, 2009, to engage stakeholders in a discussion of gaps and prioritization criteria. The entire Working Group also met monthly by teleconference. To carefully review the content of the draft ISO Agenda, the Working Group divided into four subgroups, each of which focused on one research topic (Specific Vaccine Safety Questions, Vaccines and Vaccination Practices, Special Populations, or Clinical Outcomes) and 1-2 capacity topics (VAERS Infrastructure, VSD Infrastructure, Epidemiologic and Statistical Methods, Laboratory Methods, Genomics, Case Definitions, or Clinical Practice Guidance). Research topics and capacity topics were paired in an attempt to complement each other. The Working Group chair assigned Working Group members to subgroups based on their individual expertise or members self-assigned based on interest. Subgroup composition was guided by expertise. Each subgroup elected a leader to help guide discussion and met by teleconference approximately 1-3 times per month between April 2008 and February 2009 to evaluate their focused topics in the draft ISO Scientific Agenda.

During the course of subgroup and larger Working Group calls, the Working Group discussed progress and challenging issues, and they did significant information gathering from ISO core staff and partners who were asked to participate on calls to respond to specific questions. Partners included CISA investigators, the Brighton Collaboration Secretariat, VSD biostatisticians, VAERS affiliates, and Department of Defense (DoD) Vaccine Healthcare Centers. Initial drafts of this report were internally peer reviewed and revised.

Public and Stakeholder Input Methods

From the beginning of the NVAC Working Group review process, there was a strong commitment by the Working Group to hear from the public and stakeholders about their views on and priorities for vaccine safety research. The U.S. Department of Health and Human Services (HHS) and the National Vaccine Program Office (NVPO) committed to leading public engagement activities around the draft ISO Scientific Agenda and contracted with the Keystone Center, a third party, neutral non-profit organization, to assist in planning and execution. Working Group members Tawny Buck, Trish Parnell, and Jim Mason participated in a Steering Committee on public engagement that also included staff from NVPO, ISO, ASTHO, NACCHO, and the Keystone Center to design the public and stakeholder input process.

Public and stakeholder input was solicited in four ways (Figure 1): (1) day-long community meetings were held in Birmingham AL (12/13/08), Ashland OR (1/10/09), and Indianapolis IN (1/17/09), (2) a Writing Group (described below) met in Salt Lake City, UT (2/20/09-2/22/09), (3) one stakeholder meeting was held in Washington, D.C. (3/16/09), and (4) written comments were solicited by two notices published in the Federal Register. The community meetings focused on identifying participants' concerns with vaccine safety and important values or factors to be used in prioritizing the Scientific Agenda; Working Group members were present at each community meeting. The Writing Group, comprised of 28 stakeholders, Working Group members, and federal officials, developed draft materials of gaps⁵ and prioritization criteria⁶ intended for a larger group of stakeholders to comment on. Both of these documents were reviewed by stakeholders and discussed during an open meeting of the NVAC Vaccine Safety Working Group on March 16, 2009. The criteria suggested by the public participants at the community meetings and further developed by the Writing Group were used

with a few modifications by the Working Group to rank the research priorities. Additional description of the public engagement activities and the results of the activities are available in the Keystone Center Report (not yet available). Written comments were solicited through a Federal Register Notice for two separate thirty-day periods from anyone who wished to submit. The first occurred from January 2 to February 2, 2009, and requested public input on the draft ISO Scientific Agenda itself, values related to vaccine safety research prioritization, and any other issues related to vaccine safety.⁷ NVPO received 91 comments (available for public viewing online),⁸ many with topics for additional research and personal stories, which were given in entirety to the Working Group and presented in summary on February 4, 2009. The second solicitation will occur from mid-April to mid-May 2009, and requests input on this draft Report to ISO. A schematic diagram of the public engagement process is presented in Figure 1.

The concerns and values heard most frequently by community members and stakeholders were compiled by the Keystone Center and are listed in Appendix 2. This input was compared with topics already in the draft ISO Scientific Agenda and recommendations being developed by the Working Group.

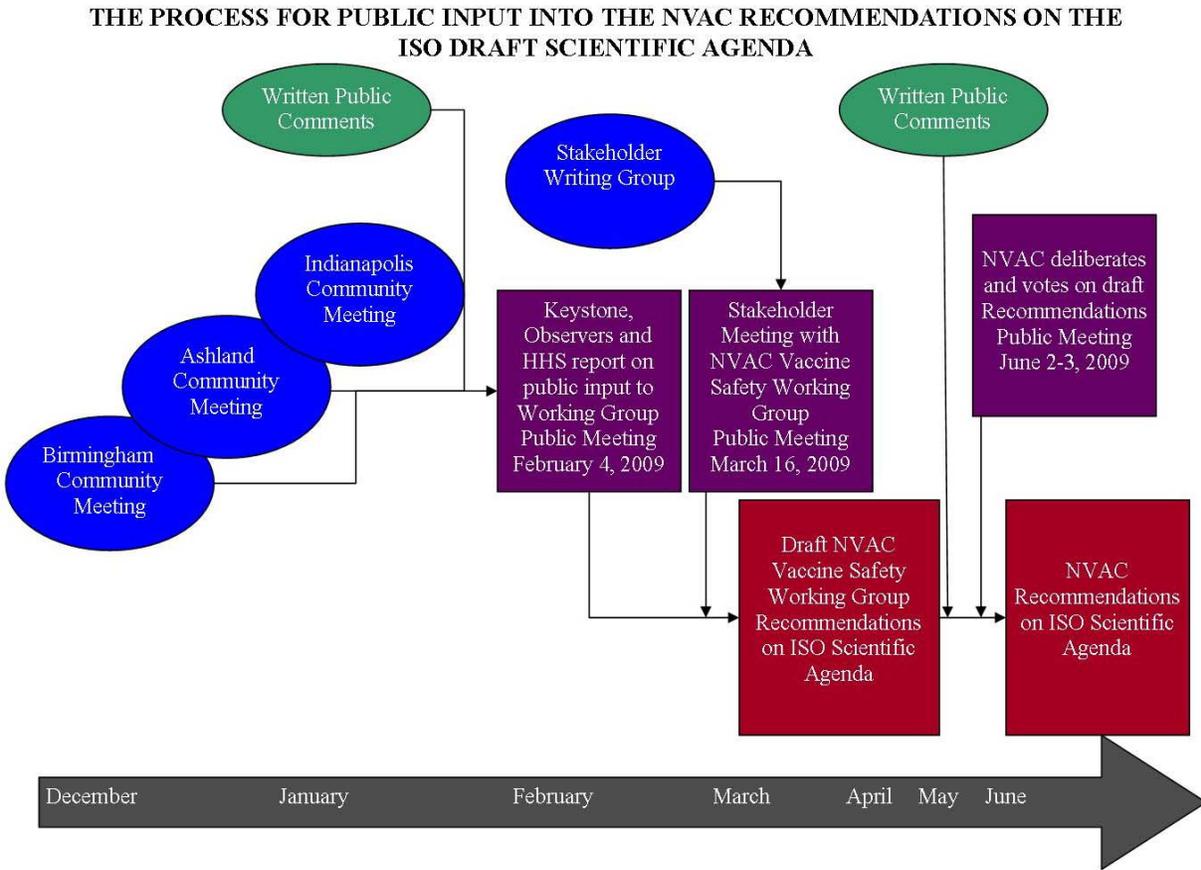


Figure 1. The Process for Public Input (April 2008-June 2009) into the NVAC Recommendations on the draft ISO Scientific Agenda

Prioritization Methods

Prioritization of the items in the draft ISO Scientific Agenda was made difficult by the varying degree of specificity of the agenda items, particularly the absence of specific hypotheses and qualitatively different categories. Only Specific Vaccine Safety Questions were prioritized. Topical categories B-D (Vaccines and Vaccination Practices, Special Populations, and Clinical Outcomes) require formulation into specific hypotheses before prioritization criteria can be applied.

The criteria shown in Figure 2 were used to prioritize the draft ISO Scientific Agenda. These prioritization criteria were based partially on suggestions made by ISO on the April 11, 2008 NVAC Safety Working Group meeting and values that were identified through a series of public meetings. Based on this information, NVPO worked with the Keystone Center to draft prioritization criteria that were discussed by the Salt Lake City Writing Group. The Writing Group revised the Keystone Center document and the revised document was widely distributed prior to a March 16, 2009, NVAC Safety Working Group Stakeholder Meeting. A broad range of stakeholders commented upon the draft Writing Group document. After considering the input compiled by the Keystone Center, the Working Group finalized a set of criteria and used them to prioritize the draft ISO Scientific Agenda items so that prioritization decisions were made in a consistent and transparent fashion.

The following general principles were followed:

- In order to limit the need to prioritize scientific research, resources for vaccine safety studies should be increased.
- Resources should be allocated to achieve maximum impact.
- It is understood that ISO will be flexible and responsive to new scientific and policy questions and issues that emerge within the 5-year window covered by this Agenda.
- It is recommended that ISO will assess whether the study is within its scope. If it is not, ISO is recommended to refer the issue to NVPO for action elsewhere in the vaccine safety system.
- ISO should convene working groups of internal and external experts to identify specific testable hypotheses within Categories B – D that can be studied.

Step 1: What to Do					Step 2: How to Do It	
Criteria	Significance of the Exposure to a Vaccine	Burden of the Adverse Health Event Following Immunization	Public Concern	Scientific Concern and Degree to which Science Warrants Further Study*	Impact on Policy	Feasibility
Issues to Consider	<ol style="list-style-type: none"> 1. Number of people who receive the vaccine(s). 2. Receipt of vaccine by infants or children. 3. Receipt of vaccine by other vulnerable populations. 4. The vaccine(s) is/are mandatory or universally recommended. 	<ol style="list-style-type: none"> 1. Severity of the health event including acute and chronic disability, treatability, and preventability. 2. Frequency of the health event. 3. Increasing incidence of the health event 	<p>Magnitude of public concern about a possible link between vaccination and the adverse health event. Concrete measures of magnitude such as survey data, refusal/delay rates, etc. should be used.</p>	<ol style="list-style-type: none"> 1. Strength 2. Consistency 3. Specificity 4. Temporality 5. Biological gradient 6. Biological Mechanism 7. Coherence 8. Experiment 9. Analogy 	<p>A study is likely to have a significant impact on the understanding of this issue, influence vaccine policy decision making, and enhance trust and confidence in the vaccine program.</p>	<ol style="list-style-type: none"> 1. Methodological feasibility 2. Ethical feasibility 3. Cost of the study and impact on the ability to do other studies (including opportunity costs) 4. Optimal sequencing with other potential studies that may be done by groups other than ISO.

* Scientific Concern and Degree to which Science Warrants Further Study is based on the Bradford-Hill causality criteria.

Figure 2. Prioritization criteria used by the Vaccine Safety Working Group.

Description of Issues to Consider when Applying Prioritization Criteria (see Figure 2)

1. Significance of Exposure

Issues to consider when evaluating the significance of exposure include the number of people receiving the vaccine, typically estimated by the size of the population recommended by the Advisory Committee on Immunization Practices (ACIP) to receive the vaccine and vaccine coverage among that population. Given societal values, vaccination of infants, children, and

other vulnerable populations should be given additional consideration when prioritizing vaccine safety research. Additionally, vaccines that are mandated by states and/or are universal ACIP recommendations should be given additional preference when prioritizing vaccine safety research. Not only are mandates and universal recommendations strongly associated with vaccine coverage, state mandates diminish parental autonomy and universal ACIP recommendations connote a standard of care and endorsement by CDC.

2. Burden of Adverse Health Event Following Immunization

Issues to consider when evaluating the burden of the health event following immunization include the severity of the event, the frequency of the event, and the overall incidence of the event. This criterion assumes that the adverse health event was temporally related to the vaccine (the event happened after receipt of the vaccine) but whether or not the vaccine caused the event is not yet known (see scientific concern criteria). Information gained from public engagement activities indicated a preference for studying severe but rare adverse events over common but mild adverse events, though both categories of adverse events were considered important for study. Additionally, studying common adverse events may be more feasible than studying very rare adverse events and may provide insight into rare adverse events if biological mechanisms are related or shared.

3. Public Concern

Issues to consider when evaluating public concern include the prevalence and strength of the concern among the public. This information may be gained through qualitative research such as focus groups and public engagement activities, by quantitative research such as surveys including the attitudinal module of the National Immunization Survey (NIS), as well as information shared by stakeholders representing segments of the public. It is important for

research to be conducted to identify parental and public concerns to inform the prioritization of research.

4. Scientific Concern and Degree to which Science Warrants Further Study

Scientific concern and the degree to which scientific considerations warrant further study is intended to measure how much is known by science and whether scientists believe a particular study would provide important information to fill gaps in knowledge, and whether the current state of scientific knowledge allows the development of a specific, testable hypothesis or whether other studies need to be done first. The issues to be considered in assessing the state of existing scientific evidence on whether a particular vaccine causes a particular adverse event are based on the Bradford-Hill causality criteria.⁹ The Bradford-Hill criteria assist in assessing the state of the current scientific body of evidence, which may help in assessing whether or not the science warrants more study in this area. The application of these criteria will depend upon the specific topic and the type of scientific study being considered; some criteria may be more relevant than others. For example, if the existing science has clearly demonstrated that all of these criteria have been met, there would be little added value in repeating studies exploring epidemiological associations between the exposure (vaccine) and health outcome (adverse health event).

However, even if causality has not been shown in existing studies in some populations, a study exploring other populations, such as different ethnic groups or groups with underlying genetic disorders or who may be genetically susceptible, may still be appropriate. The most fruitful areas for further research may be where some Bradford-Hill criteria have been met (such as a temporal relationship described through a study of a case series) and a plausible biological mechanism. In this case, studies to look at the strength and consistency of association may be warranted. On the other hand, in a situation where all or most of the Bradford-Hill criteria have

been met (either demonstrating that the vaccine is or is not causing the adverse health outcome) additional scientific study may not be considered a priority. In such a situation, if the public or other stakeholder groups have continued to express concern it may be more appropriate to consider enhanced communication of existing science. Information assisting application of this set of scientific criteria to evaluate the priority of vaccine safety studies can also be informed by the views of scientists regarding how important such studies would be.

5. Impact on Policy

Issues to consider when evaluating the impact of vaccine safety studies on public policy include the extent to which the findings of such a study are likely to have a direct impact on issues such as vaccine recommendations or public confidence in the immunization program. Safety studies for vaccines that are currently recommended for routine use clearly have the greatest likelihood for impacting current usage recommendations; however, at times it may be important to study a historical vaccine safety issue that may have an important impact on public confidence in the vaccine program.

6. Feasibility

For studies that are considered a priority using the aforementioned criteria, it is important to consider how feasible it would be to conduct such a study. Factors to consider when evaluating the feasibility include how well studies could be designed to answer the research question, to what degree there are ethical challenges in conducting the study, the cost of the study and consideration of opportunity costs, and if the study is sequenced appropriately (are there other areas of research that must be done first to adequately answer this question). How feasible a study is should not dictate how important it would be to answer the specific research question, however priority studies that have major feasibility impediments need to have such obstacles

identified and overcome whenever possible and appropriate. In some situations, poor feasibility may impact the conduct of such studies or prohibit studies from being conducted.

Application of Prioritization Criteria

The Working Group applied the prioritization criteria for each research item in the Specific Vaccine Safety Questions section of the draft ISO Scientific Agenda. The Working Group attempted to prioritize sections B-D (Specific Vaccine Safety Questions, Vaccines and Vaccination Practices, Special Populations, and Clinical Outcomes) but was unable to do so because of the breadth and lack of specificity of these topics. There are some or even many high priority items that fall under the topic categories but they need further specification for prioritization, so the list of “high” priority items is far from complete. Importantly, issues such as cost and incremental cost to acquiring new data were not considered, although these are necessary factors for ultimate decisions about vaccine safety research. For these reasons, the Working Group considers their priority designations as a starting point for ISO to deliberate further.

Working Group members individually prioritized each criterion for each question, designating a level of priority (high, moderate, or low priority) for each of the five criteria in Step 1, and determination of feasibility (yes or no) for the criterion in Step 2. Each rating of high, medium, or low was assigned a value of 3, 2, or 1, respectively. The mean scores were calculated for each question across the five Step 1 Criteria for every Working Group member, and then the median was identified. The medians for each question were then graphed on a scatter plot and three clusters were identified. The median score provided the basis for a final priority designation for each Specific Vaccine Safety Question. The lowest cluster was

designated a low priority, the middle cluster a medium priority, and the highest cluster a high priority.

Draft ISO Scientific Agenda Content Review and Recommendations

Overarching Issues

The Working Group identified a number of overarching issues while reviewing the draft ISO Scientific Agenda:

Constraints of looking at draft ISO Scientific Agenda in isolation and need to include other partners

Although the Working Group did not do an organizational review of ISO, it was clear that ISO would greatly benefit from, and will only be successful, if it has input from and collaboration with other offices within CDC and other federal agencies, particularly NIH and FDA. As discussed in the Assumptions (page 15), the Working Group did not distinguish important vaccine safety studies for which ISO is the primary group from those that should include substantial participation by offices and agencies.

Emphasis on prevention, and when prevention is not possible, amelioration of vaccine adverse events

The focus of the draft ISO Scientific Agenda is on post-adverse event studies; little attention is given to studies that would help predict the risk of adverse events before the exposure to the vaccine and to prevent the adverse event (primary prevention). A fundamental principle in

vaccine safety research should be to prevent vaccine adverse reactions whenever possible, and if that is not possible, to ameliorate the effects of the adverse reaction (secondary prevention).

General Recommendations on the draft ISO Scientific Agenda

Revision of the ISO Scientific Agenda

The Working Groups ability to comment on the broad topical categories was limited by the lack of specific hypotheses in categories B-D (Vaccines and Vaccination Practices, Special Populations, and Clinical Outcomes). The ISO Scientific Agenda requires the development of research questions for these categories that include the relevant exposures, populations and clinical outcomes to be studied. Importantly, the Working Group was unable to prioritize these areas but does not discount that there may be high priority items that are not currently formulated as Specific Vaccine Safety Questions. **(1) The Working Group recommends ISO develop the research topic sections of Vaccines and Vaccination Practices, Special Populations, and Clinical Outcomes to consist of testable research questions that can be prioritized.**

On-going development of the ISO Scientific Agenda

In addition to specific research questions for categories B-D, the ISO Agenda will also need to specify study designs to address specific research questions. Multiple studies might be required to answer complex research questions. Further work needs to be done to better define these points. In addition, since vaccine safety science and community concerns are constantly changing, there will need to be a process of continuous updating and reprioritization of the ISO Scientific Agenda. The ISO Scientific Agenda should be used as a benchmark to measure the progress of ISO in meeting its research goals. An independent and transparent scientific review of the ISO Scientific Agenda will assist in optimizing vaccine safety scientific research, and it

may enhance public trust and confidence in vaccine safety research done by ISO. **(2) The Working Group recommends periodic external review of VSD and CISA research and the ISO Scientific Agenda more broadly.**

On-Going Public Engagement into ISO vaccine safety research

The Working Group has found the public and stakeholder engagement process to be informative and constructive to their deliberation on the draft ISO Scientific Agenda. Public and stakeholder input and values have contributed to identifying gaps in the draft ISO Scientific Agenda and prioritization of Agenda items. Engaging the public and stakeholders in a participatory process may also improve trust and confidence in the federal vaccine safety program. President Obama has called for a transparent, participatory and collaborative government, stating “Public engagement enhances the Government’s effectiveness and improves the quality of its decisions.”¹⁰ Continued public engagement on ISO vaccine safety research is consistent with this guidance. **(3) The Working Group recommends ISO regularly engage the public and stakeholders as ISO conducts research, interprets the findings from their studies, and revises their research agenda.**

Proposal to study the past use of scientific data in decision making regarding vaccine safety issues, risk management, and risk perception

In the past, the United States has undergone a number of real and perceived vaccine safety “crises”. Examples include the identification of intussusception following RotaShield and its ultimate withdrawal from the market; concerns about thimerosal in vaccines and its virtual elimination in most childhood vaccines; the apparent increase in risk of Guillain-Barré Syndrome

following swine flu vaccination, which occurred to prevent an epidemic that never happened; and the switch from whole cell pertussis vaccines to acellular pertussis vaccines due to the reactogenicity of whole cell pertussis vaccines. **(4) The Working Group recommends ISO perform case studies of past decision making processes related to vaccine safety issues to identify lessons learned regarding the use of scientific data in decision making.** Analysis should not be limited to cases in which actions were taken, such as a product being pulled or an additive being removed, but to also consider major safety controversies in which no policy change was made and how these controversies evolved.

Vaccine safety in the context of pandemic and biological preparedness

In event of mass vaccination with vaccines not traditionally given to the civilian population, such as anthrax or pandemic flu vaccine, ISO should consider how vaccine safety would be monitored. For example, in the event of mass vaccination there may likely be increased off-label use of vaccines due to non-compliance with contraindications. Safety concerns must also be balanced with risk, which may be different during an infectious pandemic versus a non-infectious biological attack. The FDA has the Emergency Use Authorization (EUA) to allow the use of unlicensed products in the event of an emergency, in which vaccine safety will be of great importance. **(5) To prepare for mass vaccination use of vaccines not traditionally given to the civilian population, the Working Group recommends ISO research in advance approaches to safety monitoring, including the extent to which they would be used off-label or in new populations.** The national smallpox vaccination campaign targeting health care workers and first responders in 2003 provides a good case study in how to 1) balance the risks and benefits of vaccination, and 2) set up a post vaccination adverse event

monitoring system. The lessons from the 2003 smallpox experience would be invaluable in planning a vaccine safety component to a possible future deployment of a novel vaccine.

Other potential study populations could be laboratory workers or the military who receive some of the relevant vaccines in advance of an event, although the extent of off-label use in these populations is likely limited. Collaboration with other partners, such as the DoD, will be important in this endeavor.

Biologic mechanisms of adverse events

As part of determining the likelihood that an adverse event following immunization (AEFI) is caused by a vaccine, it is important to identify the biologic mechanism of the adverse event. An AEFI is an adverse event temporally associated with an immunization that may or may not be causally related to the immunization. A biologic mechanism is an important criterion for investment into vaccine safety research and evaluating causality, and may also lead to development of safer vaccines or vaccination practices. The Working Group has previously stated (page 28) that prevention and amelioration of vaccine adverse events is the priority, and understanding the biologic mechanism is a key strategy to achieving this objective. This topic was originally dismissed by ISO on the grounds that it was not adequately defined. **(6) In order to better understand the biological mechanisms of action responsible for adverse events following immunization, the Working Group recommends that ISO should coordinate with other agencies to support basic research into such mechanisms and that CISA should conduct clinical research on the pathophysiologic basis of adverse events.** ISO may need to use both its internal resources and collaborate with other agencies, such as NIH, for much of this work.

Feasibility study of Vaccinated/Unvaccinated/Alternatively Vaccinated Children

Members of the public, stakeholders, and the Interagency Autism Coordinating Committee (IACC) have articulated interest in a study of vaccinated vs. unvaccinated children to determine if there are differences in health outcomes between groups with varying exposures to vaccines. The Working Group considered drafting a recommendation for an IOM review of the science, epidemiology and feasibility of studies of unvaccinated, vaccine delayed, and vaccinated children. The Writing Group Draft Document on Gaps in Research Agenda⁵ further developed this idea. The Working Group wishes to clarify several points on this topic. First, the Working Group believes that the strongest study design, a randomized clinical trial that includes a study arm receiving no vaccine or vaccine not given in accord with the current recommended schedule, is not ethical, would not pass IRB review, and cannot be done. The type of study that is being suggested would be an observational study of populations looking at natural variation in vaccination schedules including some children where vaccination is declined through parental intent. All children in the study should be recommended to receive the standard immunization schedule. **(7) The Working Group endorses the Writing Group’s recommendation for an external expert committee, such as the Institute of Medicine, with broad methodological, design, and ethical expertise to consider “strengths and weaknesses, ethical issues and feasibility including timelines and cost of various study designs to examine outcomes in unvaccinated, vaccine delayed and vaccinated children and report back to the NVAC.”⁵**

The Working Group does not necessarily agree with all of the language in the Writing Group’s statement, but with its general intent. The process should be open and transparent, engaging

individuals from a broad range of sectors. Considerations as outlined by the Writing Group and modified by the Working Group are as follows:

- This review should consider strengths and weaknesses, ethical issues and feasibility including timelines and cost of various study designs and report back to the NVAC
- Consideration should be given to broad biomedical research including laboratory studies, and animal studies.
- Consideration should also be given to study designs comparing children vaccinated by the standard immunization schedule with unvaccinated children (by parental intention), and possibly partially vaccinated children or children vaccinated by alternative immunization schedules
- Outcomes to assess include biomarkers of immunity and metabolic dysfunction, and outcomes including but not limited to neurodevelopmental outcomes, allergies, asthma, immune-mediated diseases, and other developmental disabilities such as epilepsy, intellectual disability and learning disabilities.
- The inclusion of autism as an outcome is desired. This review should also consider what impact the inclusion of Autism Spectrum Disorders (ASD) as an outcome would have on study designs and feasibility, as referenced in the IACC letter to NVAC.
- This review should be conducted expeditiously, in a transparent manner, and involving broad public and stakeholder input.

Vaccine Safety in Individuals of Different Racial/Ethnic Minorities and Gender

(8) The Working Group recommends that ISO studies are designed and adequately powered to assess the role of differences in race/ethnicity and gender when appropriate.

Factors of race/ethnicity and gender should be considered when designing, implementing and analyzing the vast majority of vaccine safety studies. In 1994, NIH issued guidance on the inclusion of women and minorities in clinical research, emphasizing the importance of examining differential effects in such groups.¹¹ The same attention should be paid to post-licensure surveillance of vaccine safety.

One rationale for studying racial/ethnic populations is that the distribution of alleles that could be involved in differential genetic susceptibility to adverse events may differ by racial/ethnic groups. Thus, differential rates of adverse events by racial/ethnic groups might provide an insight into the genetic bases for susceptibility to adverse events. One example of a differential risk based on race is myopericarditis following smallpox vaccination: there is a higher risk in Europeans and for males, demonstrating that ethnicity can be important. Also, there is emerging literature that genetic differences in certain drug metabolism enzymes have differential expression among different racial/ethnic groups.¹² There could be substantial difficulty researching different racial or ethnic populations using existing safety monitoring infrastructure, because such data are not collected by VAERS or VSD.

How race/ethnicity should be defined is complicated. For example, the current broad categories encompass people who may be very genetically different (e.g. South East Asian, Hispanic, or African American). Race also may be associated with socioeconomic status which in itself can confer susceptibility in numerous ways.¹³ Therefore, it may be clinically important, but race should not be overstated and should be considered carefully in the context of biology and genetic ancestry and socioeconomic status.

The same holds true for women; there is evidence to suggest that women may have immunological differences (e.g. higher prevalence of many autoimmune diseases). Studies have

found differential immune responses to vaccines in women compared to men,¹⁴ and in some cases females may be at greater risk for AEFI, particularly with respect to local reactions.^{15,16,17} There have also been more reports of adverse events to VAERS for females than males (prior to the routine use of Gardasil exclusively among females).¹⁸ This evidence makes heightened attention to vaccine safety in females an important consideration in designing vaccine safety studies.

Risk Communication Research

Communications research is not currently part of the draft ISO Scientific Agenda. However, one of ISO's charges is to "communicate the benefits and risks of vaccines to the public, media, and healthcare communities"³. This charge recognizes that communication activities are critical, and whether or not it is part of the draft ISO Scientific Agenda, CDC needs to assure that there is a robust communication effort including scientific research into understanding and addressing public concerns about vaccine safety. In a 2002 IOM report on multiple immunizations, the committee recommended "that an appropriate panel of multidisciplinary experts be convened by the Department of Health and Human Services. It would develop a comprehensive research strategy for knowledge leading to the optimal design and evaluation of vaccine risk-benefit communication approaches" (p.16).¹⁹ The Working Group reaffirms the IOM recommendation and **(9) recommends ISO have an active role in risk communications research.**

Recommendations on Vaccine Safety Public Health and Clinical Guidance Capacity

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

VAERS is a very important component of the federal vaccine safety system in two broad ways; first for generating signals of AEFI, and second for generating signals to determine whether particular lots of vaccines are more reactogenic than others. The Working Group agrees generally with priority areas outlined in the draft ISO Scientific Agenda but proposes ISO focus on research activities that will enhance these primary aims. Efforts to increase reporting should focus on research activities that improve VAERS capability to detect important signals quickly. Of highest value are reports of important events, defined as those that are severe, unexpected, and/or associated with new vaccines (licensed for less than three years). Severe events may be defined as those that interrupt a patient's usual daily activity and may require systemic drug therapy or other treatment.

(10) The Working Group recommends ISO identify and evaluate ways to (1) increase the number of severe events that are reported to VAERS; and (2) improve the quality and completeness of the reports received. A component of this strategy should include targeting physicians in specialties outside pediatrics to report AEFI and evaluating the impact of such targeted interventions.

The Working Group recommends that ISO identify and evaluate ways to improve the quality of VAERS reports from medical providers. This could include education materials and online technical assistance on filling out VAERS report forms, such as encouraging the use of well-defined medical terms, providing complete vaccination information, including listing all concomitant vaccines given at the index visit, and complete and detailed clinical descriptions of

the AEFI. Complete information greatly enhances the value of submitted reports. A second potential area of emphasis should be to evaluate and improve awareness and reporting practices of physicians in subspecialties who may be consulted regarding complicated and serious events that may follow a vaccination. Physicians who do not administer vaccines but treat clinical syndromes that could be vaccine-related illnesses may be unaware of the VAERS reporting system and may not have access to the person's full immunization history. Evaluating and improving awareness would increase the likelihood that VAERS will detect severe, new or unexpected AEFI that may occur. Additionally, as immunizations are increasingly available to and recommended for adolescents and adults, ISO should evaluate the effectiveness of approaches to make health care providers such as internists, gynecologists, nurse practitioners and physician assistants, who serve adolescents and adults, familiar with VAERS and the importance of reporting appropriate events that occur following immunization.

(11) The Working Group recommends ISO evaluate approaches to follow up individuals reported to VAERS with rare or unusual AEFI for further study, including the collection of biological specimens, when appropriate. VAERS can be an important tool to identify subjects for study, especially for rare vaccine-related conditions. Even at specialty clinics, recruitment for rare conditions can be very challenging. CISA is piloting the use of VAERS to identify subjects for in-depth study and biospecimen collection for the CISA repository and for identifying subjects to recruit for ongoing protocols of specific AEFI (C. Dekker; personal communication; 2008). If VAERS is used as a recruitment tool for patients with important AEFI, it will reinforce the need to increase the reporting of severe events, particularly those associated with new vaccines. The Working Group recognizes privacy considerations will need to be taken into account.

The Draft National Vaccine Plan²⁰ includes the objective 2.2.4: “Improve the process for assessing AEFI signals to determine which signals should be evaluated further in epidemiological and clinical studies.” Considerations that are used to decide which signals should be followed up are not well known outside the vaccine research community. Better understanding by the policy makers, health care providers and the public about how such decisions are made (such as relative importance of biological mechanisms, signal strength, and other metrics) would benefit ISO and their partners by increasing public trust through increased transparency. However, the Working Group understands that strict criteria for which signals to follow up may not be feasible, hence judgment will always be involved.

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

The Working Group recognizes the value of the VSD to vaccine safety research and is supportive of the VSD. Many of the challenges faced by the VSD fall under the category in the draft ISO Scientific Agenda of Epidemiologic/Statistical Methods (see Item C, page 39). There are also issues of support for the VSD infrastructure which will be addressed in the second charge of the Working Group. Therefore, the Working Group has no specific recommendations for VSD here. However, there is one consideration the Working Group would like to raise. The Working Group acknowledges that Rapid Cycle Analysis (RCA), one of the primary analytic tools used by the VSD, is a cutting-edge methodology that has demonstrated its utility through studies such as the safety of the measles-mumps-rubella-varicella (MMRV) vaccine.²¹ However, the potential exists to prematurely report results that could lead to changes in policy based on single studies using relatively new methods. The Working Group urges caution and consideration until RCA has been further refined. At the same time, the VSD represents a wealth

of information and the Working Group strongly encourages publication of all completed studies, including negative studies.

Item C: Epidemiologic and Statistical Methods for Vaccine Safety

The focus of the Working Group's review of epidemiologic and statistical methods was the methods development process for signal detection and hypothesis testing in the VSD. In this section the Working Group is not commenting on the adequacy of the infrastructure of VSD (see above). The VSD is a unique tool for vaccine safety research. By virtue of inherent challenges in immunization safety research (such as rare outcomes, challenges in defining control groups, etc.), the VSD has needed to find and adapt or further develop novel epidemiologic methods. Two examples include the self-controlled case series methods and rapid cycle analysis for near-real time analysis.^{22,23}

The Working Group reviewed how the VSD identifies appropriate existing methodologies for possible application to VSD and the process of adapting these for use. The Working Group supports VSD's continued focus on methods development in two ways. First, the VSD should continue to efficiently survey the epidemiologic and broader literature on an ongoing basis to identify existing methods that could be applied to improve VSD studies. Second, the VSD should continue to assure collaboration between theoretical statisticians and applied statisticians, particularly because new methods are frequently developed by theoreticians.

The VSD utilizes a committee (referred to as the Methods Working Group) with multi-disciplinary membership of academia and VSD statisticians. The committee meets by teleconference regularly to discuss methodologic strategies and holds annual in-person meetings.

In its review, the Working Group determined that this process, which importantly includes the appropriate composition of VSD investigators and academic statisticians, is working well and should be continued. It may also be beneficial for there to be a periodic review of this overall process by an outside group of statisticians.

Item D. Laboratory Methods

The Working Group encountered difficulties in understanding how the ISO plans to implement the laboratory section of their plan. Because the Working Group was not given specific laboratory-based hypotheses to evaluate, the Working Group can only comment generally. The review of the laboratory section was made difficult by the lack of clarity about the inter-relationships among the various entities that could be involved in the laboratory component, including which laboratories should take the lead for various activities. The Working Group recognizes that CDC may not be responsible for, or be able to carry out, all of the laboratory work that might benefit vaccine safety research broadly. Therefore, **(12) the Working Group recommends that the ISO Scientific Agenda specify the laboratory capacity needed for vaccine safety research and identify potential collaborations with other Federal agencies or private entities for those areas where ISO lacks capacity. For the laboratory capacity that CDC/ISO currently possesses, ISO should request input from external experts to advise on the ongoing work and development of new laboratory methodologies.** The Working Group will also comment on the federal infrastructure around laboratory methods in its second charge, which reviews the federal vaccine safety system more broadly.

The laboratory methods section in the draft ISO Scientific Agenda appears to rely on relatively standard molecular biological approaches and does not provide much depth in the area of immunology. Cytokine analyses are proposed, but it is not clear for which studies of AEFI they would be used. Ideally, biological samples would be obtained both pre- and post-vaccination using a standard protocol. Cytokine samples may be hard to collect from rare populations or for rare events.

Immune responses to vaccines likely have considerable inter-individual variation. Some persons under-respond and are consequently not protected against the diseases intended. Other persons may over-respond immunologically, which could theoretically contribute to an adverse event. Immunologic phenotypes that mediate the response to vaccination (cytokine profiles, antibody titres, etc.) may well play a role in AEFI, so studying immunologic phenotypes in the context of adverse events may lead to a deeper understanding of the biological mechanisms behind AEFI. Therefore, **(13) the Working Group recommends ISO study molecular immune responses to vaccinations, including common adverse events such as fever or rash, as subclinical correlates that might predict severe adverse events.** We would encourage the consideration of prospective study designs in this context, as such studies might allow for the prediction and prevention of severe AEFI.

Item E. Genomics and Vaccine Safety

The long-term goals for genomics research laid out in the draft ISO Scientific Agenda are appropriate, but this section requires additional focus. **(14) The Working Group recommends ISO create an expert advisory group on genomics and vaccine safety to assist with developing a focused genomics research agenda and protocol development.** This advisory

group will help ISO strategically approach research in vaccine safety genomics, and should address the issues discussed below.

In reviewing this section of the ISO report, questions emerged in three areas. In summarizing these issues, the Working Group did not attempt to be comprehensive, but to illustrate the type of considerations that might go into a more detailed plan and be guided by an advisory group.

Size and Composition of the Target Population (s) for Genomic Study

1. Types of alleles to be examined. Some evidence already exists that can be used to judge the likelihood of rare alleles that correlate strongly with AEFI vs. more common alleles with weaker correlations to AEFI.²⁴ Given the high rates of immunization coverage in the US population, rare, high-risk alleles for AEFI probably do not exist because studies have not shown familial aggregation of the rare, severe AEFI phenotypes, such as Guillain-Barré Syndrome or HHE. Thus, to the extent that risk alleles for AEFI exist, then these alleles are likely to be modest risk alleles (relative risk below 4). The identification of common alleles associated with modest risk of AEFI will require large numbers of affected cases (ideally, greater than 1000 cases with matched controls). Collecting this many cases can pose a major challenge for rare, severe AEFI such as Guillain-Barré Syndrome or Smallpox vaccine associated myocarditis.
2. Delineation of potentially informative subgroups. Identifying pre-vaccination risk profiles to predict individuals at risk of rare AEFI is prohibitively expensive in the general population. Such studies would be more feasible if analyses were focused on subpopulations that might be expected to have relatively higher rates of adverse events. Examples of these high-risk subpopulations might be siblings of those with adverse reactions, or (for AEFI that have a

plausible autoimmune component, such as GBS) individuals with a family history of autoimmune disease.

3. Consider common, less severe AEFI as proxies for rare, severe AEFI. Achieving adequate sample sizes for genetic analysis might also be achieved through study of less severe but relatively common AEFI as proxies for severe AEFI. To the extent that AEFI such as fever or rash share risk factors with more severe AEFI, these subclinical outcomes could be very useful in the same context that genetic factors influencing cholesterol levels has meaning for clinically overt cardiovascular disease. Moreover, rash and fever are common enough that it may be feasible to study these outcomes prospectively and therefore to collect pre-vaccination samples in a standardized format using other laboratory techniques. Pre-vaccine specimens are of particular value in developing profiles that could be used to screen for individuals at high-risk of AEFI.

Types of Data to Be Collected

In the Laboratory Methods section of the draft ISO Scientific Agenda a biorepository was suggested, and we support this as a foundation for future studies, under the assumption that details of the funding, consent, location and storage issues related can be worked out. In this context, the Working Group members considered several questions that would need to be addressed to maximize the utility of such an effort.

1. Types of biospecimens to be obtained. A variety of biospecimens could be collected in a biorepository, and the biorepository should carefully consider the value of each type of sample before deciding to accept the responsibility of storing it for future studies. Some biological specimens are relatively stable, while others are heavily dependent upon specimen collection procedures. A centralized biorepository will have greatest value for stable biospecimens that are

robust to a variety of collection procedures (e.g. DNA), and can therefore be usefully collected by a repository across multiple, independent studies. Biospecimen types that are more sensitive to protocol/handling (e.g. plasma or RNA) are more effectively collected en masse by a single study under a standardized procedure, but to the extent that a single study collects a large number of such specimens, these could also be usefully stored within the biorepository for future access.

Thus, consideration of additional biological specimens such as whole blood, plasma, serum, saliva, and urine should be part of the planning for the biorepository. Additionally, markers of immune system function and response, such as cytokines and antibody titers, may be important for predicting adverse events. A repository may also be helpful for looking at endophenotypes/intermediary phenotypes, such as cytokine profiles, in conjunction with a core lab that could generate these data on samples stored within the repository.

2. Phenotyping. Ideally, rich covariable data should accompany samples deposited to the repository (records of the SOP under which the samples were collected; demographic variables such as patient age, sex, and ethnicity; clinical course and history; and environmental exposures such as smoking status, etc.), but standardizing these data is very important. The Brighton Collaboration²⁵ provides a very useful context for standardized AEFI phenotype definitions, so each sample submitted should be accompanied by all relevant Brighton phenotypes.
3. Environmental data. Given that adverse events resulting from a single genetic locus are probably unlikely, a combination of multiple genetic and environmental factors seems likely for AEFI. This makes important the measurement of environmental exposures and the consistent definitions of these measurements across research study sites.

Types of Analyses to Be Performed

The draft ISO Scientific Agenda is not explicit about the types of genomic research being considered. The Working Group has some concern of the utility of a biological repository to look at a Genome-Wide Association Study (GWAS) of serious adverse events because of low sample number. A proper genome-wide association analysis requires around 1,000 cases, which can be difficult to obtain for rare adverse events. As an example, in collecting specimens for myopericarditis following smallpox vaccination, after 3-4 years investigators obtained less than 100 cases for study (C. Carlson; personal communication; 2008). Thus, the number of samples obtainable for severe AEFI may be more appropriate for proteomic or expression studies, rather than genomic analysis. From the perspective of understanding AEFI, careful expression/proteome profiling of a modest number of samples is more likely to be valuable than genome-wide association analysis of an inadequate number of samples, and we recommend consideration of such studies for rare AEFI.

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

In this section the Working Group is not commenting on the adequacy of the infrastructure of the Brighton Collaboration. However, the Working Group in a future report will be examining the vaccine safety system more broadly and this subsequent review will consider infrastructure issues related to the Brighton Collaboration.

The Working Group appreciates the need for standardized case definitions in vaccine safety studies and commends the ISO, Brighton Collaboration and their worldwide network of volunteers for undertaking this task. In addition to case definition development, the Secretariat facilitates evaluation of case definitions for their sensitivity and specificity, and implementation of the definitions for standardization in studies around the world. Because the Working Group

was asked to comment on the draft ISO Scientific Agenda and ISO's research priorities, the Working Group's review of the Brighton Collaboration was limited to the aspects for which it is appropriate for ISO to conduct further research. **(15) The Working Group recommends ISO focus Brighton Collaboration research efforts on the adequacy of the case definitions and their usefulness in ongoing safety research conducted by VSD and other groups.**

Particular research questions to focus on in the program evaluation include evaluating the process by which outcomes are prioritized for development of case definitions, how such case definitions are developed, the timeliness of the development process, and the use of the final products by the VSD and other groups. Assessing usage of definitions and reasons for failure to use case definitions is important to improve the utility of Brighton Collaboration case definitions. One approach may be a survey of academic, industry, and governmental researchers on how the Brighton Collaboration case definitions perform in practice and suggestions for modification or improvement.

Since the conception of the Brighton Collaboration in 2000, the group has developed 23 case definitions that have been published for general use.²⁶ Case definitions are targeted for development by the needs of researchers. While the use of a variety of volunteers for development of case definitions allows the Brighton Collaboration to tap into a wide range of knowledge and experience with these topics, it can also make the maintenance of a consistent organizational structure difficult. Because the general timeline for developing a case definition is at least 18 months, (J. Gidudu; personal communication; 2008) an additional factor in usage may be the time currently required to develop a case definition. Methods to expedite the process without compromising the quality of the definition should be evaluated.

The Working Group found one recently published study of evaluation for sensitivity and specificity of Brighton Collaboration case definitions.²⁷ Such studies are important and should be continued. Acknowledging there is not a mechanism present for case definition evaluation through ISO's other entities (VSD, CISA, and VAERS), the Working Group advises increased collaboration for evaluation of the Brighton Collaboration case definitions within ISO. This collaboration could further enhance utilization of standardized case definitions across ISO.

Item G. Vaccine Safety Clinical Practice Guidance

The Working Group is concerned with two types of clinical guidance; 1) guidance to the clinician regarding how to document and report the AEFI and 2) how the clinician should manage the case to treat the AEFI and to prevent additional complications. **(16) The Working Group recommends ISO create a single written guide dedicated to comprehensive clinical guidance, including identification, reporting, and treatment, for vaccine adverse events.**

While some of this information is in the Pink Book²⁸ and Red Book²⁹, the Working Group identified a need for an authoritative single report or book in which all proven and accepted vaccine adverse events are cataloged with their diagnostic features, management recommendations, options for treatment, possible complications, and guidance for reporting AEFI, including what data to report. At the very least, this report should include management for all adverse events that have been identified on the Vaccine Injury Table³⁰ by the Vaccine Injury Compensation Program or by the Institute of Medicine. Well-identified signals with evidence for a causal relationship should also be included, with a distinction made between more or less well established possible vaccine adverse events. Such a report should also include mention of AEFI that have been shown to not be causally related to vaccination and a summary

of the evidence. Additional important information for such a report would be contact information for important resources, such as CISA, DoD's Vaccine Healthcare Centers, manufacturers and their registries, indexed by adverse event, vaccine, and manufacturer. This report should be updated annually.

Developing, implementing, and evaluating treatment protocols for persons experiencing adverse events caused by vaccines should be a priority. CISA was noted as the primary entity to research and provide clinical guidance, both in terms of studies and for patient consult, and algorithms for treatment of patients following vaccine adverse events. The Working Group agrees that the priority scientific areas and goals outlined in the draft ISO Scientific Agenda are very important. In addition, due to a theoretical hypothesis but without any data to support it, **(17) the Working Group recommends ISO include the vaccination of children with mitochondrial disease, mitochondrial dysfunction, and other metabolic diseases as a priority scientific area for clinical guidance.** The Working Group acknowledges that natural infections may cause regression in children with metabolic disorders, and considering that vaccines may elicit similar immunologic responses as infections, further research is needed.

Additional Considerations

Although the scope of the first charge to NVAC was restricted to making recommendations about the draft ISO Scientific Agenda, the Working Group feels it imperative to comment on the collection of immunization history for the NIH-lead National Children's Study (NCS). The Working Group understands that currently, the NCS protocol does not include collecting provider-verified immunization records. Because of poor validity of parent-maintained records, this will represent a tremendous impediment to any vaccine safety research

conducted in the context of the NCS. The Working Group strongly urges further consideration of incorporating provider-verified immunization histories into standard NCS data collection.

Recommendations on 5-Year Research Needs

The NVAC was asked to provide input on the content and prioritization of the draft ISO Scientific Agenda; however, several portions of the draft agenda did not include testable hypotheses or well-defined research questions. Specifically, sections of the draft ISO Agenda were devoted only to exposures (Vaccines and Vaccination Practices), outcomes (Clinical Outcomes) or populations (Special Populations). It is necessary for these components to be fully developed into testable research questions in order for specific feedback on content and prioritization. Consequently, comments on Vaccine and Vaccination Practices, Clinical Outcomes and Special Populations are limited. Discussion in this report is limited to those items for which the Working Group has specific recommendations; items without discussion below (A-II, A-IV, A-V, A-VI, B-VI, C-I, C-II, C-IV, C-V, C-VII, D-I, D-II, D-III, D-V, D-VI, D-VII, D-VIII) were considered appropriate by the Working Group for study and were prioritized.

Item 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)?

The Working Group agrees question A-I is appropriate for study. This issue has most recently been highlighted with Menactra (MCV4)^{31,32} and is currently under investigation through VSD and CISA. However, the Working Group is not aware of other signals of GBS following vaccination other than for influenza and meningococcal conjugate vaccine, and so

recommends the question be better specified. **(18) The Working Group recommends question A-I be reworded to read, “Are influenza vaccines or meningococcal conjugate vaccine [MCV4] associated with increased risk for Guillain-Barré Syndrome (GBS)?”**

A-III: Is exposure to thimerosal associated with increased risk for clinically important tics and/or Tourette syndrome?

The Working Group agrees question A-III is appropriate for study. The IOM has looked at thimerosal twice. In 2001, the IOM concluded there was inadequate evidence to assess a causal relationship with broad neurological outcomes.³³ In 2004, the IOM looked only at autism and did not re-examine other neurodevelopmental outcomes.³⁴ Since then, there have been a few studies that have suggested that thimerosal exposure may be a risk factor for tics.^{35,36,37} The first study, in which there were inconclusive findings, was completed by CDC through VSD. In HMO A, there was a significant increased risk for tics, but not in HMO B. At HMO B, there was a significant increased risk for language delay at 3 months and 7 months, but not at HMO A.³⁵ This study has been criticized for its methods. A second VSD study with improved methods was undertaken, and statistically significant associations with tics and speech/language delays were found.³⁶ Protective associations with thimerosal for other neuropsychological disorders were found as well. A third study in the UK suggested a relationship between thimerosal and tics³⁷.

Because two of the studies above also found associations between thimerosal and speech and language delays^{35,36}, the Working Group felt that these were valid outcomes to pursue further although there are substantial difficulties with defining outcomes of interest. **(19)The Working Group recommends question A-III be expanded to include speech and language delays as potential outcomes of interest.**

The Working Group notes that thimerosal, where present, is now present only in trace amounts in vaccines other than influenza and is still present in most influenza vaccine doses distributed, although thimerosal-free influenza vaccine presentations are available. This makes studies of thimerosal challenging. The study, “Early thimerosal exposure and neuropsychological outcomes at 7 to 10 years,”³⁶ found increasing exposure to mercury both prenatally and postnatally to have no consistent pattern of effect, with few significant associations being both beneficial and deleterious. The Working Group was impressed by the study design and that the data are publicly available but feels further evidence on whether any associations suggested are real, spurious, or artificial is needed. Methodological considerations regarding certain aspects of how the data were analyzed (failure to evaluate the cumulative exposure to thimerosal and methyl mercury prenatally and thimerosal after birth, and cumulative prenatal and infant exposure; and liberal criteria for inclusion of covariates in the models) should be readdressed to better elucidate any possible associations between thimerosal and neurodevelopmental delays. **(20) The Working Group recommends ISO sponsor an external and multidisciplinary reanalysis of data published in 2007 by Thompson et al. ISO should formulate and issue an RFP pursuant to awarding a contract to an independent organization to reanalyze the data. Additionally, the Working Group recommends that ISO work with VSD sites involved in this study to use information in the available medical records (thimerosal exposure and appropriate health outcomes) of children selected for the study and examine who did and did not agree to participate in order to assess the potential for selection bias.**

The Working Group also notes significant public concern (Appendix 2) related to thimerosal, particularly with respect to autism/ASD. The Working Group is assured by the many

epidemiological studies of the effects of mercury exposure done in a variety of populations, which have demonstrated that thimerosal in vaccines is not associated with autism spectrum disorders in the general population.^{35,37,38,39,40,41,42,43}

A-VII: Are varicella vaccines (varicella and MMRV) associated with increased risk for clinically important events related to varicella vaccine virus reactivation?

The Working Group agrees question A-VII is appropriate for study. There have recently been reported cases of vaccine virus reactivation that occurred a relatively long time following vaccination.⁴⁴ This is new information and the group agreed it was important to look at. As Zostavax is a more concentrated formulation of Varivax, zoster should also be studied. **(21) The Working Group recommends ISO expand A-VII to include zoster vaccine.**

Gaps in Specific Vaccine Safety Questions

A-VIII: Do multiple vaccinations increase risk of immune system disorders?

(22) The Working Group recommends adding multiple vaccination and immune system disorders as a Specific Vaccine Safety Question. This question, limited to low birth weight/pre-term infants, was included in an interim list of specific questions that ISO considered (K. Broder; personal communication; 2008). In a report by IOM Immunization Safety Review Committee in 2002, the IOM examined the possibility that multiple immunizations may increase risk of heterologous infections (rejected), increase risk of type 1 diabetes mellitus (rejected) and increased risk of allergic diseases - asthma (inadequate evidence).¹⁹ Since publication of that report, there are several new publications in the literature with respect to diabetes and asthma, most of which dealt with full-term infants or children.^{45,46,47,48,49,50,51} The Working Group does

not recommend limiting the study to premature and low birth weight infants (also Special Population C-I), but acknowledges that this population may be at increased risk and should be included in any studies.

This addition addresses one aspect of the vaccination schedule. A driving force of this recommendation is to suggest ISO consider studies to examine more alternative immunization schedules vs. the current one. Of interest, the IOM Immunization Safety Review Committee that reviewed this issue “encourages an exploration of the merits of accommodating requests for alternative vaccine-dosing schedules and development of appropriate clinical guidance for any such alternatives” (p.13) though cautions that this might contribute to lower immunization coverage and consequently increased morbidity and mortality from vaccine-preventable illnesses. Variations in the actual immunization scheduled used by parents due to flexibility in the existing immunization schedule, practice patterns and parental preferences may offer the possibility to study immune system disorders and other relevant vaccine safety outcomes.

Item B. Vaccines and Vaccination Practices

This section of the draft ISO Scientific Agenda included broad exposures to consider in vaccine safety research, but did not specify outcomes or the details of these topical categories. These topics require additional development to appropriately capture the range of issues encapsulated and worthy of study.

B-I: Bivalent human papillomavirus (bivalent HPV) vaccine (Cervarix)

The Working Group does not believe the topic area B-I is appropriate for study at this time. **(23) The Working Group recommends removing B-I from the Scientific Agenda.**

Cervarix is not yet licensed, making it inappropriate for ISO to be engaged in such research.

This is true also for AS04, which is not yet used in vaccines licensed in the United States. If and when a vaccine with AS04 is licensed, at that point it would be appropriate to include in the ISO Scientific Agenda as a defined research question and the Agenda can be modified at that time.

B-II: Zoster Vaccine (Zostavax)

The Working Group advises against specifying a product without a defined and specific hypothesis or at least a testable research question, and **(24) recommends removing B-II from the Scientific Agenda.** When reference is made to a vaccine when only one product is available for the disease (e.g. zoster), doing so without a research question or a signal runs the risk of raising unnecessary and unwarranted concerns. However, the Working Group does appreciate the value of studying vaccination in the elderly. In order to be comprehensive and capture all individuals for whom Zostavax is currently indicated, the ISO Scientific Agenda should capture all of those individuals for whom the zoster vaccine is recommended, adults over 60 years of age.⁵² **Therefore, (29) the Working Group recommends that under Special Populations, C-III be expanded to include adults aged ≥ 60 years of age** (see page 61).

B-III: Annual influenza vaccination of children and adolescents (trivalent inactivated influenza vaccine [TIV] and LAIV)

The Working Group agrees the topic area B-III is appropriate to study. The Working Group recognizes that with 2009 recommendations for nearly 262 million people to receive the influenza vaccine,⁵³ a significant portion of the population will be exposed to influenza vaccines repeatedly over decades. Given the unprecedented large population use of influenza vaccines

and its extension into new age groups, the Working Group feels that safety surveillance of annual influenza vaccination deserves more attention than a routine activity. The Working Group encourages ISO to monitor potential safety signals using their safety surveillance infrastructures, and if any safety signals arise, active surveillance or ad hoc studies, as appropriate, should be initiated. Other than enhanced surveillance, until signals arise there are no specific safety questions the Working Group recommends researching.

(25) The Working Group recommends ISO prepare a regular summary report on the safety profile of the expanded influenza vaccination program that would be made publicly available. Close surveillance is important to assessing the safety of annual influenza vaccination and could also feed back into safety preparations in the event of emergency use of a new pandemic influenza vaccine.

B-IV: Non-antigen components of vaccines (other than thimerosal or ASO4 in bivalent HPV vaccine)

The Working Group agrees the topic area B-IV is appropriate to study. Although this category requires further definition, the safety of non-antigen vaccine ingredients^{vi} should be carefully assessed. While the FDA licenses individual vaccines, the CDC is responsible for the immunization schedule. **Therefore, (26) the Working Group recommends ISO evaluate cumulative levels of non-antigen component exposure possible through the schedule of recommended vaccinations.** Research here may be linked with research done in the Simultaneous Vaccination research topic (B-V).

^{vi} See Appendix B, Vaccine Excipient & Media Summary in the CDC's Epidemiology and Prevention of Vaccine-Preventable Diseases. Atkinson W, Hamborsky J, McIntyre L, Wolfe S, eds. 10th ed. 2nd printing, Washington DC: Public Health Foundation, 2008.

An expert panel, such as National Toxicology Program, that includes government experts from agencies such as CDC National Center for Environmental Health (NCEH) and Agency for Toxic Substances and Disease Registry (ATSDR), U.S. Environmental Protection Agency (EPA), National Institute of Environmental Health Sciences (NIEHS), FDA and U.S Consumer Product Safety Commission (CPSC) should develop a carefully designed screening process that places ingredients into groups that are: (1) minimal concern; (2) potential for concern and deserving of research; (3) in need of further risk analysis and consideration for risk management. Industry may be able to provide information to refine initial assessments. The determination of which ingredients have a higher priority for study should be based both on the intrinsic nature of the compound and potential levels of exposure.

ATSDR exposure guidelines may not be applicable to vaccine routes of administration. ATSDR toxicological profiles review all routes of exposure for which there are data, including via injection. If ATSDR does not have such data, then the route has not been studied. It may, then, be a priority for study, depending on what is known about the toxicokinetics of the ingredient.

Risk assessment should consider other environmental exposures. Cumulative exposures should be considered when environmental exposures are comparable to vaccine ingredient exposures. For a cumulative assessment, exposures in the ambient environment should be considered, including the same substance or substances that are structurally similar and may possibly share a similar mode of action. There may also be situations where consideration of interactions between vaccine ingredients and environmental exposures is worthwhile.

Examining the exposure to non-antigen components of vaccines as administered by the immunization schedule may facilitate identification of outcomes to be studied based upon known biological mechanisms and adverse health outcomes.

(27) The Working Group recommends removing the parenthetical statement “other than thimerosal or ASO4 in bivalent HPV vaccine.” As with B-I, ASO4 is not licensed and thus should not be included in the ISO Scientific Agenda.

The Working Group also notes a previous NVAC report, “Dose Optimization Strategies for Vaccines: The Role of Adjuvants and New Technologies,”⁵⁴ and reaffirms NVAC’s previous safety recommendation:

“Support long-term safety studies for vaccines containing novel adjuvants

1. Designs for safety evaluation of repeated and concurrent exposure to adjuvanted vaccines and longer-term safety data are needed.
2. Search for early biomarkers of adjuvant activity/toxicity to aid in clinical study evaluation and post-marketing surveillance studies” (p12)

This recommendation applies to ISO once novel adjuvants are licensed.

B-V: Simultaneous vaccination

The Working Group agrees the topic area B-V is appropriate to study. Simultaneous vaccination is an important feature of the vaccination schedule and the safety of such use should be looked at carefully. The working group recognizes the efficiency and cost effectiveness of simultaneous vaccination and the probability of missed vaccinations if more visits were required to receive all recommended vaccinations. Although the compatibility of candidate vaccines with routinely used vaccines is evaluated during development, the potential exists for complex

interactions amongst vaccines that may not be apparent until large scale use post-licensure, such as with the use of MMRV.²¹ The Working Group urges ISO to determine if the current recommended vaccination schedules, which are based on an age range for each vaccine, result in sufficient variation in the sequence in which vaccines are administered in practice to allow for an assessment of the safety of simultaneous vaccination. If sources of information regarding the simultaneous administration of vaccines, such as vaccine registries or VSD, do not adequately track such data then the Working Group advises extension of the information requested from providers.

B-VII: Off label use of vaccines

Generally speaking, the definition of off label use is the use of a product for an indication not in the FDA approved labeling.⁵⁵ It should be recognized that usage recommendations issued by the ACIP, and potentially other professional organizations, may differ in some specifics from the approved labeling. Such differences would be considered off label use. This definition is insufficient to consider all possible off-label use, so the Working Group is only able to give general recommendations. It is first necessary for ISO to better assess the landscape of off-label use of vaccines. **(28) The Working Group recommends off-label vaccination practices should be characterized and quantified. The Working Group further recommends that off-label use recommendations sometimes included in ACIP statements that are not indicated on the label should be considered as research agenda topics for the ISO.** The Working Group recognizes that it is the appropriate responsibility of the ACIP to use its judgment in including such recommendations and believes it is the appropriate role of the ISO to address the safety of such use. Off-label use should be considered in the context of alternative

vaccination schedules that may currently be practiced, use in contraindicated persons, alternative routes of administration, and partial dose regimes. With respect to alternative vaccination schedules, like simultaneous vaccination (see above), if there is sufficient variability in administration timing in clinical practice, the Working Group advises ISO to begin preliminary analysis of data from sentinel vaccine registry sites, the NIS, and VSD sites. If preliminary analysis suggests that there is sufficient variation in the timing of vaccine administration, ISO should consider outcomes of interest and consider appropriate studies. It may be that sources of information regarding off-label use of vaccines, such as vaccine registries or VSD, do not adequately track such data, in which case the Working Group recommends extension of the information requested from providers.

B-VIII: Vaccine-drug interactions

The Working Group agrees the topic area B-VIII is appropriate to study. Simultaneous administration of a vaccine and one or more drugs could have an impact in two directions: the drugs could impact the safety or utility of a vaccine or the vaccine could impact the metabolism of a drug. There are few examples of possible interactions currently reported in the published literature.^{56,57} The Working Group notes ISO should consider the safety of live vaccines when used in patients receiving immunomodulatory drugs such as anti-TNF. While such administration would be rare, safety monitoring during such occasions will be helpful. Vaccines containing pharmacologically active adjuvants or immunomodulators such as TLR agonists should also be monitored for adverse drug interactions, as the adjuvant could induce changes in drug compartmentalization or clearance.

Item C. Special Populations

The Special Populations category requires additional development. The Working Group considered a population to be “special” if there is an underlying genetic, medical, or contextual condition that could theoretically predispose that group to differential risks and benefits to vaccination compared with the general population.

Without exposures and outcomes to consider in the context of each special population, the Working Group is very limited in its ability to comment. The ISO Scientific Agenda should be more explicit in the linkage between the identification of special populations and the risk of AEFI. As with the agenda in general, there was no overarching framework for considering the special populations in the research agenda beyond some very specific hypotheses that might be relevant to one or more groups. It was strongly felt that a key element in identifying special populations for the purposes of studying immunization safety is to specify the basis for the designation of special population. Is there evidence to suggest that this population is at increased risk for AEFI? What is the potential biological mechanism (or mechanisms) that raises concerns specific to vaccination? Does a population have a particular risk window that is important for consideration, such as times of substantial neurodevelopment? As stated before, one important principle for designation as a high priority for vaccine safety research would be the potential to enhance capacity to prevent adverse events whenever possible, and when not possible, to ameliorate post-vaccination events. A more thorough analysis laying out the rationale for the selection of these populations would help to link the research in this area to the potential to achieve these goals. Additionally, the Working Group advises ISO to collect data to quantify the extent to which vaccine adverse events are more likely in these special populations to inform the development of research agendas for such populations.

The Working Group agrees that all of the special populations listed in the draft ISO Scientific Agenda (premature and low birth weight infants, pregnant women, adults aged ≥ 65 years, persons with primary immunodeficiency, persons with secondary immunodeficiency, persons with autoimmune disorders, and children with inborn errors of metabolism) are important for ISO to study in that these groups are at increased risk for many adverse health outcomes. Additionally, there are other groups that may be at increased risk for adverse events, or may respond to dosing regimens differently that were not included in this list.

The Working Group would like to distinguish these special populations from those that may be under-represented in clinical trials and warrant additional study for that reason. Some groups may fall into both of these categories, such as pregnant women. When a population is under-represented in a clinical trial yet will be a recipient of the vaccine, there should be an extension of surveillance in phase IV trials in these groups.

C-III: Adults over 65 years of age

The Working Group agrees population C-III is appropriate to study. The major issues for this population include the potential increase in risk of adverse events to new vaccines, issues with boosters, waning immunity from live vaccines, and travel vaccines; responses to vaccines and/or immunosenescence may be different in the elderly population, which justifies the need for additional study in these areas. Zostavax was recently licensed and is the only live viral vaccine given to the elderly. **(29) Because ACIP recommendations for Zoster vaccine include adults aged ≥ 60 years, the Working Group recommends that the Special Populations category C-III be extended to include adults aged ≥ 60 years** (also see page 54).

C-VI: Persons with autoimmune disorders

The Working Group agrees population C-VI is appropriate to study in several contexts, including the administration of vaccines to affected individuals, the study of correlations between vaccine exposure and autoimmune disease onset, and the possibility that predisposition to autoimmune disease might indicate more global immune dysregulation and thereby increase risk of AEFI. As most autoimmune disorders do not present in the first few years of life, during which the majority of immunizations are given, family history of autoimmune disorders should also be a consideration in the prospective identification of individuals at high risk of developing autoimmune disorders. **(30) The Working Group recommends C-VI should be expanded to include persons with autoimmune disorders or a well-documented family history of autoimmune disorders.**

Gaps in Special Populations

C-VIII: Children with siblings or parents who experienced an adverse event following immunization

(31) The Working Group recommends adding children with siblings or parents who experienced an adverse event following immunization. One of the greatest challenges faced in studies of rare AEFI is that it is very difficult to collect samples from cases pre-vaccination. This severely limits opportunities to develop profiles that might be used to prevent AEFI by screening out children at elevated risk of AEFI. A special population that might allow for prospective studies of this sort is the siblings of AEFI cases. While it is unlikely that a sib will also experience a severe AEFI, it is entirely plausible that subclinical AEFI (fever, rash) might be enriched, or immune response phenotypes (antibody titers or cytokine profiles) might be more enthusiastic in this population, due to shared genetics with the AEFI cases. If so, then

prospective study of these traits in the sibs may provide valuable insights into idiosyncratic factors that predispose individuals to severe AEFI.

C-IX: Children who have previously suffered an adverse event following immunization who are recommended to receive additional doses in a booster regime

(32) The Working Group recommends adding children who have previously suffered an adverse event following immunization who are recommended to receive additional doses in a booster regime. Some children who suffer from an AEFI may be able to be vaccinated with additional doses and/or other vaccines. To best protect these children from vaccine-preventable infectious diseases, continued vaccination is preferable when possible. Given the priority to prevent AEFI whenever possible, it is important that these children are vaccinated safely and when appropriate, as determined by additional research. Studying these children may also inform more basic questions about immune responses in AEFI-susceptible children.

Item D. Clinical Outcomes

The Clinical Outcomes section did not include defined research questions, or relevant exposures and populations to be studied. Important questions include, what is the incidence, prevalence, and mortality for each of the clinical conditions listed? How much of the morbidity of each is due to known versus idiopathic causes? It is necessary for these components to be fully developed into testable research questions in order for specific feedback on content and prioritization. The Working Group felt it was outside of its mandate to develop these components of research questions into testable research questions.

Furthermore, the Working Group felt the Clinical Outcomes section consisted of a listing of research projects already underway by CDC and did not adequately provide a research agenda for the future. While the Working Group agrees that these research areas are appropriate to continue, they do not present a way forward. Given these limitations, the Working Group generally agrees that the listed Clinical Outcomes topics seem appropriate, but cannot comment on the completeness of the list.

Acknowledging perceived public concern over autism spectrum disorder, the Working Group will comment specifically only on D-IV: Neurodevelopmental disorders, including ASD. The relationship between vaccine exposure and autism/ASD is an area of intense public interest. As stated previously, the Working Group is assured by the many epidemiological studies that have demonstrated no association between vaccination and autism spectrum disorders in the general population.

The 2004 IOM review of links between MMR vaccine and thimerosal-containing vaccines and autism concluded that “the evidence favors rejection of a causal relationship at the population level between MMR vaccine and autistic spectrum disorders (ASD).”³⁴ While the IOM rejected the overall hypothesis that the rise in reported ASD is attributable to vaccines or thimerosal, the IOM committee also concluded that “further research on the possible occurrence of ASD in a small number of children subsequent to MMR vaccination is warranted.” This caveat is of particular import in light of recent case studies and research reports⁵⁸ around the incidence of mitochondrial dysfunction in children with an ASD phenotype by DSM-IV Criteria; mitochondrial dysfunction is rare at the population level, but carries an established risk of brain damage subsequent to infectious disease. Thus, a small and specific subset of the general population (such as those with mitochondrial dysfunction) may be at elevated risk of reduced

neurological functioning, possibly including developing ASD, subsequent to live virus vaccination. Mitochondrial dysfunction provides an example of a small subset of the general population within which vaccination may be a risk factor for neurological adverse events; however, the size of the subpopulation is too small for population-level epidemiological studies to have sufficient power and precision to detect such a risk factor.

In the context of vaccination research, the ASD clinical subset of particular interest is regressive autism, wherein children achieve normal developmental milestones in language and social skills until 18-24 months of age, and subsequently lose those milestones or experience a plateau in terms of their development. This subset has been estimated at 15% of ASD in several studies.^{59,60,61,62} The temporal occurrence of this regression and the vaccination schedule is not evidence of a causal relationship, but regressive autism does fit the recommendations of the IOM committee for further research in rigorously defined subsets of ASD. Studies in this subpopulation might involve comparison of immune cytokine profiles between regressive and non-regressive ASD to screen for differential immune system profiles, or prospective vaccination response profiling in siblings of children with regressive ASD, a subpopulation who are at higher risk (somewhere between 3%-35% increased risk, depending on the study and number of siblings affected)⁶³ of ASD than the general population.

Another clinically refined phenotypic definition of a subset of ASD that might be usefully studied is the intersection of ASD cases with Brighton Case definition AEFI, such as fever, febrile seizure, or hypotonic-hyporesponsive episode (HHE). Some overlap will be expected by coincidence, and given the publicity of the autism-vaccination debate it will be hard to avoid reporting bias, but it would be worthwhile to assess whether Brighton AEFI correlate with risk of ASD. On a molecular level, it might be feasible to compare ASD cases with history

of AEFI against cognitively normal controls with a similar history of AEFI, to assess whether there are significant differences in immune response profiles between groups.

In summary, the conclusions of the IOM committee in 2004 regarding the lack of a population-level relationship between MMR and thimerosal-containing vaccines and ASD risk remain sound, but recent developments around mitochondrial dysfunction reinforce the importance of studies of AEFI in rigorously defined subsets of the ASD spectrum. Vaccination almost certainly does not account for the recent rise in ASD diagnoses; however, public concern regarding vaccines and autism coupled with the prevalence and severity of ASD warrant additional study in well defined subpopulations.

Priorities and Setting the Way Forward

While significant progress has been made in developing the 5-year draft ISO Scientific Agenda, substantial work remains to be done. For all research topics, specific research questions need to be developed by multi-disciplinary experts. As research topics gain specificity, the prioritization criteria will need to be reapplied to appropriately reflect the vaccine, population, and outcome of interest. The Working Group previously stated that there will undoubtedly be specific testable hypotheses that develop out of the three topical areas (B-D) that will fall into the high category, so the priorities given in Table 3 is far from complete.

Using the prioritization methodology described above (see page 21), the Working Group provided some guidance on research priorities. Due to the general nature of most research topics, it was challenging and inappropriate to provide rank order. Rather, the Working Group has organized the Agenda's research topics as high, moderate, and low. Three questions fell into the high category, four into the medium category, and one into the low category. The

prioritization exercise, while useful, has some clear limitations. For example, Specific Vaccine Safety Question A-III emerged as a low priority using the Prioritization Criteria. However, there may be some factors that could influence later priority or a decision to conduct the study in advance of higher priority studies, including that data may be obtained easily and inexpensively using previously collected data, as recommended by the Working Group. This example merely highlights the limitations of the prioritization exercise done by the Working Group and the need to consider the prioritization ratings as a start for further discussion and deliberation by decision makers.

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Table 3. Summary of the Vaccine Safety Working Group’s prioritization of Specific Vaccine Safety Questions in the draft ISO Scientific Agenda. Percentages represent proportion of Working Group members who rated a question in the high, medium, or low category for each of the Step 1 criteria, and a yes or no in the Step 2 criteria.

Question	Rating	Significance of the Exposure to a Vaccine	Burden of the Adverse Health Event Following Immunization	Public Concern	Scientific Concern and Degree to which Science Warrants Further Study	Impact on Policy	Feasibility	Final Rating
3 Is exposure to thimerosal associated with increased risk for clinically important tics, Tourette syndrome and/or speech and language delays?	High	7%	14%	43%	0%	0%	Yes: 77% No: 23%	Low
	Medium	7%	36%	43%	43%	21%		
	Low	86%	50%	14%	57%	79%		
2 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?	High	62%	14%	7%	27%	14%	Yes: 93% No: 7%	Medium
	Medium	23%	64%	43%	27%	36%		
	Low	15%	21%	50%	45%	50%		
7 Are varicella vaccines (varicella, MMRV, and Zoster) associated with increased risk for clinically important events related to varicella vaccine virus reactivation?	High	86%	14%	7%	23%	7%	Yes: 93% No: 7%	Medium
	Medium	14%	29%	29%	46%	57%		
	Low	0%	57%	64%	31%	36%		
4 Are acellular pertussis vaccines associated with increased risk for acute neurological events, particularly hypotonic-hyporesponsive episodes (HHE)?	High	100%	29%	21%	0%	7%	Yes: 79% No: 21%	Medium
	Medium	0%	21%	36%	69%	21%		
	Low	0%	50%	43%	31%	71%		

Table 3 Continued.

Question	Rating	Significance of the Exposure to a Vaccine	Burden of the Adverse Health Event Following Immunization	Public Concern	Scientific Concern and Degree to which Science Warrants Further Study	Impact on Policy	Feasibility	Final Rating
6 Is combination measles, mumps, rubella, and varicella vaccine (MMRV) associated with increased risk for febrile seizure and if so are there sequelae?	High	77%	8%	8%	15%	31%	Yes: 100% No: 0%	Medium
	Medium	15%	38%	69%	62%	31%		
	Low	8%	54%	23%	23%	38%		
1 Are influenza vaccines and meningococcal conjugate vaccine [MCV4] associated with increased risk for Guillain-Barré Syndrome (GBS)?	High	93%	57%	14%	21%	43%	Yes: 100% No: 0%	High
	Medium	7%	21%	43%	29%	43%		
	Low	0%	21%	43%	50%	14%		
8 Do multiple vaccinations increase risk of immune system disorders?	High	100%	31%	79%	0%	64%	Yes: 77% No: 23%	High
	Medium	0%	38%	14%	50%	14%		
	Low	0%	31%	7%	50%	21%		
5 Is immunization associated with increased risk for neurological deterioration in children with mitochondrial dysfunction?	High	86%	36%	93%	29%	62%	Yes: 100% No: 0%	High
	Medium	7%	36%	7%	57%	31%		
	Low	7%	29%	0%	14%	8%		

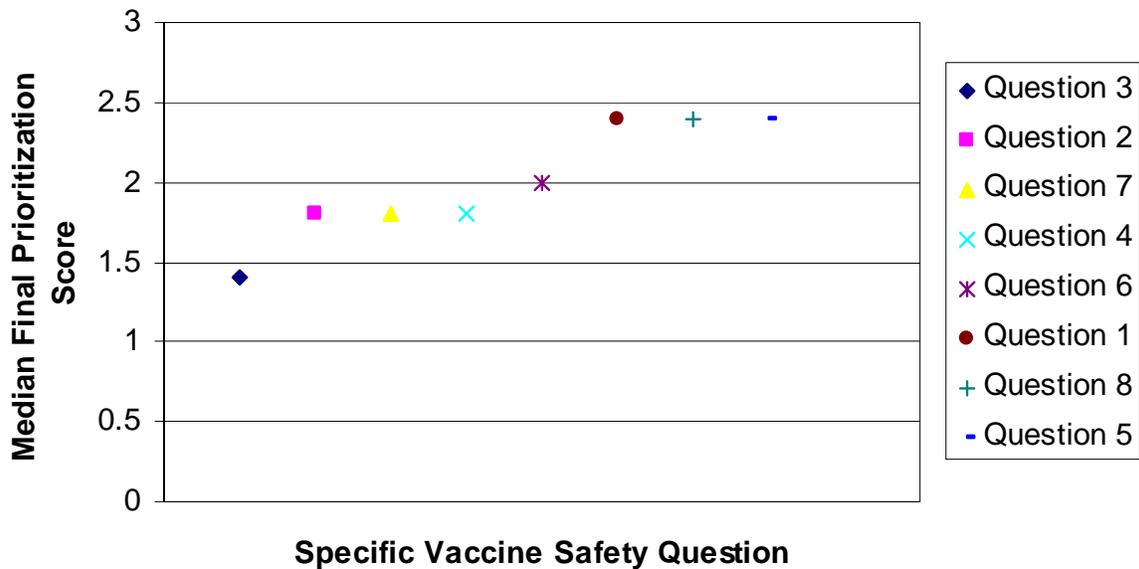


Figure 3. Scatter plot of median prioritization scores for Specific Vaccine Safety Questions 1-8, ranked by mean score.

The Working Group is aware of budget limitations of the ISO, which operates on an annual budget of approximately \$21.7 million (Figure 4)⁶⁴. This budget is insufficient to meet the needs of vaccine safety research; in addition to providing additional funds to ISO, interagency collaboration is critical in domains that span agency interests and duties. Additionally, there is a strong need for a federal vaccine safety research agenda that encompasses research undertaken by non-ISO CDC offices, FDA, and NIH. A federal vaccine safety research agenda requires increased collaboration and coordination between all federal agencies with a stake in vaccine safety. Further discussion of the federal safety system will resume in the second phase of the Working Group’s charge, to “review the current federal vaccine safety system and develop a White Paper describing the infrastructure needs for a federal vaccine safety system to fully characterize the safety profile of vaccines in a timely manner,

reduce adverse events whenever possible, and maintain and improve public confidence in vaccine safety.⁴³

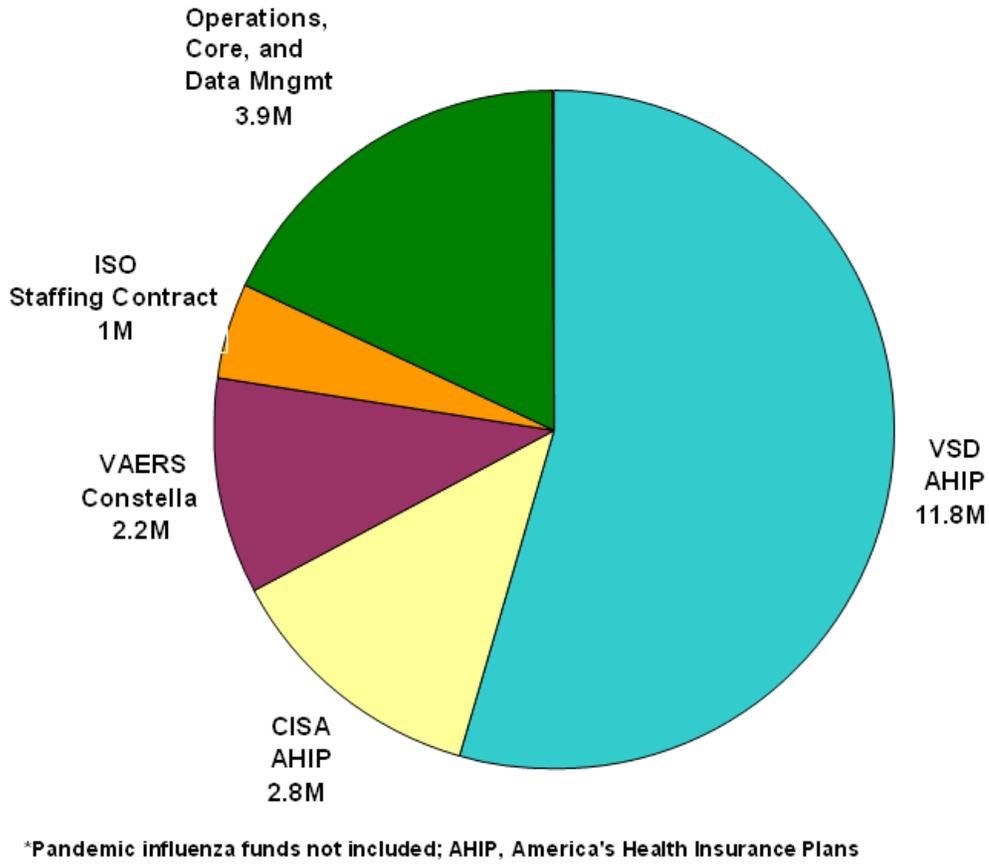


Figure 4. ISO/CDC Vaccine safety expenditures for fiscal year 2008 (total \$21.7 million)⁶⁴

Appendix 1. Major elements of the CDC/ISO draft Scientific Agenda³

The objective of the ISO Scientific Agenda was to develop a comprehensive 5-year ISO Scientific Agenda with extensive expert input. The scope of the Agenda included vaccine safety research, selected surveillance, and selected clinical guidance activities 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.⁶⁵

The draft ISO Scientific Agenda recommendations are organized into three categories:

1. Respond to emerging issues and conduct core, required scientific activities
2. Enhance vaccine safety public health and clinical guidance capacity in 7 areas
3. Address 5-Year research needs

Responding to emerging issues and conducting core, required scientific activities was defined as follows:

- Monitor the safety of all newly licensed and ACIP recommended vaccines and previously licensed vaccines with new recommendations
- Respond to new vaccine safety concerns and hypotheses, which are not always predictable
- Provide technical consultation to CDC immunization experts and other stakeholders for collaborative and multidisciplinary scientific activities
- Prepare to monitor vaccine safety in the event of a mass vaccination campaign or other vaccine safety emergency

As these activities are required, ISO did not ask the NVAC Vaccine Safety Working Group to comment on the appropriateness of research in emerging issues and core activities.

Enhance vaccine safety public health and clinical guidance capacity in 7 areas:

The following seven areas were highlighted in the draft ISO Scientific Agenda:

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

Address 5-Year research needs

ISO proposed 30 research needs for the next five years. The 30 research needs were organized as Specific Vaccine Safety Questions (7 items), or thematic areas (23 items). The thematic were Vaccines and Vaccinations (8 items), Special Populations (7 items), and Clinical Outcomes (7 items). ISO acknowledged content overlap in the list of thematic areas, and did not specify hypotheses or study designs.

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 disorders?
- A-VI Is combination measles, mumps, rubella, and varicella (MMRV) vaccine associated with increased risk for febrile seizure and, if so, are there sequelae?
- 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 and AS04 adjuvant 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 related to postimmunization fever
- D-VIII Postvaccination syncope and sequeale

Appendix 2. Overlap of Issues Identified by the Public and/or Stakeholders, the draft ISO Scientific Agenda, and the NVAC Vaccine Safety Working Group Recommendations

Issue or Question Identified by the Public and/or Stakeholders*♦	Draft ISO Agenda (Truncated)	NVAC Safety Working Group Draft Recommendations and Considerations (as of April 14, 2009)
<p>Ingredients <i>Are there harmful ingredients?</i> ♦</p> <ul style="list-style-type: none"> • mercury/thimerosal*♦ • additives • aborted fetal cells • preservatives • eggs • aluminum and other adjuvants ♦ • anti-freeze • gelatin and gelatin proteins ♦ • adventitious agents ♦ • formaldehyde ♦ • newly-released types of adjuvants ♦ 	<p>A-III: Thimerosal and increased risk for clinically important tics and/or Tourette syndrome</p> <p>B-IV: Non-antigen components of vaccines (ingredients)</p> <p>B-V: Simultaneous vaccination</p>	<p>(19) The Working Group recommends question A-III be expanded to include speech and language delays as potential outcomes of interest.</p> <p>(20) The Working Group recommends ISO sponsor an external and multidisciplinary reanalysis of data published in 2007 by Thompson et al.</p> <p>(22) The Working Group recommends adding multiple vaccination and immune system disorders as a Specific Vaccine Safety Question.</p> <p>(26) The Working Group recommends ISO evaluate cumulative levels of non-antigen component exposure possible through the schedule of recommended vaccinations.</p>

* Issues marked with an asterisk (*) indicate those that were also raised in comments received through the Request for Information (RFI).

♦ Issues marked with a diamond indicate those that were raised by stakeholders participating in the Writing Group meeting in Salt Lake City and/or the March 16 Stakeholder meeting in Washington, D.C. in both of these meetings, participants were asked to identify *any additional gaps* that were missing from what the public, RFI, and NVAC Safety Working Group had previously identified.

Issue or Question Identified by the Public and/or Stakeholders*♦	Draft ISO Agenda (Truncated)	NVAC Safety Working Group Draft Recommendations and Considerations (as of April 14, 2009)
<p>Schedule/Number of Vaccines Given*♦ <i>Should we be worried about the # of vaccines given?</i> (especially to babies)</p> <ul style="list-style-type: none"> Do vaccinations that occur during key developmental periods have increased risk of adverse effects? ♦ 	<p>A-VI: MMRV vaccine and risk for febrile seizure</p> <p>B-IV: Non-antigen components of vaccines (ingredients)</p> <p>B-V: Simultaneous vaccination</p> <p>C: Special Populations</p>	<p>(7) The Working Group endorses the Writing Group’s recommendation for an external expert committee, such as the Institute of Medicine, with broad methodological, design, and ethical expertise to consider “strengths and weaknesses, ethical issues and feasibility including timelines and cost of various study designs to examine outcomes in unvaccinated, vaccine delayed and vaccinated children and report back to the NVAC.”</p> <p>(22) The Working Group recommends adding multiple vaccination and immune system disorders as a Specific Vaccine Safety Question.</p> <p>(26) The Working Group recommends ISO evaluate cumulative levels of non-antigen component exposure possible through the schedule of recommended vaccinations.</p> <p>Consideration of whether a population has a particular risk window that is important for consideration, such as times of substantial neurodevelopment (p. 59)</p>

Issue or Question Identified by the Public and/or Stakeholders**	Draft ISO Agenda (Truncated)	NVAC Safety Working Group Draft Recommendations and Considerations (as of April 14, 2009)
<p>Do vaccines trigger or contribute to any of the following diseases or conditions?</p> <ul style="list-style-type: none"> • Autism* • Asthma • Diabetes • Arthritis • Autoimmune disease • Afebrile seizure♦ • Neurological problems, mental illness, or neurodevelopmental delays (including speech/language delays, PPD, NOS, sleep disorders, schizophrenia, bipolar disorder, ADD, ADHD) ♦ 	<p>A-II: Live, attenuated influenza vaccine and asthma</p> <p>A-V: Neurologic deterioration in children with mitochondrial dysfunction</p> <p>D-I: Autoimmune diseases</p> <p>D-IV: Neurodevelopmental disorders, including autism spectrum disorder</p>	<p>(7) The Working Group endorses the Writing Group’s recommendation for an external expert committee, such as the Institute of Medicine, with broad methodological, design, and ethical expertise to consider “strengths and weaknesses, ethical issues and feasibility including timelines and cost of various study designs to examine outcomes in unvaccinated, vaccine delayed and vaccinated children and report back to the NVAC.”</p> <p>(19) The Working Group recommends question A-III be expanded to include speech and language delays as potential outcomes of interest.</p> <p>(20) The Working Group recommends ISO sponsor an external and multidisciplinary reanalysis of data published in 2007 by Thompson et al.</p> <p>(22) The Working Group recommends adding multiple vaccination and immune system disorders as a Specific Vaccine Safety Question.</p> <p>(30) The Working Group recommends C-VI should be expanded to include persons with autoimmune disorders or a well-documented family history of autoimmune disorders. Autism research should be focused and based on improved understanding of biology and phenotype with consideration of subpopulations (p. 64-65)</p>

Issue or Question Identified by the Public and/or Stakeholders**	Draft ISO Agenda (Truncated)	NVAC Safety Working Group Draft Recommendations and Considerations (as of April 14, 2009)
<p>Combinations of Vaccines** <i>Should we worry about the combination of vaccines and their interaction in our bodies?</i></p> <p>Combinations of Ingredients* <i>Should we worry about the combination and interaction of ingredients in our bodies?</i></p>	<p>B-IV: Non-antigen components of vaccines (ingredients)</p> <p>B-V: Simultaneous vaccination</p>	<p>(7) The Working Group endorses the Writing Group’s recommendation for an external expert committee, such as the Institute of Medicine, with broad methodological, design, and ethical expertise to consider “strengths and weaknesses, ethical issues and feasibility including timelines and cost of various study designs to examine outcomes in unvaccinated, vaccine delayed and vaccinated children and report back to the NVAC.”</p> <p>(22) The Working Group recommends adding multiple vaccination and immune system disorders as a Specific Vaccine Safety Question.</p> <p>(26) The Working Group recommends ISO evaluate cumulative levels of non-antigen component exposure possible through the schedule of recommended vaccinations.</p>

Issue or Question Identified by the Public and/or Stakeholders*♦	Draft ISO Agenda (Truncated)	NVAC Safety Working Group Draft Recommendations and Considerations (as of April 14, 2009)
<p>Side Effects (short-term, long-term) <i>Do we really know what the long-term health effects are of vaccination?</i> <i>How are adverse reactions treated?</i> ♦</p>	<p><i>Contained throughout the ISO Agenda (Focus in sections A and D)</i></p>	<p>(7) The Working Group endorses the Writing Group’s recommendation for an external expert committee, such as the Institute of Medicine, with broad methodological, design, and ethical expertise to consider “strengths and weaknesses, ethical issues and feasibility including timelines and cost of various study designs to examine outcomes in unvaccinated, vaccine delayed and vaccinated children and report back to the NVAC.”</p> <p>(16) The Working Group recommends ISO create a single written guide dedicated to comprehensive clinical guidance, including identification, reporting, and treatment, for vaccine adverse events.</p> <p>Developing, implementing, and evaluating treatment protocols for persons experiencing adverse events caused by vaccines should be a priority (p. 48)</p> <p>The Working Group strongly urges further consideration of incorporating provider-verified immunization histories into standard NCS data collection (p. 48)</p>

Issue or Question Identified by the Public and/or Stakeholders*♦	Draft ISO Agenda (Truncated)	NVAC Safety Working Group Draft Recommendations and Considerations (as of April 14, 2009)
<p>Interactions with medicines, allergies, cosmetics, personal care products, environmental factors <i>How do vaccines interact with the other things we are putting in or on our body? ♦</i></p>	<p>B-VIII: Vaccine-drug interactions</p>	<p>(26) The Working Group recommends ISO evaluate cumulative levels of non-antigen component exposure possible through the schedule of recommended vaccinations.</p> <p>The Working Group strongly urges further consideration of incorporating provider-verified immunization histories into standard NCS data collection (p. 48)</p>
<p>Do vaccines cause the disease they target <i>Does the flu vaccine cause the flu? (as one example)</i></p>	<p>A-VII: Varicella vaccine virus reactivation</p>	<p>(21) The Working Group recommends ISO expand A-VII to include zoster vaccine.</p>
<p>Study of Vaccinated vs. Un-Vaccinated* <i>What are the health differences between people who have been vaccinated and those who have not been vaccinated?</i></p>		<p>(7) The Working Group endorses the Writing Group’s recommendation for an external expert committee, such as the Institute of Medicine, with broad methodological, design, and ethical expertise to consider “strengths and weaknesses, ethical issues and feasibility including timelines and cost of various study designs to examine outcomes in unvaccinated, vaccine delayed and vaccinated children and report back to the NVAC.”</p>
<p>Are vaccines effective?</p> <ul style="list-style-type: none"> • <i>Do vaccines really work?</i> • <i>Should titer test to determine if people need boosters? ♦</i> 		<p>Not a vaccine safety question</p>
<p>Do we have ample supply of vaccines? <i>Do we have enough vaccines for those who need it?</i></p>		<p>Not a vaccine safety question</p>

Issue or Question Identified by the Public and/or Stakeholders*♦	Draft ISO Agenda (Truncated)	NVAC Safety Working Group Draft Recommendations and Considerations (as of April 14, 2009)
<p>Are some people pre-disposed to having adverse effects?*</p> <ul style="list-style-type: none"> • Can we identify vulnerable individuals early using biomarkers? ♦ • Does a personal or family history of autoimmune disease increase vulnerability to adverse effects? ♦ • Does a personal or family history of allergies increase vulnerability to adverse effects?♦ • Do the children of fully immunized mothers have a weaker immune response than children of mothers who received the wild virus? ♦ • Children with a personal or family history of allergy or autoimmune disease? ♦ • Children who have had a previous adverse event who are scheduled for re-vaccination? ♦ • Persons or families who have had specified previous illnesses that may be related to vaccination more broadly that could be contraindications? ♦ • Children with a concurrent acute illness, with or without fever. ♦ • Children in families where a sibling has had an adverse effect. 	<p>A-V: Neurological deterioration in children with mitochondrial dysfunction</p> <p>All of Category C: Special Populations (C-I through C-VII)</p>	<p>(13) The Working Group recommends ISO create an expert advisory group on genomics and vaccine safety to assist with developing a focused genomics research agenda and protocol development.</p> <p>(30) The Working Group recommends C-VI should be expanded to include persons with autoimmune disorders or a well-documented family history of autoimmune disorders.</p> <p>(31) The Working Group recommends adding children with siblings or parents who experienced an adverse event following immunization.</p> <p>(32) The Working Group recommends adding children who have previously suffered an adverse event following immunization who are recommended to receive additional doses in a booster regime.</p>

Issue or Question Identified by the Public and/or Stakeholders**	Draft ISO Agenda (Truncated)	NVAC Safety Working Group Draft Recommendations and Considerations (as of April 14, 2009)
<p>Does race or gender affect how well a vaccine will work, or what any adverse events might be? Are there differences in the rates of vaccine adverse events among ethnic groups? *</p>	<p>All of Category C: Special Populations (C-I through C-VII)</p>	<p>(8) The Working Group recommends that ISO studies are designed and adequately powered to assess the role of differences in race/ethnicity and gender when appropriate</p>
<p>Are people with immune compromised systems more at risk for adverse events?</p>	<p>C-IV: Persons with primary immunodeficiency C-V: Persons with secondary immunodeficiency</p>	
<p>Are the elderly at greater risk for adverse events? *</p>	<p>B-II: Zoster vaccine C-III: Adults aged ≥ 65 years</p>	<p>(29) Because ACIP recommendations for Zoster vaccine include adults aged ≥ 60 years, the Working Group recommends that the special populations category C-III be extended to include adults aged ≥ 60 years</p>
<p>Are children at certain developmental stages, or in the pre-adolescent, adolescent to young adult spectrum, more at risk for adverse events? *</p>	<p>Special Populations</p>	<p>Consideration of whether a population has a particular risk window that is important for consideration, such as times of substantial neurodevelopment (p. 59)</p>
<p>Are pre-mature babies more at risk for adverse events?</p>	<p>C-I: Premature and low birth weight infants</p>	

Issue or Question Identified by the Public and/or Stakeholders*♦	Draft ISO Agenda (Truncated)	NVAC Safety Working Group Draft Recommendations and Considerations (as of April 14, 2009)
<p>Are pregnant women more at risk for adverse events?</p> <ul style="list-style-type: none"> • Does vaccination of a pregnant women have impacts on fetal development? ♦ 	C-II: Pregnant women	
<ul style="list-style-type: none"> • How are people in the “safety net” population treated? <ul style="list-style-type: none"> • those who do not have regular health care, have poor nutrition and incomplete or nonexistent vaccination records? ♦ 	All of Category C: Special Populations (C-I through C-VII)	
<ul style="list-style-type: none"> • How are people with additional vaccine-environmental exposure treated, i.e. people who use tobacco? ♦ 	All of Category C: Special Populations (C-I through C-VII)	(26) The Working Group recommends ISO evaluate cumulative levels of non-antigen component exposure possible through the schedule of recommended vaccinations.
<ul style="list-style-type: none"> • How are matters handled in cases of errors in the administration of vaccines? ♦ 	Vaccines and Vaccination Practices	

Issue or Question Identified by the Public and/or Stakeholders [♦]	Draft ISO Agenda (Truncated)	NVAC Safety Working Group Draft Recommendations and Considerations (as of April 14, 2009)
<p>Specific questions about:</p> <ul style="list-style-type: none"> • MMR • Gardasil • Flu 	<p>A-II: Live, attenuated influenza vaccine and asthma</p> <p>A-VI: MMRV vaccine and risk for febrile seizure</p> <p>B-I: Human papillomavirus (HPV) vaccines (CervarixTM)</p> <p>B-III: Annual influenza vaccination in children and adolescents</p>	<p>(23) The Working Group recommends removing B-I from the Scientific Agenda.</p> <p>(25) The Working Group recommends ISO prepare a regular summary report on the safety profile of the expanded influenza vaccination program that would be made publicly available.</p>
<p>Treatment of Adverse Reactions[♦]</p>	<p>Clinical Practice Guidance</p>	<p>(16) The Working Group recommends ISO create a single written guide dedicated to comprehensive clinical guidance, including identification, reporting, and treatment, for vaccine adverse events.</p> <p>Developing, implementing, and evaluating treatment protocols for persons experiencing adverse events caused by vaccines should be a priority (p. 48)</p>
<p>Perceptions of Safety[♦]</p>		<p><i>Pertinent to Task II</i></p>
<p>Vaccine Preparation and Administration[♦] (Vaccine delivery system)</p>		<p><i>Pertinent to Task II</i></p>

Issue or Question Identified by the Public and/or Stakeholders**	Draft ISO Agenda (Truncated)	NVAC Safety Working Group Draft Recommendations and Considerations (as of April 14, 2009)
Reasons Families Choose Not to Vaccinate*		(9) The Working Group recommends ISO have an active role in risk communications research. <i>Pertinent to Task II</i>
Capabilities Assessment Regarding: * <ul style="list-style-type: none"> • Reporting* • Infrastructure* • Methodology* 		<i>Pertinent to Task II</i>
Reporting Data** <ul style="list-style-type: none"> • Is the system for reporting adverse events effective? * • Is the data accurate? • Are there ways to improve reporting? • How can reporting and detection of adverse events (common, rare, severe, and mild) be improved? * • Does the reporting system capture both short- and long-term adverse effects? * 		(10) The Working Group recommends ISO identify and evaluate ways to (1) increase the number of severe events that are reported to VAERS; and (2) improve the quality and completeness of the reports received. A component of this strategy should include targeting physicians in specialties outside pediatrics to report adverse events and evaluating the impact of such targeted interventions. (11) The Working Group recommends ISO evaluate approaches to follow up individuals reported to VAERS with rare or unusual adverse events for further study, including the collection of biological specimens, when appropriate. <i>Pertinent to Task II</i>

Issue or Question Identified by the Public and/or Stakeholders**	Draft ISO Agenda (Truncated)	NVAC Safety Working Group Draft Recommendations and Considerations (as of April 14, 2009)
<p>Increasing Transparency* Secrecy of decision making, reporting, and studies</p>		<p>(2) The Working Group recommends periodic external review of VSD and CISA research and the ISO Scientific Agenda more broadly.</p> <p>(3) The Working Group recommends ISO regularly engage the public and stakeholders as ISO conducts research, interprets the findings from their studies, and revises their research agenda.</p> <p><i>Pertinent to Task II</i></p>
<p>Citizen Participation and Oversight* Is there a way to increase citizen interaction, oversight, and dialogue with decision-makers?</p>		<p>(3) The Working Group recommends ISO regularly engage the public and stakeholders as ISO conducts research, interprets the findings from their studies, and revises their research agenda.</p> <p><i>Pertinent to Task II</i></p>
<p>Independent Science*</p> <ul style="list-style-type: none"> • Who’s doing the science? Is it trustworthy? • Worry about the government/ pharmaceutical connections 		<p>(2) The Working Group recommends periodic external review of VSD and CISA research and the ISO Scientific Agenda more broadly.</p> <p><i>Pertinent to Task II</i></p>

Issue or Question Identified by the Public and/or Stakeholders**	Draft ISO Agenda (Truncated)	NVAC Safety Working Group Draft Recommendations and Considerations (as of April 14, 2009)
<p>Good Information How do we identify good, trustworthy information about the benefits, and especially the risks associated with vaccines?</p>		<p><i>Pertinent to Task II</i></p>
<p>Healthcare’s Role in Vaccines</p> <ul style="list-style-type: none"> • How do we ensure that our doctors can spend quality time with us talking about the benefits and risks of vaccination? • Insurance companies roles in vaccines (access, coverage of vaccines, and coverage of consultation hours between doctor and patient). 		<p><i>Pertinent to Task II</i></p>
<p>Parental* and Scientific Concerns Are Important Concerns of parents and of scientists are valid and should be respected.</p>		<p>Prioritization Criteria highlighted dual importance of public and scientific concern (p. 22-25)</p> <p><i>Pertinent to Task II</i></p>
<p>Mandates Mandated vaccinations are of particular concern</p>		<p><i>Pertinent to Task II</i></p>
<p>Manufacturing security <i>Are our vaccines safe from those who want to harm the U.S.?</i></p>		<p><i>Pertinent to Task II</i></p>

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