

**National Vaccine Program Office (NVPO)
Individual Simultaneous Consultation:
Input from Vaccine Manufacturers' Representatives
On the ISO Research Agenda
November 16, 2007
Meeting Summary**

In Attendance:

Centers for Disease Control and Prevention (CDC)

Karen R. Broder
John K. Iskander
Dixie E. Snider (CDC moderator)
by telephone:
Nelson Arboleda
James M. Baggs
Gabrielle L. Fowler
Paul M. Gargiullo
Tanya Johnson
Barbara Slade
Eric S. Weintraub

Food and Drug Administration (FDA)

Robert Ball
Carmen M. Collazo-Custodio

National Vaccine Advisory Committee (NVAC)

Andrew T. Pavia

National Vaccine Program Office (NVPO)

Kenneth J. Bart
Bruce Gellin
Daniel Salmon (Chair)

GlaxoSmithKline

Harry Seifert

MedImmune

Aaron Mendelsohn
Jeff Roncal

Merck

Fabio Lievano
Luwy Musey

Novartis

Barbara Mahon

sanofi pasteur

David R. Johnson
Alena Khromava

Wyeth

Ann Strauss
Laura York

Disclaimer: This document does not represent Centers for Disease Control and Prevention (CDC) or National Vaccine Program Office (NVPO) policy, nor does it necessarily reflect which ideas will be incorporated into CDC's final Immunization Safety Office Scientific Agenda. This document has been reviewed by meeting participants.

Background and Administrative Summary:¹

CDC's Immunization Safety Office (ISO) is developing a comprehensive, scientifically robust Research Agenda with extensive input in a transparent manner; the horizon is 3-to-5 years. ISO is working with the National Vaccine Program Office (NVPO) and National Vaccine Advisory Committee (NVAC) to respond to a recommendation from the 2005 Institute of Medicine (IOM) report: "Vaccine Safety Research, Data Access, and Public Trust." IOM recommended that a subcommittee of NVAC advise CDC on the Vaccine Safety Datalink (VSD) Project research agenda. Because carrying out high-quality research requires integration across the ISO research and surveillance components, the scope of the research agenda being developed will include the full ISO research agenda, including the VSD Project.

In this context, ISO collaborated with NVPO to obtain input from scientists representing vaccine manufacturers to inform development of the ISO draft research agenda before the NVAC scientific review. NVPO organized an individual simultaneous consultation with vaccine manufacturers and federal scientists. Two representatives from each manufacturer with vaccines that were licensed (as of August 24, 2007) in the United States and routinely used in the civilian population were invited. Scientists from other agencies and operating divisions of HHS who serve on the Interagency Vaccine Group (IAVG) were also invited to attend. Participants received briefing material before the meeting that included a charge and lists of current ISO scientific activities.

The meeting convened in the Humphrey Building, Washington DC at approximately 9 am on November 16, 2007. It followed the agenda provided in the Appendix (A), with a few minor changes to accommodate the schedule. Dr. Salmon led the meeting and Dr. Snider moderated the group discussions. During the meeting Dr. Broder reminded manufacturers' representatives of the goal to obtain individual input from the participants, rather than a consensus. Participants were encouraged to speak freely and were informed that documents would note the ideas that were discussed without using names. In addition they were asked to complete anonymous feedback worksheets at the end of each brainstorming session. These were summarized by Dr. Broder (Appendix B).

¹ Terms in the document reflect those that were in use at the time of the meeting on 11/16/2007.

Disclaimer This document does not represent Centers for Disease Control and Prevention (CDC) or National Vaccine Program Office (NVPO) policy, nor does it necessarily reflect which ideas will be incorporated into CDC's final Immunization Safety Office Scientific Agenda. This document has been reviewed by meeting participants.

Meeting Events and Discussion

Welcome From the NVPO—Bruce Gellin and Daniel Salmon

Dr. Gellin thanked the participants for coming. He stressed the importance of input from vaccine manufacturer representatives in the development of the ISO Research Agenda.² The process of putting together that Agenda with input from federal agencies and stakeholders stems from a 2005 Institute of Medicine (IOM) recommendation for NVAC to review and provide advice on the Vaccine Safety Datalink (VSD) research plan. That charge has been expanded to include the ISO scientific activities as a whole.

Dr. Salmon informed participants that they were encouraged to complete worksheets at the end of the brainstorming session. The participants would be asked to note research topics in each of the areas addressed during the meeting. He asked that any ideas for research topics that occurred to the participants after the meeting should be sent to him or to Drs. John Iskander or Karen Broder.

Welcome from the ISO—John Iskander

Dr. Iskander provided background information on the ISO Research Agenda as a context for the present meeting. Since 2005, the ISO's mission has focused on vaccine risk assessment although it remains engaged in broader science and policy initiatives concerned with vaccine safety.

Dr. Iskander noted a series of IOM reports on the assessment of the possible causal relationship between vaccines and adverse events in the 1980's and 1990's that found inadequate scientific evidence to determine whether or not a causal relationship existed in more than half of safety concerns investigated. IOM determined that this finding was due to limitations in knowledge and research capacity.

Gaps in vaccine safety knowledge persist because of the rarity of serious adverse events, the difficulty of performing high-quality scientific studies, the relative newness of vaccine safety science, and the broad scope of the field. There is, therefore, a need to collect, organize, and prioritize vaccine safety studies.

² The ISO Research Agenda is also referred to as the "Agenda" in this document.

***ISO Research Agenda Development: Process and Discussion Framework—
Karen Broder***

Dr. Broder spoke about the ISO's Research Agenda development process. First, CDC will develop a draft research agenda with input from scientists with diverse expertise. Today's meeting is the last component of this first phase. Earlier input was received from other Department of Health and Human Services and Department of Defense agencies (8/2007) and programs and from an external scientific consultancy (5/2007).

The input will be synthesized, and the key research themes prioritized to develop an ISO draft ISO Research Agenda. After this draft is complete, NVAC will facilitate a scientific review of the draft Research Agenda. CDC will have an opportunity to respond to the NVAC feedback and will finalize the Agenda.

Dr. Broder also spoke about the mission of the ISO, the interrelationships of its main research and surveillance components, and the general research themes that had emerged from the earlier input from external consultants and federal scientists. These themes included research on specific vaccines, vaccination practices, host factors (e.g., genomics), clinical outcomes, vaccine adjuvants and nonantigen components, and risk perception.

The charge to the manufacturers' representatives was similar to that given to the previous groups. They should identify vaccine safety research areas and gaps in knowledge that are or will be important for public health and could be studied by the ISO. They were also encouraged to indicate why these topics are important, suggest feasible approaches to their study them, and advise ISO as to their relative priority.

Objectives and Format for the Day—Dixie Snider

The meeting was divided into five brainstorming sessions: One on vaccine adjuvants and other nonantigen vaccine components and new vaccine technologies and four sessions divided according to life stages of the vaccine recipients (Appendix A).

Discussion

In response to a question, Dr. Snider said that a report will be generated from the series of discussions and will be in the public domain.

One participant noted that the data could be useful in the creation of physician guidance. The example offered had to do with immunocompromised children inappropriately vaccinated.

Disclaimer This document does not represent Centers for Disease Control and Prevention (CDC) or National Vaccine Program Office (NVPO) policy, nor does it necessarily reflect which ideas will be incorporated into CDC's final Immunization Safety Office Scientific Agenda. This document has been reviewed by meeting participants.

Another participant hoped that there would be FDA “buy-in” to the current solicitation of input from manufacturers. Dr. Snider replied that the ISO would be working with the FDA. He noted that there is some overlap of interest between the two bodies but that ISO’s primary concern is the safety of vaccines already being used in the national vaccine program rather than with the approval of new individual vaccines as they emerge from Phase III clinical trials.

The question was raised whether vaccine failure is a safety issue. Dr. Iskander replied that although there is the potential for overlap, most studies are focused primarily on either safety or efficacy. For example, VSD conducts influenza vaccine efficacy studies that are separate from VSD influenza vaccine safety studies. We will also look to international standards (e.g. Council for International Organizations of Medical Sciences) for guidance.

Brainstorming Session 1: Vaccine Adjuvants, Other Nonantigen Vaccine Components, and New Vaccine Technologies

The following were suggested as areas for research or topics of concern:

- VSD and the Vaccine Adverse Event Reporting System (VAERS) are not designed to assess whether events are transient or long-lasting outcomes. It would seem important to assess the severity and duration of an event as well as its incidence in order to judge its importance.
- Although clinical trials may be considered by some to be the gold standard, they aren’t always easy to interpret. There are a lot of confounding variables in clinical trials; for example, the patient dropout rate may be due to anxiety related events rather than to anything intrinsic to a specific vaccine.
- In clinical studies, false signals can also appear. In addition, when studies are put on hold because of concern about an adverse event, other patients are lost to the study, making the final interpretation more difficult.
- New adjuvants are undergoing a degree of scrutiny not applied to alum, an existing adjuvant. This scrutiny may obscure the benefit of new adjuvants.
- A database of background adverse event rates might help in deciding which outcomes after vaccination warrant further study.
- Because of proprietary or confidentiality concerns, manufacturers are sometimes told by regulators to look at particular adverse events or groups of events without knowing any of the specifics (e.g., the reason for the concern, what factors to look for). More open communication from manufacturers should be provided about the frequency of the event and the biological relationship with the specific molecules or antigens.
- Particular receptors in laboratory animals may occur in different numbers than in humans. Bench work is great, but clinical studies are needed.
- Appropriate animal models are needed.

Disclaimer This document does not represent Centers for Disease Control and Prevention (CDC) or National Vaccine Program Office (NVPO) policy, nor does it necessarily reflect which ideas will be incorporated into CDC’s final Immunization Safety Office Scientific Agenda. This document has been reviewed by meeting participants.

Brainstorming Session 1: Vaccine Adjuvants, Other Nonantigen Vaccine Components, and New Vaccine Technologies (continued)

- Case definitions of serious outcomes should be standardized to define outcomes.
- When background rates of a putative adverse event are given, the characteristics of the population must be specified because the rates of an event will often vary depending upon a number of demographic and other variables.
- Attributable risk should be given as well as relative risk.

Brainstorming Session 2: Pregnant Women and Exposed Infants

- Research on vaccines in pregnant women and neonates has been minimal. This is considered a “taboo” subject in the research arena due to legal and cultural concerns.
- Given the current litigious environment and lack of robust data on pregnancy outcomes and variables, companies are unable to support studies evaluating vaccines in pregnant women. Also the point was made that there should be an overall approach to research in pregnant and lactating women and newborns.
- Studies involving pregnant women are not conducted, not only due to legal and cultural reasons, but also due to moral concerns (uncertainty about the effect of exposure to the offspring). However, in the post-marketing arena, spontaneous reports of vaccine exposure during pregnancy are collected and actively followed-up for outcome.
- Current vaccines and vaccine schedule are designed to provide immunity prior to the time of greatest risk to infants (e.g. differences in schedules used in developed countries versus the World Health Organization Expanded Program on Immunisation (EPI) schedule). There are important vaccines given to neonates like hepatitis B. Also, Influenza vaccination of pregnant women was recommended due to increased risk of influenza complications in the vaccinee, though there may be benefit to the newly born child (risks versus benefits).
- The data addressing benefits of vaccines to pregnant women are mostly anecdotal.
- There should be efforts to coordinate the existing data.
- There should be a national pregnancy registry with data on women who have been inadvertently vaccinated during pregnancy.
 - This would be problematic for vaccines that have not yet been licensed.
 - Data on smoking, drinking, etc., may be lacking in a clinical study or in databases like VSD. Follow-up interviews would be necessary to collect information on confounders such as these.
 - Several control groups might be needed to address all confounding variables.

Disclaimer This document does not represent Centers for Disease Control and Prevention (CDC) or National Vaccine Program Office (NVPO) policy, nor does it necessarily reflect which ideas will be incorporated into CDC’s final Immunization Safety Office Scientific Agenda. This document has been reviewed by meeting participants.

Brainstorming Session 2: Pregnant Women and Exposed Infants (continued)

- If there is an H5N1 epidemic, we will be seeing many inadvertently vaccinated pregnant women despite the lack of rigorous safety data on influenza vaccine or H5N1 vaccine in pregnant women. This situation is already seen with existing such as licensed trivalent inactivated influenza vaccine.
- CDC is beginning an adolescent and young adult initiative. There will be inadvertently vaccinated pregnant women. We should begin accumulating data, even anecdotal, and get it into a registry.
- The Organization of Teratology Information Specialists³ (OTIS) collects information on pregnancy outcome and follows exposed infants for up to 1 year. They should be contacted to see if they have, or could obtain, data on outcomes among women who were vaccinated. Ideally OTIS should be the basis for National Vaccine Pregnancy Registry. The infrastructure is already in place.
- Most concerns center on pregnancy loss. Data on background rates of pregnancy loss are limited and imprecise. The baseline rate of early pregnancy loss has been estimated to be as high as 50%, so that with any vaccine given in early pregnancy, this rate of loss would be expected, even with a perfectly safe vaccine.
- Vaccination programs in Third World countries are often eager to vaccinate people whenever they can catch them; this will necessarily include some pregnant women. Outcomes data could be collected from these countries. Although this might be perceived as exploitation, the information would otherwise be wasted.

Brainstorming Session 3: Adults Over 18 Years (Nonpregnant)

- Older adults are more likely to be taking other medications. This could confound the problem of detecting true vaccine associated adverse events in this age group.
- People with chronic illness or repeated episodes of acute illness are more likely to see doctors regularly. They may also be more likely to be vaccinated. Because these individuals are more likely to get sick again, their post-vaccination illness may be more likely to be attributed to the vaccine.
 - But since they are seeing doctors, they will also be likely to be diagnosed when there really is a vaccine adverse event.

³ Information about OTIS is available at <http://www.otispregnancy.org/>, accessed on November 17, 2007.

Brainstorming Session 3: Adults Over 18 Years (Nonpregnant) (continued)

- Virus reactivation is a concern. Whether any instance should be viewed as a safety issue or not depends on whether the infection is more prevalent among vaccinated individuals than among a similar population without the vaccine.
- Why do some people overrespond and others underrespond?
 - Could be a safety issue. Could be an efficacy issue.
- Case definitions of expected serious events are important but they are not yet standardized. Brighton collaboration has done some but more work is still needed.
- The VSD is not robust enough to detect very rare events.
- Vaccine coverage is low for some vaccines.
- The size of a cohort for study depends on the background rate of a vaccine adverse event.
 - Time is also a factor. Even a small cohort will eventually yield results.
- The seriousness of a disease speaks to the importance of a study.
- Administration errors are a problem e.g., over-immunization.
 - Since safety is balanced against benefit, and as it is hard to imagine a benefit deriving from overimmunization, this is a safety issue.
- Are additional doses of vaccine needed in old age? Are they safe?
 - Adverse events in this population would be especially subject to misinterpretation.
 - Clinical trials would have to change to address these issues. They would have to include not only the elderly but also the frail elderly.
- Anxiety related events can be frequent (up to 2.9% in some studies) in adolescents and young adults. It is important to consider the possibility of such events when observing an increased diagnosis of hypersensitivity reactions.

Brainstorming Sessions 4 and 5: Adolescents, Infants, and Children

Sessions 4 and 5 were combined because of time constraints. The following issues were raised:

- With combination vaccines, there may sometimes be inadvertent administration of one of the components, i.e., an additional and unnecessary dose may be given.
- Reactogenicity is an issue with combination vaccines.
- The level of antigen may need to be boosted.
- In postmarketing surveillance, it is difficult to know which vaccine caused an adverse event.
 - For systemic events, in particular, this will often be unclear.
 - This is true especially in large postlicensure studies with subjects who have received multiple vaccines.

To add a new adjuvant to a combination vaccine, a Phase I study will be done, but adverse events may not arise until a postmarketing study is undertaken.

Disclaimer This document does not represent Centers for Disease Control and Prevention (CDC) or National Vaccine Program Office (NVPO) policy, nor does it necessarily reflect which ideas will be incorporated into CDC's final Immunization Safety Office Scientific Agenda. This document has been reviewed by meeting participants.

Brainstorming Sessions 4 and 5: Adolescents, Infants, and Children (continued)

- We hear from advocacy groups that every combination of vaccines that has not been studied in a Phase III trial is an “experiment.”
- Vaccine interference is a subsidiary safety issue. New studies are needed.
- After a vaccine is licensed, we have no control over how it is administered. The Advisory Committee on Immunization Practices (ACIP) has recommendations, but no one has data on interference, for instance.
- Manufacturers of new vaccines should conduct studies evaluating the concomitant use of their vaccine with existing vaccines and demonstrate lack of interference in immunogenicity/efficacy or impact on safety profile.
- An NVPO representative commented that manufacturers need to take more responsibility for postlicensing studies investigating off-label use.
- Companies do not want to appear to promote off-label use. The ability to conduct studies is becoming limited by the number of subjects available to participate in studies. It may not be practical to propose a large increase in studies, e.g. to evaluate every off-label indication that arises in practice. This situation is currently true for oncology trials, in which the number of subjects needed to run the current trials is more than the number of people with the diseases being studied.
- Voluntary recruitment may become a problem. We should examine some of the data collection methods used in Europe.
- We do not know the effects of repeated influenza vaccination in children.
- Demographic factors need to be better researched.
- Vaccines are tested on relatively small groups of high risk individuals. There is a need for research on special groups of infants; e.g., low birth weight or premature infants and those with apnea or bradycardia.
 - Sudden infant death syndrome and sudden unexpected death need more research.
 - Also, asthma in older children needs more research. But it is difficult to measure wheezing or exacerbation of cough.
- Risk-benefit for the company should be considered when doing this kind of research.
- Any institution or agent interested in off-label use must take more responsibility in designing and conducting studies to evaluate off-label use.
- More information is needed on the right schedule of administration and on modification of antigen levels in infants.
- What can be done to improve the environment/conditions in which vaccine is administered?

Disclaimer This document does not represent Centers for Disease Control and Prevention (CDC) or National Vaccine Program Office (NVPO) policy, nor does it necessarily reflect which ideas will be incorporated into CDC’s final Immunization Safety Office Scientific Agenda. This document has been reviewed by meeting participants.

Synthesis, Prioritization, and Potential Collaboration

The following points were raised:

- Establishment of baseline rates of AEs that may have biological plausibility are helpful in design of both pre-licensure and post-licensure trials. The establishment of baseline rates is needed in order to determine how large a study must be or to determine the threshold. For example, which proportion of subjects seropositive to measles in a population is needed in order to determine the estimated proportion of seronegative subjects to be evaluated for vaccine response?
- Though there were questions regarding genomics, there was agreement that this is an interesting area of research. New discoveries to generate or improve immune responses are readily evaluated by vaccine manufacturers, the goal being new and improved vaccines that are generally applicable on a global basis (with benefit far outweighing risk). As science identifies individuals with a genetic background that may be associated with heightened responses (to infectious pathogens or possibly vaccines), it will be important to determine the benefit and risk of vaccination for that particular set of individuals. (A recent paper on the ability to identify infants at high risk of severe RSV bronchiolitis may be useful in thinking about this. Janssen et al. JID 2007; 196: 826. Genetic susceptibility to respiratory syncytial virus bronchiolitis is predominantly associated with innate immune genes.).
- The VSD should be expanded. Among other things, it should include background rates for various conditions of interest.
- Products come out in a staged way. Therefore, the ISO must stage its involvement with manufacturers.
- Priorities must depend on the highest safety concerns.
- Establish clear criteria of prioritization.
 - When there is a biological basis for vaccine involvement in an adverse event, the priority is clear.
 - It is not clear how much weight to give to public concern in the absence of compelling biological evidence.
 - Do we care more about adverse events in infants than we do about adverse events in the elderly?
 - Public input could help us sort through this kind of value-laden issue.
 - What the public, in general, cares about is to be distinguished from the concerns of small, but vocal, advocacy groups. (But do such groups merely advocate, or do they activate?)
 - Ambiguity around issues of value helps the claims of litigants.
 - How do we find out from the public what their concerns are without raising their concerns?

Disclaimer This document does not represent Centers for Disease Control and Prevention (CDC) or National Vaccine Program Office (NVPO) policy, nor does it necessarily reflect which ideas will be incorporated into CDC's final Immunization Safety Office Scientific Agenda. This document has been reviewed by meeting participants.

Synthesis, Prioritization, and Potential Collaboration (continued)

- People may avoid vaccination because of a perception that the disease prevented is not observed in the population anymore.
 - But continued protection of the public health requires high vaccination rates.
- Genomics, applied to vaccine safety, is an appealing notion from a scientific perspective.
 - It almost sounds as if designer vaccines would become the new paradigm for specific populations.
 - The concern is the low yield to the manufacturer for the effort involved.

Closing Remarks—Daniel Salmon, Bruce Gellin, John Iskander, and Andrew Pavia

Dr. Salmon thanked the participants for sharing their ideas. He said he thought they had had a very open conversation and he hoped that it would continue.

Dr. Gellin said that he believed there had been some initial wariness and that he appreciated the level of candor in the ideas and opinions that had been expressed.

Dr. Iskander added his personal thanks and said that there will be times when the ability to share specific information will be limited (on both sides) but that he knew the public interest is of paramount significance to everyone at the meeting.

Dr. Pavia thanked the participants on behalf of NVAC.

Appendix A: Meeting Agenda

Final Meeting Agenda, November 16, 2007

Hubert Humphrey Building, Room 305A
Washington, D.C.

Time	Topic	Speaker
9:00 – 9:05	Welcome from the National Vaccine Program Office (NVPO)	Dr. Daniel Salmon, Vaccine Safety Specialist, NVPO
9:05 – 9:10	Welcome from the Immunization Safety Office (ISO), CDC	Dr. John Iskander, Acting Co-director, ISO, Office of the Chief Science Officer (OCSO), CDC
9:10 – 9:25	ISO research agenda development: process and discussion framework	Dr. Karen Broder, Senior Medical Advisor, ISO, OCSO, CDC
9:25 – 9:35	Objectives and format for the day	Dr. Dixie Snider, Senior Advisor, CDC
9:35 – 10:00	Session 1: Across the life stages: Vaccine adjuvants, other non-antigen vaccine components, and new vaccine technologies	Dr. Broder presents information and Dr. Snider moderates session; manufacturer representatives discuss topics and complete feedback worksheets
10:00 – 10:25	Session 2: Life stage: Pregnant women and exposed infants (all ages)	As above
10:25 – 10:45	Break	
10:45 – 11:10	Session 3: Life stage: Adults aged ≥ 19 years (non-pregnant)	As above
11:10 – 11:35	Session 4: Life stage: Adolescents aged 11-18 years (non-pregnant)	As above
11:35 – 12:00	Session 5: Life stage: Infant and child aged 0-10 years	As above
12:00 – 12:50	Synthesis, prioritization and potential collaboration	Manufacturer representatives and Drs. Snider, Broder, Iskander, and Salmon
12:50 - 1:00	Closing remarks	Dr. Salmon, NVPO

Disclaimer This document does not represent Centers for Disease Control and Prevention (CDC) or National Vaccine Program Office (NVPO) policy, nor does it necessarily reflect which ideas will be incorporated into CDC's final Immunization Safety Office Scientific Agenda. This document has been reviewed by meeting participants.

Appendix B

Summary of Brainstorming Session Worksheets

Overview:

At the completion of each brainstorming session, at least one scientist from each vaccine manufacturer was encouraged to complete a worksheet. They were asked to list the top 5 vaccine safety research topics in rank order, note the reason for importance, and identify potential approaches to study the topic. Participants were requested not to list their name or affiliation on the forms. An ISO medical officer reviewed and summarized the individual suggestions into scientifically relevant categories; no attempt was made to achieve consensus. Participants had an opportunity to review and comment on this summary.

Findings:

Forms Returned:

Nine worksheets were completed by scientists representing vaccine manufacturers. Participating federal scientists contributed to the brainstorming discussions but did not submit worksheets.

Suggested Research Topics Identified by ≥ 1 Rater:

If the at least one rater ranked the topic as a first (1) or second (2) priority level.

Bolded superscripts are used to show the priority level. Other levels of priority are not shown.

Session 1: Across the Life Stages

Vaccine Adjuvants, Other Non-antigen Vaccine Components and New Vaccine Technologies

- Research areas
 - Adjuvant safety across the life stages¹
 - Long-term safety of new and traditional adjuvants
 - Rare serious adverse events (AEs)¹
 - Common reactogenicity events
 - Repeated dosing with adjuvanted vaccines²
 - Mechanisms of adverse events (AEs) related to adjuvants (basic understanding of how adjuvants work)²
 - Dose ranging studies of adjuvants (minimum dose to achieve desired outcome)
 - Safety of new technologies (other vaccine delivery, e.g., inhaled vaccines)
 - Thimerosal, mercury
- Other areas not directly related to vaccine safety research
 - Education for professionals regarding new adjuvants, noting that adjuvants are different from thimerosal
 - Efficacy of new and traditional adjuvants

Other cross-cutting research areas

- Vaccine-specific: Live, attenuated virus vaccines²
- Clinical outcomes
 - Baseline rates of
 - Common events, adjusting for age, race and gender¹
 - Uncommon events (Guillain-Barre syndrome [GBS] and Kawaskai disease), adjusting for age, race/ethnicity, and gender.^{1,2}
 - Neurological events, including GBS, Bell's palsy, encephalitis, ADEM, convulsions, and transverse myelitis²
- Other research areas
 - Autoimmune diseases after vaccination¹
 - Biologic plausibility of AEs and mechanisms of action
 - Case definitions for AEs
 - The influence of ethnicity and other demographic factors on AEs

Session 2: Pregnant Women and Exposed Infants

- Vaccine-specific: influenza vaccine²
- Clinical outcomes
 - Background rates of
 - congenital conditions¹
 - clinical conditions in different trimesters (conditions not specified)²
 - Diseases, including long-term outcomes, in babies born to women exposed to vaccines (not specified)¹
 - Maternal outcomes following various vaccinations¹
 - Congenital malformations¹
 - Early pregnancy loss
- National pregnancy registry:^{1,2} need methods to incorporate all registries
- Risk perception: psychosocial issues of acceptance of vaccination during pregnancy
- Other research areas
 - How applicable are animal models to human populations?
 - Immune function issues during pregnancy and vaccine effects¹
- Other areas not directly related to vaccine safety research
 - National pregnancy registry infrastructure
 - Suggestion to limit to Organization of Teratology Information Services (OTIS)⁴
 - Consider questions of: feasibility? Responsibility for maintaining? Reside where?
 - Coordinate registries and studies to avoid competition for subjects
 - Communication of information to pregnant women to inform their decisions
 - Clinical trials in pregnant women not supported for ethical reasons

⁴ Information about OTIS is available at <http://www.otispregnancy.org/>, accessed on November 17, 2007.

Session 3: Adults Aged ≥19 Years (non-pregnant)

- Vaccine-specific
 - Zoster (by race, age, season, US vs. elsewhere)
 - Varicella: rates of reactivations vs. risks of disease
 - Safety of repeated influenza vaccines²
- Vaccination practices
 - Vaccination errors/misadministration¹ by region and vaccine type, including pediatric vaccines
 - Revaccination and AEs
- Host factors
 - Immunocompromised persons¹
 - Presence of chronic medical conditions²
 - How do we address frail vs. healthy adults in the datasets?
 - Elderly populations, especially frail persons and the very old group¹
- Clinical Outcomes
 - Background rates of
 - Serious conditions by age and gender (in absence of vaccination¹ and post-licensure²)
 - Chronic diseases/ prevalence of common co-morbidities
 - AEs in adults >65 years (including common AEs, and rates in persons with underlying conditions)¹
 - Autoimmune diseases¹
 - Demyelinating diseases¹
 - Characterization of rare AEs in adult populations¹
- Epidemiology/methods
 - Bias in reporting (e.g., physicians unaware of VAERS; “sick worker syndrome”)²
 - Case definitions (chronic conditions, immunocompromising conditions)
 - Algorithms for product quality data mining
 - Better surveillance for type B AEs^{5 1}
- Other areas related to vaccine safety research
 - Immunosenescence and adverse events²
 - Isolation of virus/bacteria responsible for AEs and laboratory data to support association
- Other areas not directly related to vaccine safety research: Educate internists regarding vaccines

⁵ Type B adverse events are defined as “unpredictable” events,
<http://www.fda.gov/medwatch/articles/dig/recognit.htm>, accessed on November 18, 2007.

Session 4: Adolescents (non-pregnant) Aged 11-18 Years

- Vaccine-specific: Combination vaccines (not specified)^{1,2}
- Vaccination practices
 - Safety of simultaneous administration vaccines¹
 - Vaccine safety when a person has received vaccines from different manufacturers (e.g., HPV vaccines)
 - Off-label use of vaccines¹
 - Vaccine and drug interaction¹
- Host factors
 - Immunocompromised²
 - Chronic medical conditions²
- Clinical Outcomes
 - Background rates of
 - Common AEs, including syncope, pain, other local reactions¹
 - Autoimmune diseases (e.g., juvenile rheumatoid arthritis)¹
 - GBS (suggest studying using animal models)
 - Syncopal events
- Other areas related to vaccine safety research: evaluation of ways to improve tolerability of vaccines²
- Other areas not related to vaccine safety research
 - Vaccine efficacy when persons are exposed to vaccines from different manufacturers (e.g., HPV vaccines)
 - Vaccine efficacy of combination vaccines (not specified)²

Session 5: Infants and Children

- Vaccine
 - Intranasal vaccine and Bell's palsy
 - Combination vaccines (not specified)²
- Vaccination practices
 - Repeated immunization
 - Simultaneous vaccination, especially catch-up vaccination^{1,2}
 - Off label use, including rotavirus vaccine and LAIV¹
 - Vaccination errors, including management algorithms (e.g., for immunocompromised infant)²
- Host factors
 - Premature birth^{1,2} (specific concerns about apnea and reactogenicity)
 - Immunocompromised persons
 - Other chronic medical conditions²
 - Demographics, ethnicity
- Clinical outcomes
 - Background rates of diseases in infants, including premature infants and children¹

Disclaimer This document does not represent Centers for Disease Control and Prevention (CDC) or National Vaccine Program Office (NVPO) policy, nor does it necessarily reflect which ideas will be incorporated into CDC's final Immunization Safety Office Scientific Agenda. This document has been reviewed by meeting participants.

Session 5: Infants and Children (continued)

- Common AEs observed with licensed vaccines
- Rare AEs observed with licensed vaccines
- Asthma and wheezing events
- Other allergic conditions
- Sudden infant death syndrome (SIDS) by age sex, and number of vaccines
- Developmental milestones/conditions^{1,2}
- Local reaction rates (e.g, pain, cellulitis, erythema)²
- Autoimmune conditions
- Other areas not directly related to vaccine safety research
 - Vaccine efficacy
 - Premature infants
 - Combination vaccines²
 - Anticipate that ecologic trends in the incidence of various diseases may be alleged to be related to increased use of vaccines¹

Appendix C
Abbreviations Used in the Report

Abbreviations

Abbreviation	Definition
ACIP	Advisory Committee on Immunization Practices
AE	adverse event
CDC	Centers for Disease Control and Prevention
CISA	Clinical Immunization Safety Assessment
DoD	Department of Defense
FDA	Food and Drug Administration
GBS	Guillain-Barré syndrome
HPV	Human papillomavirus
IOM	Institute of Medicine
ISO	Immunization Safety Office
LAIV	live, attenuated influenza vaccine
NVAC	National Vaccine Advisory Committee
NVPO	National Vaccine Program Office
OTIS	Organization of Teratology Information Services
SIDS	Sudden infant death syndrome
VAERS	Vaccine Adverse Event Reporting System
VSD	Vaccine Safety Datalink

Disclaimer This document does not represent Centers for Disease Control and Prevention (CDC) or National Vaccine Program Office (NVPO) policy, nor does it necessarily reflect which ideas will be incorporated into CDC's final Immunization Safety Office Scientific Agenda. This document has been reviewed by meeting participants.