

**National Vaccine Advisory Committee (NVAC)
May 7, 2009, Meeting Minutes**

Meeting Overview

The Committee discussed the NVAC Vaccine Safety Working Group draft report¹, a scientific review of the draft Immunization Safety Office (ISO) 5-year Scientific Agenda. The meeting was a special meeting of the NVAC and occurred by teleconference.

Committee Members in Attendance

Guthrie S. Birkhead, M.D., M.P.H., Chair
Jon R. Almquist, M.D.
Richard D. Clover, M.D.
Cornelia L. Dekker, M.D.
Jaime Fergie, M.D., F.A.A.P.
Lance K. Gordon, Ph.D.
James O. Mason, M.D., Dr.P.H.
Marie McCormick, M.D., Sc.D.
Christine Nevin-Woods, D.O., M.P.H.
Andrew T. Pavia, M.D.
Laura E. Riley, M.D.

NVAC Ex Officio Members

George Curlin, MD
Jeffrey A. Kelman, MMSc, MD

NVAC Liaison Representatives

Dale Morse, M.D., Advisory Committee on Immunization Practices (ACIP)
Wayne Rawlins, M.D., M.B.A., America's Health Insurance Plans
Magdalena Castro-Lewis, Advisory Commission on Childhood Vaccines
Mahnaz FarhangMehr, Public Health Agency of Canada

Committee Members Absent

Mark Feinberg, MD
Sharon G. Humiston, MD, MPH
Lisa A. Jackson, MD, MPH
Charles Lovell, Jr., MD, FACP
Trish Parnell

Invited Speakers

Karen Broder, MD, Centers for Disease Control and Prevention (CDC)
Daniel Salmon, PhD, NVPO
NVAC Vaccine Safety Working Group Members

¹ <http://www.hhs.gov/nvpo/nvac/documents/NVACVaccineSafetyWGReport041409.pdf>

Opening Remarks, Introduction, and Report of the Chair—Dr. Guthrie Birkhead

Dr. Birkhead called the meeting to order and welcomed the participants. He explained that the purpose of this call was to present the draft report and recommendations of the NVAC Vaccine Safety Working Group to the full committee for discussion prior to an anticipated vote at the June 2, 2009 meeting. This special meeting was being held by teleconference and was open to the public with a period for public comment at the end. As an official NVAC meeting, the meeting was being recorded and official minutes were being taken and would be posted on the NVAC website following approval by the committee. Dr. Birkhead outlined the agenda for the call and asked NVAC members and Vaccine Safety Working Group members to introduce themselves.

Presentation of the NVAC Vaccine Safety Working Group draft report—Dr. Daniel Salmon

Dr. Salmon presented the report of the NVAC Vaccine Safety Working Group on their behalf, noting that the recommendations did not represent the position of the U.S. government or employees who may have assisted the Working Group with the report. The first charge of the Working Group was to undertake and coordinate a scientific review of the draft ISO research agenda and advise on the content of the ISO draft research agenda, prioritization of research topics on the agenda, and identify possible scientific barriers. Dr. Salmon reviewed the expertise of the members of the Working Group and the methods that went into developing the report, including breaking into subgroups, reviewing the agenda, reviewing the literature, a series of conference calls with ISO, the Clinical Immunization Safety Assessment Network (CISA), the Vaccine Safety Datalink (VSD), the Brighton Collaboration, and the Vaccine Healthcare Centers (VHC). Following initial drafting of sections of the report by subgroups, there was an internal peer review process and additional revision. The report is currently under consideration by the full NVAC, and the draft report was posted online for public comment.

A robust public engagement process occurred. The Keystone Center facilitated public and stakeholder engagement, including three community meetings in Birmingham, AL, Ashland, OR, and Indianapolis, IN. Ashland, OR was chosen for its high rates of vaccine exemptions. There was also a Writing Group meeting in Salt Lake City with a variety of stakeholders who drafted materials for additional stakeholder consideration at the March 16, 2009 stakeholder meeting in Washington D.C. There were two formal solicitations for written comments; both made available through notices in the *Federal Register*.

A vote on the recommendations is anticipated for the June NVAC meeting. If passed, the recommendations will be given to the Assistant Secretary for Health (ASH), and the ASH can communicate the recommendations to CDC/ISO.

Dr. Salmon described the prioritization criteria used by the Working Group and reviewed the 32 recommendations of the Working Group. Criteria used to prioritize 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 of study (Appendix 1). The first five criteria consider “what to do,” while the last considers “how to do it.” For each of these criteria, the specific vaccine safety questions were rated low, medium, or high.

Dr. Salmon discussed two overarching issues for the Vaccine Safety Working Group: 1) the constraints of looking at the draft ISO Scientific Agenda in isolation, as ISO/CDC is only one component of federal vaccine safety system, and 2) the belief that emphasis should be placed on the prevention of vaccine adverse events, and if not possible, amelioration of those events.

Dr. Salmon read through the nine general recommendations, eight capacity recommendations, and 15 research recommendations (Appendix 2). He described how the prioritization criteria were applied by the Working Group to each specific vaccine safety questions (Appendix 3). For each of the five prioritization criteria, the proportion is given of Working Group members who rated the topic high, medium, or low as well as the proportion believing each study is feasible. Dr. Salmon used the question, “Is exposure to thimerosal associated with increased risk for clinically important tics, Tourette syndrome, and/or speech and language delays?” as an example. The overall priority rating was low, and since thimerosal has been taken out of most vaccines in all but trace amounts, the overall amount of exposure, and thus significance of exposure in the U.S., was low. Furthermore, the impact on policy of any study would also be low. This question received a low priority overall, but the Working Group did recommend further analysis of the Thompson study (Thompson WW et al. *N Engl J Med* 2007;357(13):1281-92). Because the marginal cost would be low, it was considered an important item.

Discussion

Dr. Pavia thanked everyone for their hard work, including the Working Group members, NVPO staff, and everyone who participated in the community and stakeholder meetings. Dr. Salmon explained that there were two subsequent Working Group calls scheduled, one to discuss NVAC comments and one to discuss public comments, after which the report would be revised as appropriate. Those changes would be highlighted to the NVAC at the June meeting, when a vote is anticipated. The call was opened up to questions and comments from NVAC members on the presentation or on the report itself. Dr. Rawlins asked if there would be a communications strategy around publicizing the results of vaccine safety studies. Dr. Salmon responded that this is not part of the first charge. The second charge to the Working Group, which will start with a kick off meeting July 15-16, 2009, in Washington DC, is to look at the system more broadly; the Working Group may decide to include discussion of communications when addressing the second charge.

Dr. Morse commented from the ACIP perspective. There were two issues that have come up at ACIP meetings. The first is the importance of VSD. Dr. Pavia noted in the report that it would be addressed more fully in the second charge. Because the VSD is so much more valuable than the Vaccine Adverse Event Reporting System (VAERS), Dr. Morse said he would like it to be enhanced. The second issue is the absence of research on vaccine safety during pregnancy; while it is mentioned in Special Populations section, Dr. Morse would have liked to see a subcategory that covers the need for further research on vaccine safety in pregnancy. Dr. Pavia noted that while identifying a population as special is a start, a research agenda should start to develop what the questions are and how to answer them. The Working Group therefore recommended that CDC better define what they specifically hope to study.

Dr. Dekker reported feedback from CISA investigators that because the Working Group only prioritized the specific vaccine safety questions, some people are tending to focus on those. It may be important to better emphasize that these are not the only priorities, and not to the exclusion of research in the topical areas. Dr. Pavia explained that the Working Group had long discussions over whether it was possible to prioritize sections B-D but came to the conclusion that the topics were too general to be appropriately prioritized. Dr. Gordon pointed out that it also highlights the need for periodic review, so that research questions on non-specific areas be formulated and those should be prioritized in future rounds of review. It was decided to highlight this point in the executive summary.

Dr. Birkhead asked the NVAC members if they felt that the prioritization approach was reasonable. Dr. Rawlins and Dr. Almquist agreed that it was the right approach.

Dr. Fergie commented that the background should frame the discussion of ISO with a few comments on pre-licensure safety evaluation, and how the results of post-licensure safety studies feedback to the FDA. Dr. Gordon agreed, noting that the report should differentiate the types of questions that can only be answered post-licensure, and why. There was some discussion about how much background to insert. A few sentences or a paragraph were felt to be sufficient. This can also be emphasized in the report where the Working Group recommends ISO coordinate with other agencies. Dr. Salmon recommended page 14 for this statement, and everyone agreed.

Dr. Dekker noted a comment from a CISA Principal Investigator that it would be good to emphasize the benefits of vaccination.

Dr. Birkhead asked for additional comments from the NVAC by noon on Monday, May 11th, 2009, for the Working Group to discuss on their next call on Tuesday, May 12th. Ms. Vannice reported that there had been few public comments received to date, but she expected more prior to the deadline for submission, which is Wednesday, May 13th.

Dr. Almquist noted that in the executive summary, there are some acronyms that are not identified and recommended a page listing all of the acronyms be added.

Dr. Birkhead then opened the call for comments from public attendees.

Jim Moody, SafeMinds

Mr. Moody thanked the committee for allowing public input and their excellent report. Mr. Moody focused on the recommendation for a feasibility study of vaccinated and unvaccinated children; he recommended this be upgraded to a recommendation for a study itself, rather than single it out for feasibility based on metrics that all studies are held by. Mr. Moody argued for the importance of baseline data for health outcomes of unvaccinated and alternatively vaccinated children, as parents are being asked to choose between risks of infectious disease versus the risks of chronic adverse events following the vaccination schedule. Mr. Moody stated we are close to a tipping point and that this study needs to be done so that either public concern is alleviated or necessary changes can be made. Thus, it should be put at the top of the list. Mr. Moody also requested that the Working Group make a strong recommendation for good data quality in the National Children's Study and the importance of looking at unvaccinated children in this context.

Dr. Birkhead thanked Mr. Moody for his comments and noted that the feasibility study has been a major topic of discussion. The National Children’s Study is not part of ISO’s research, but NVAC has taken a strong stance that immunization histories from medical records be obtained. Dr. Pavia said this will also be tackled in charge 2.

Rebecca Estep, Talking About Curing Autism

Ms. Estep referred to a CDC report from April 2007 (page 33) that included a statement that simultaneous vaccination is incompletely studied at the time of licensure. That vaccines are not being studied in a manner in which they are being given alarmed her. Ms. Estep asked if this is a topic the committee would be looking at.

Dr. Broder pointed out that simultaneous vaccination was originally part of the initial ISO draft Scientific Agenda. Dr. Pavia reminded everyone that the Working Group does not execute studies, only makes recommendations to ISO.

Dr. Birkhead thanked everyone for all of their work and reminded NVAC members to send additional comments on the draft report. Dr. Pavia also thanked Janesse Brewer and The Keystone Center for their tremendous work getting public input. Dr. Salmon also thanked the Working Group for all of their time. Dr. Birkhead closed the meeting.

I hereby certify that, to the best of my knowledge, the foregoing minutes are accurate and complete.

/Guthrie S. Birkhead/	<u>July 31, 2009</u>
Guthrie S. Birkhead, M.D., M.P.H. Chair, National Vaccine Advisory Committee	Date

Appendix 1. Prioritization criteria used by the Vaccine Safety Working Group.

**Step 1:
What to Do**

**Step 2:
How to Do It**

Criteria

<p>Significance of the Exposure to a Vaccine</p>	<p>Burden of the Adverse Health Event Following Immunization</p>	<p>Public Concern</p>	<p>Scientific Concern and Degree to which Science Warrants Further Study*</p>	<p>Impact on Policy</p>	<p>Feasibility</p>
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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.
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Appendix 2. 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. ⁱ 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

Appendix 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%		

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%		

ⁱ Thompson WW, Price C, Goodson B, et al. Early thimerosal exposure and neuropsychological outcomes at 7 to 10 years. N Engl J Med. 2007 Sep 27;357(13):1281-92.