

Draft NVAC Vaccine Safety Working Group Report

Institute of Medicine
Fourth National Stakeholder Meeting
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Working Group Charge 1

1. Undertake and coordinate a scientific review of the draft ISO research agenda.
Advise on:
 - a. Content of ISO draft research agenda (e.g., are the topics on the agenda appropriate? Should other topics be included?)
 - b. Prioritization of research topics
 - c. Possible scientific barriers to implementing the research agenda and suggestions for addressing them

Working Group Members

Name	Discipline	Group Representation
Andy Pavia	Pediatric and Adult Infectious Diseases, NVAC Member	Academia
Bennett Shaywitz	Neurology	Academia
Chris Carlson	Genomics	Academia
Corry Dekker	Pediatrics, NVAC Member	Academia
Gerald Medoff	Immunology	Professional Organization
Gus Birkhead	Epidemiology, NVAC Member	State Health Department
Jim Mason	Public Health, NVAC Member	CDC Director/ASH
Lance Gordon	Immunology, NVAC Member	Industry

Working Group Members, cont.

Name	Discipline Used for Initial Selection	Group Representation
Lawrence Gostin	Ethics/Law	Academia
Lynn Goldman	Toxicology/Environmental Health	Academia
Marie McCormick	Maternal and Child Health, NVAC member	Academia
Mark Feinberg	Immunology, NVAC Member	Industry
Paul-Henri Lambert	Global aspects of vaccine safety	Professional Organization
Sean Hennessy	Pharmacoepidemiology	Academia
Steve Goodman	Biostatistics	Academia
Tawny Buck	Parent of a child injured by a vaccine	Consumer Groups
Trish Parnell	Parent of a child with an infectious disease, NVAC member	Consumer Groups

Summary of ISO Scientific Agenda

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

ISO Agenda Draft Recommendations

#2: Enhance Vaccine Safety Public Health and Clinical Guidance Capacity in 7 Areas

Item	Capacity Area
A	Infrastructure for Vaccine Safety Surveillance: Vaccine Adverse Event Reporting System (VAERS)
B	Infrastructure for Vaccine Safety Surveillance and Research: Vaccine Safety Datalink (VSD) Project
C	Epidemiologic and Statistical Methods for Vaccine Safety
D	Laboratory Methods for Vaccine Safety
E	Genomics and Vaccine Safety
F	Case Definitions, Data Collection, and Data Presentation for Adverse Events Following Immunization
G	Vaccine Safety Clinical Practice Guidance

ISO Agenda Draft Recommendations

#3 5-Year Research Needs (30 items)

Item	5-Year Research Needs (30 items)
A	Specific Vaccine Safety Questions (7 items)
B	Thematic Area: Vaccines and Vaccination Practices (8 items)
C	Thematic Area: Special Populations (7 items)
D	Thematic Area: Clinical Outcomes (8 items)

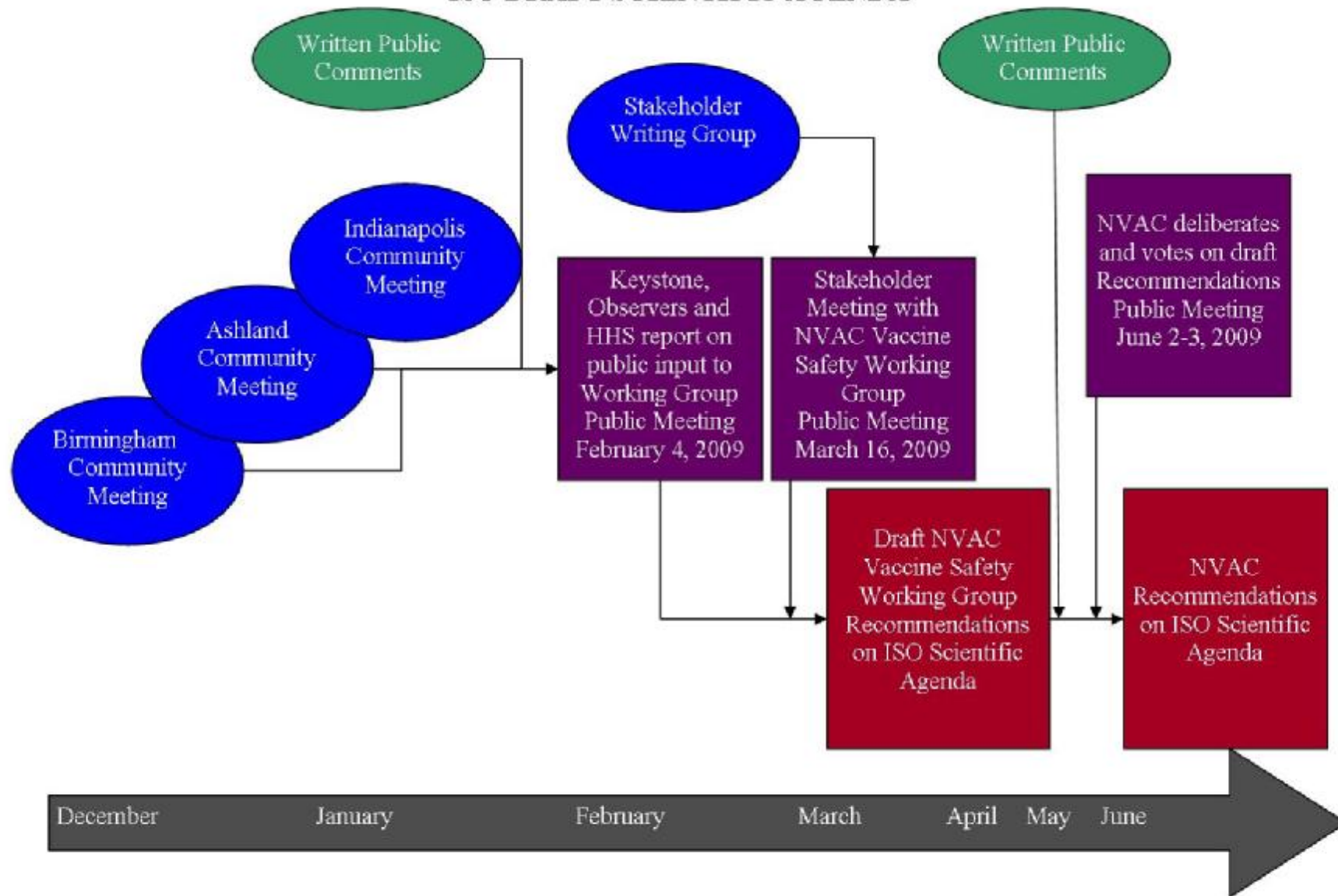
Methods

- Information gathering
- Content review by subgroups
- Drafting of recommendations
- Internal peer review
- Revision
- Currently under consideration by NVAC, and soliciting public input on the draft report
 - Federal Register
<http://edocket.access.gpo.gov/2009/E9-8399.htm>

Public Engagement

- Meetings facilitated by the Keystone Center
- Three community meetings (Birmingham AL, Ashland OR, Indianapolis IN)
- Writing Group meeting in Salt Lake City UT
- Stakeholder meeting in Washington DC
- Two formal solicitations for written public comments (one currently)

THE PROCESS FOR PUBLIC INPUT INTO THE NVAC RECOMMENDATIONS ON THE ISO DRAFT SCIENTIFIC AGENDA



Prioritization of Research Topics



Overarching Issues

- *Constraints of looking at draft ISO Scientific Agenda in isolation and need to include other partners*
- *There should be clear emphasis on prevention, and when prevention is not possible, amelioration of vaccine adverse events*

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. ISO should regularly engage the public and stakeholders as ISO conducts research, interprets the findings from their studies, and revises their research agenda.

General Recommendations

4. ISO should 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, ISO should investigate in advance approaches to safety monitoring, including the extent to which they would be used off-label or in new populations.

General Recommendations

6. To better understand the biological mechanisms responsible for adverse events following immunization, ISO should coordinate with other agencies to support basic research and 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 IOM, with broad methodological, design, and ethical expertise to consider "strengths and weaknesses, ethical issues and feasibility, including timelines and cost of various study designs to examine outcomes in unvaccinated, vaccine delayed and vaccinated children

General Recommendations

8. ISO studies should be designed and adequately powered to assess the role of differences in race/ethnicity and gender when appropriate.
9. ISO should have an active role in risk communications research.
10. ISO should 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.

Capacity Recommendations

10. ISO should 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.

11. The ISO Scientific Agenda should 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.

Capacity Recommendations

13. ISO should 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. ISO should create an expert advisory group on genomics and vaccine safety to assist with developing a focused genomics research agenda and protocol development.
15. 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.

Capacity Recommendations

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. ISO should 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 Recommendations

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)?	(18) Modify Specify influenza and meningococcal conjugate vaccines	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?	(19) Modify Expand to include speech and language delays as potential outcomes of interest. (20) Expand	Is exposure to thimerosal associated with increased risk for clinically important tics, Tourette syndrome, and/or speech and language delays?
		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.

Research Recommendations

Research Needs Recommendations		
Draft ISO Agenda Item	Recommended Action	Recommended Rewording
A-VII: Are varicella vaccines (varicella and MMRV) associated with increased risk for clinically important events related to varicella vaccine virus reactivation?	(21) Modify Expand to include zoster vaccine.	Are varicella vaccines (varicella, MMRV, and Zoster) associated with increased risk for clinically important events related to varicella vaccine virus reactivation?
None	(22) Add Specific Vaccine Safety Questions	Do multiple vaccinations increase risk of immune system disorders?
B-I: Bivalent human papillomavirus (bivalent HPV) vaccine (Cervarix™)	(23) Remove	
B-II: Zoster vaccine (Zostavax®)	(24) Remove	

Research Recommendations

Research Needs Recommendations		
Draft ISO Agenda Item	Recommended Action	Recommended Rewording
B-III: Annual influenza vaccination in children and adolescents (trivalent inactivated influenza vaccine [TIV] and LAIV)	(25) Expand	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)	(26) Expand (27) Modify Remove the parenthetical statement “other than thimerosal or ASO4 in bivalent HPV vaccine.”	ISO should evaluate cumulative levels of non-antigen component exposure possible through the schedule of recommended vaccinations.
		B-IV: Non-antigen components of vaccines
B-VII: Off label use of vaccines	(28) Expand	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.

Research Recommendations

Research Needs Recommendations		
Draft ISO Agenda Item	Recommended Action	Recommended Rewording
C-III: Adults aged ≥ 65 years	(29) Modify Expand to include adults aged ≥ 60 years of age.	Adults aged ≥ 60 years.
C-VI: Persons with autoimmune disorders	(30) Modify Expand to include well-documented family history.	Persons with autoimmune disorders or a well-documented family history of autoimmune disorders.
None	(31) Add New Special Population	Children with siblings or parents who experienced an adverse event following immunization
None	(32) Add New Special Population	Children who have previously suffered an adverse event following immunization who are recommended to receive additional doses in a booster regime

Priorities

Question	Rating	Significance of the Exposure to a Vaccine	Burden of the Adverse Health Event After Vaccination	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%			

Priorities

	Question	Rating	Significance of the Exposure to a Vaccine	Burden of the Adverse Health Event After Vaccination	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%		

Current Solicitation for Public Comment

- Working Group draft report may be found at following page:

<http://www.hhs.gov/nvpo/nvac/reports.html>

- Federal Register Notice soliciting public comment at

<http://edocket.access.gpo.gov/2009/E9-8399.htm>

Working Group Charge 2

2. 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.

Charge 2

“rethinking vaccine safety for the 21st Century”

- What are the characteristics of an optimal system?
- What are the roles of evolving scientific disciplines in genomics, proteomics, informatics, data base linkage and data mining?
- What can we learn from best practices of other safety systems, not limited to vaccine safety?
- How can we achieve greater integration of basic, translational and public health science?

Charge 2 Draft Plans

- Two-day meeting: July 15-16, 2009
 - Joint IACC/NVAC Vaccine Safety Working Group meeting
 - Panels of sectors
 - Vaccine safety thought leaders
 - Vaccine safety advocates
 - Vaccine manufacturers
 - Other safety sectors (e.g. drug, chemical)
 - Information technology
 - Federal officials in vaccine safety