Interagency Vaccine Group (IAVG)

Meeting on the Development of CDC's

Immunization Safety Office (ISO)

Research Agenda

August 3, 2007, Washington D.C.

Meeting Summary

Disclaimer: The ideas and recommendations of this report reflect those of federal scientists. This report does not represent Centers for Disease Control and Prevention (CDC) or Department of Health and Human Services policy, nor does it necessarily reflect which ideas will be incorporated into CDC's final Immunization Safety Office Research Agenda.

Interagency Vaccine Group Meeting on the Development of CDC's ISO Scientific Agenda – Final 3/21/08

Background

The Centers for Disease Control and Prevention's (CDC) Immunization Safety Office (ISO) is developing a comprehensive, scientifically robust research agenda with extensive input in a transparent manner. 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 will include the full ISO research agenda, including the VSD Project.

In this context, ISO collaborated with NVPO to obtain input from Federal scientists to inform development of the ISO draft research agenda before the NVAC scientific review. ISO solicited input from Federal scientists representing relevant Department of Health and Human Services (HHS) and Department of Defense (DoD) agencies and programs during an Interagency Vaccine Group (IAVG) meeting, convened by NPVO in Washington, D.C. on August 3, 2007. HHS meeting participants included representatives from the NVPO, FDA, NIH, HRSA, and CDC. All participants received briefing materials, including the charge, before the meeting. A summary of the meeting is provided below. Additional information from the meeting's brainstorming sessions is available in Appendix A.

In Attendance:

COL Randall G. Anderson
Robert Ball, M.D., M.P.H.
Kenneth Bart, M.D., M.P.H.
Brigid Batten, M.P.H.
CDR Karen R. Broder
Carmen M. Collazo, Ph.D.
George Curlin, M.D.
COL Renata J.M. Engler
Geoffrey Evans, M.D.
LT Kent Forde
Paul M. Gargiullo, Ph.D.
Bruce Gellin, M.D., M.P.H.
Marion Gruber, Ph.D.
LTC Wayne Hachey
Florence Houn, M.D.
CDR John Iskander
Rosemary Johann-Liang, M.D.
Laura Leidel, M.S.N., M.P.H.
Bill G. Kapogiannis, M.D.
Feng-Ying (Kimi) C. Lin, M.D.
Alison Mawle, Ph.D.
Karen Midthun, M.D.
Jennifer Reid, M.D.
Dan Salmon, Ph.D.
CAPT Ben Schwartz
LCDR Angela Shen (by phone)
Barbara Slade, M.D., M.S. (by phone)
Dixie Snider, M.D., M.P.H.
(Rear Admiral, retired) (Chair)

Welcome—John Iskander

CDR John Iskander welcomed the participants and thanked them for their attendance. He spoke briefly of the events leading to the present meeting.

In 1986, Congress asked the Institute of Medicine (IOM) to assess the causal relationship between vaccines and purported adverse events. The IOM found that, in two-thirds of the cases investigated, there was inadequate scientific evidence to determine that relationship. The IOM gave the following reasons for the limitations in knowledge at that time:

- An inadequate understanding of the biologic mechanisms underlying adverse events;
- Inconsistent information from case reports and case series;
- Inadequate size and followup of many population-based epidemiologic studies; and
- Limitations of existing surveillance systems.

To address these problems, the CDC created the the Vaccine Adverse Event Reporting System (VAERS), in collaboration with the Food and Drug Administration (FDA), the Vaccine Safety Datalink (VSD) Project, and the Clinical Immunization Safety Assessment (CISA) Network.

CDR Iskander addressed the reasons for the remaining gaps in our knowledge of vaccine safety. These include the rarity of serious adverse events, the difficulty of conducting high-quality scientific studies, the relative infancy of vaccine safety as a science, and the large number of licensed vaccines and of alleged vaccine-related adverse events.

Though, in 2005, ISO's mission refocused on vaccine risk assessment, CDR Iskander noted that the ISO remains in engagement with broader science and policy initiatives concerned with vaccine safety.

ISO Program Overview, Research Agenda Development Process, and Meeting Organization—Karen Broder

CDR Karen Broder said that the ISO works with US and international partners to develop and support research to identify adverse events after vaccination and to assess their causality and risk factors, to communicate the results of research, and to establish scientific methodology and standardize case definitions for vaccine adverse events.

Key ISO research and surveillance components include

- VAERS, a passive surveillance system that identifies vaccine safety signals of possible concern and allows the formation of hypotheses;

- The Brighton Collaboration, offering standardized case definitions to provide a common vocabulary for vaccine research and surveillance;
- The VSD, a collaboration between the Centers for Disease Control and Prevention (CDC) and eight managed care organizations (MCOs) with comprehensive medical and immunization histories of 5.5 million people per year; VSD is a resource for testing hypotheses and conducting surveillance; and
- CISA, a collaboration of the CDC with six academic centers to study the pathophysiology of adverse events, identify risk factors, and offer evidence-based guidance for clinicians.

In 2005, the IOM recommended that a subcommittee of NVAC advise CDC on the Vaccine Safety Datalink (VSD) Project research agenda. In response, ISO is developing a comprehensive research agenda with extensive internal and external input. The research agenda development is currently structured as a three-phase process: CDC develops a draft agenda; the National Vaccine Advisory Committee (NVAC) facilitates a scientific review of the draft; and CDC finalizes the agenda, taking the NVAC feedback into account.

A meeting of external scientific consultants was held in May of 2007. CDR Broder discussed the composition of the body of consultants, the charge to the group, the framework of that meeting, and the areas of research they suggested.

CDR Broder then described the charge to the participants of the present meeting. Participants were asked to identify:

- Vaccine safety topics that are, or will be, important for public health and could be studied by the ISO;
- Vaccine safety research priorities; and
- Areas for research collaboration between the ISO and other Federal programs.

The VSD Project—Paul Gargiullo

Dr. Gargiullo began by outlining the historical background of the project, noting that the VSD was established in 1990 to monitor immunization safety and address the gaps in scientific knowledge about rare and serious events following immunization. The VSD incorporates demographic data such as age and gender, vaccination records, and diagnoses in the form of ICD9 codes and offers the ability to review medical charts. Dr. Gargiullo said that, in practice, the codes are used to cast a wide net, while the charts furnish specificity. VSD data support cohort, case control, case series, and sequential monitoring studies. Limited access minimizes the risk of loss of confidentiality.

The VSD Project MCO sites are:

- Group Health Cooperative of Puget Sound, Seattle, WA, US
- Kaiser Permanente Northwest, Portland, OR, US

- Kaiser Permanente Medical Care Program of Northern California, Oakland, CA
- Southern California Kaiser Permanente Health Care Program, Los Angeles, CA
- HealthPartners Research Foundation, Minneapolis, MN
- Marshfield Clinic Research Foundation, Marshfield, WI
- Kaiser Permanente Colorado, Denver, CO
- Harvard Pilgrim Health Care, Boston, MA

More than 85 articles using VSD data have been published in peer-reviewed journals; more than 75 studies are now in progress. Current studies are looking at the safety of newly licensed vaccines, evaluating the safety implications of new recommendations for existing vaccines, examining clinical disorders following immunization, and assessing vaccine safety in special populations.

Dr. Gargiullo noted that the possibility of continuous monitoring of newly licensed vaccines has stimulated the development of new statistical methods. He discussed self-control case series methodology in which the probability of an adverse event during a defined risk period (following vaccination) is compared with the probability during control periods for the same person. He also noted that different statistical methods may be combined to fit epidemiological needs.

Dr. Gargiullo discussed the origin of VSD research ideas and the process of initiating and performing VSD studies. He noted that the number of researchers wanting access to VSD data make prioritization a critical issue.

Dr. Gargiullo also addressed current challenges facing the project. These include the need to expand the number of MCOs providing adult data, the trade-off between timeliness and quality of vaccine safety studies, public perception of data-sharing issues, and a need to be open to the possibility of adverse events that have yet to be considered.

CISA Network—John Iskander

The CISA Network has been in existence for approximately 5 years. Its goals are

- To study the pathophysiology of adverse events following immunization;
- To identify risk factors associated with the development of adverse events following immunization; and
- To develop evidence-based guidance for use by clinicians.

The CISA Network sites are

- Boston Medical Center;

- Columbia University Medical Center;
- Johns Hopkins University;
- Northern California Kaiser Permanente;
- Stanford University Medical Center; and
- Vanderbilt University Medical Center.

Accomplishments of the CISA Network include

- The establishment of a registry and repository for the enrollment of persons experiencing an adverse event following immunization and for the collection and storage of specimens;
- The development of an algorithm for the management of hypersensitivity reactions immediately following vaccination; and
- Contribution to the characterization and monitoring of adverse events following smallpox vaccination of civilian healthcare workers.

Priorities of research studies are determined by the CISA team leader and ISO director after input from CISA team members and principal investigators at the network sites and are based not only on CISA's own goals, outlined above, but on VAERS and VSD signals and on the severity or high incidence of particular adverse events. Research proposals must be scientifically sound and logistically and financially feasible.

CDR Iskander outlined the process for initiating a CISA research project, from initial discussion of the concept, through presentation to CISA investigators and the establishment of working groups, to institutional review board approvals and Health Insurance Portability and Accountability Act (HIPAA) data use agreements. He spoke, also, of the challenges facing CISA, which include the rarity and geographic dispersion of cases, the costliness of clinical and DNA studies, and the maintenance of HIPAA requirements for data privacy.

CDR Iskander closed his remarks with examples of CISA projects.

Discussion

CDR Iskander opened the floor to questions on the presentations on the VSD and CISA.

In response to a question about how CISA interfaces with other agencies in research, CDR Iskander said that the focus is on the feasibility of the proposed study, including the feasibility of enrollment, the availability of the required expertise, and an appropriateness of fit between the research needs and the agency resources.

Dr. Gargiullo was asked how many of the 85 papers published using VSD data required chart review. He replied that most do and added, because the question implied a concern

regarding the time a study could take, that it is rare that a VSD study is complete within a few years.

This led to a discussion of research priorities. A participant voiced the concern that suggestions from the present meeting would not be in the research queue for years and asked for a commitment to shift priorities if the discussion raises issues of immediate concern. CDR Iskander replied that that was the intent of the meeting.

A participant expressed admiration of the case series method that Dr. Gargiullo had discussed and asked whether there was ever the temptation to redo earlier studies with more recently developed statistical tools. CDR Broder acknowledged that there could be such a desire, for several reasons, although for any previous study to be revived, it would need to be viable in terms of current research needs.

Dr. Gargiullo was asked whether the backlog of VSD research projects was due to limited resources. He responded that the major difficulty was that there were not enough researchers at the MCOs.

Brainstorming Session 1: Infant and Child

For each of the brainstorming sessions, CDR Broder provided background information in the form of the concerns raised, and suggestions made, at a previous meeting of ISO external consultants. She also reviewed US immunization recommendations for civilians for each life stage. She reminded the participants that they should

- Identify the important gaps in our current knowledge;
- Indicate why these areas were important; and
- Suggest possible approaches to address the areas identified.

She noted that the focus would be on the first two of the three tasks but that insights as to possible approaches would be welcome. The ideas, she said, could be either thematic or specific.

Following each brainstorming session, participants were asked to fill in a form asking for the five most important research topics; this information is summarized in Appendix A.

Dr. Dixie Snider served as moderator for the brainstorming sessions.

The following were suggested as areas for research or issues of concern. Responses are listed in the order in which the suggestions were made.

- Mumps/measles/rubella vaccine (MMR) and thrombocytopenia—mechanisms
- Mumps/measles/rubella/varicella vaccine (MMRV) versus MMR and Varivax given separately

- Reimmunization protocols (challenge/rechallenge)
  - Systematic guidelines for medical exemption following an adverse event, including identifying false contraindications
- Causality assessment, particularly in complex clinical cases
    - Improved data in VAERS to support this
    - Rechallenge reproducibility (worsening of AE)
- Sudden unexpected death following infant vaccination (up to 18 mo.)
  - Record individual level, birth dose
  - Epidemiological studies, mortality rates
- How high a priority should thimerosal/autism studies be?
  - Raises questions of communication among physicians, patients, and researchers
  - Focus on other neurological conditions than autism
    - Use the self-control case series statistical method to screen for neurological visits/neurodevelopmental disabilities within specified time periods after vaccination
    - Focus on special populations (e.g., low birth weight)
    - Focus on other issues involving autism and vaccines but not thimerosal
    - Adjuvants, combination vaccines- other potential etiology for autism caused by vaccines that do not contain thimerosal
- Risk perception research (e.g., level of public concern regarding multiple vaccinations)

Brainstorming Session 2: Adolescent (ages 11 to 18)

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

- Human papillomavirus (HPV) vaccine use in immunocompromised adolescents
    - May apply to other vaccines (e.g., second dose of varicella vaccine)
- Immunocompromised hosts
    - Effects of vaccination on disease (viral load, CD4 counts, etc)
    - Local and systemic unanticipated AEs
    - Replacement serotypes
    - How does immunodeficiency or immunoreactivity affect vaccine dose
- General issue of special populations in adolescence
    - It may be possible to use existing networks (e.g., for HIV clinical care or research)
- Seek out adolescent minority groups for study
- Establish baseline rates of neuropsychiatric, rheumatic, and autoimmune disease
- Need for improved risk-benefit calculations
- There is a need to look for rare adverse events (especially for vaccines, like quadrivalent meningococcal conjugate (Menactra®), that are preventing rare diseases)

- Studies to rule out spurious associations of vaccines with normal adolescent phenomena (e.g., acne, onset of menses)
- Safety of concomitant vaccines (e.g., quadrivalent meningococcal conjugate, tetanus-diphtheria-pertussis (Tdap), and HPV vaccines together or separately)
- Changes in disease incidence, by gender, in adolescence
- Establish baseline side-effect profiles of specific vaccine components (e.g., novel adjuvant for bivalent HPV)
- Improved communication regarding expected side effects of vaccines

Brainstorming Session 3: Adulthood and Pregnancy

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

- Relevant safety information from passive immunization (e.g., intravenous immunoglobulin, Rh-immune globulin)
- Establish a single national registry for vaccine exposures in pregnancy
- Better ways to study intended/unintended vaccine exposures during pregnancy
- Chronic fatigue syndrome as an adverse event (e.g., anthrax vaccine, new adjuvanted influenza vaccines)
- Safety of reimmunization using pneumococcal polysaccharide vaccine
- Ways to study previously unstudied vaccine combinations
- "Disability" as an outcome following vaccination
  - Quantify level of disability- include in registry
- Issues of immunosenescence for zoster vaccine
  - As immunity wanes, potentially increased incidence and increased severity of wild type disease: how does vaccine impact?
- Are current systems adequate to study off-label use? (e.g., Tdap, zoster vaccines)
  - If vaccines are expensive, are they given to people outside of recommendations
  - Unintentional/Intentional Off label use
- Rare adverse events (e.g., vasculitis) following influenza vaccine
- Travel vaccines—off-label use
- Travel clinics—potential setting for research
- Dose response to adjuvants
- Framework needed to study multiple near-concurrent vaccination
- "Hyperimmunization" within the Department of Defense
- ACIP adult guidelines extrapolated from children recommendations?
  - Guidelines based on civilian population that does not receive as many vaccines
- Gender and race considerations, generally
- Myopericarditis as an outcome following vaccines other than smallpox vaccine
- Other cardiac adverse events
- Age-specific considerations within the adult age range
  - Study design considerations

Brainstorming Session 4: Vaccine Adjuvants and New Vaccine Technologies

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

- Subpopulation affects
- Gender effects
- Dose response
- Better definition of baseline reactivity
- More emphasis on nonclinical studies
- Difficulty of ascribing causality to specific components of vaccines
- Better characterization and communication of vaccine components (e.g., by the FDA and by the manufacturer), including changes made in vaccine composition, over time, by the manufacturer
- Much research in this area will need to be led and/or conducted by agencies and programs outside CDC
- "Class effect" as a postlicensure surveillance strategy
- Need to look across age groups
  - Broad age categories an oversimplification
  - Immune response functions in complex ways (e.g., autoimmune functions may be affected by age, race, and gender
  - Younger age groups may have more reactive immune systems, while older persons' immune systems may be less reactive?
- Need to define the adverse events of most interest
- Formal risk assessments needed for each vaccine component
- Vectors—"class effects" (e.g., poxvirus for human immunodeficiency virus vaccines)
- How to list vaccine components (e.g., in package insert) in order to be detailed but easy to understand?
- It is possible that 2 vaccines being licensed may never be given together until both are licensed, so no information about potential adverse events from the combination may be available before licensure

Discussion and Input from Federal Scientists: Synthesis, Prioritization, and Potential Collaboration

Dr. Snider moderated the discussion. The following points were raised:

- Strive for balance between "external" (i.e., what the public perceives as important) and "internal" safety issues as a focus for research
- Real-time active surveillance systems (e.g., for pandemic influenza)
- Linkage among existing registries/immunization information systems to enhance real-time surveillance

- Establish a national registry and repository to aid in tracking long-latency exposures (e.g., simian virus 40)
  - Need for multisite clinical linkages
- Overcome barriers to research (e.g., remote enrollment)
- Pandemic influenza integrated into research agenda
  - Identify new projects to be taken on by other agencies

CDR Broder thanked the participants. She said that the next step would be to incorporate the suggestions from today's meeting and the previous meeting of external consultants into the draft research agenda for NVAC's review. It will be important for the research undertaken to provide meaningful information that will enhance public health.

Closing Remarks—Bruce Gellin

In his closing remarks, Dr. Gellin stressed the need for readiness across all Department of Health and Human Services agencies when the research agenda is finalized in 2008.

APPENDIX A: Summary of Brainstorming Session Worksheets

Overview:

At the completion of each brainstorming session, participants were asked to complete worksheets listing the top 5 vaccine safety research topics in rank order. For each topic, participants were also asked to note the reason for importance and identify potential approaches to study it. An ISO medical officer reviewed the worksheets and summarized the feedback by key research themes.

Findings:

Forms Returned:

Fifteen individuals completed forms for at least one of the four sessions. At least one scientist from each of the following agencies completed a form for each session: NVPO, NIH, FDA, CDC (outside ISO), DoD, and HRSA. Staff from ISO, CDC did not complete forms.

Suggested Research Topics Identified by ≥1 Rater:

Superscripts are used to show if at least one rater ranked the topic as a first (1) or second (2) priority level. Other levels of priority are not shown.

Session 1: Infants and Children

- Vaccine:
  - Newly licensed vaccines
  - MMR and thrombocytopenia (including genetic risk factors and prevention strategies)[1]
  - Rotavirus and intussusception, including genetics[2]
  - MMRV (different than individual MMR and varicella vaccines)
  - Combination vaccines[2]
  - Pediatric bioterrorism vaccines
  - Pediatric pandemic vaccines (especially with novel adjuvants)[2]
- Vaccination practices:
  - Multiple vaccines at same visit, including risk for neurodevelopmental disorder (also nearly concurrent vaccination)[1,2]
  - Analysis of medical exemptions for vaccination
  - Off label use of vaccines[1]
  - Clinical guidelines for medical exemptions, outcomes rechallenges[1]
  - Clinical guidelines for adverse event causality assessment[2]
- Adjuvants and non-antigen components of vaccines
  - Cumulative exposure to proteins (e.g., diphtheria, aluminum)
  - Thimerosal and neurodevelopmental disorders, including those other than autism[1]
  - Novel adjuvants: need long-term follow-up[1]
- Host:
  - Premature, low birth weight[2]
  - Presence of genetic and metabolic conditions
  - Immunocompromising conditions (nephrotic syndrome, HIV)
  - Genetic risk factors[1]
  - Race
- Reported adverse event following immunization (AEFI)
  - Serious adverse events for newly licensed vaccines[1]
  - Life threatening disorders, including allergic
  - Allergic disease (e.g., wheeze after LAIV)[2]
  - Unexpected death in infancy/ deaths[2]
  - Encephalopathy, including acute disseminated encephalomyelitis (ADEM)
  - Medically attended events after vaccination (case series method)[1]
  - Chronic disease onset long after vaccination
  - Autism and other neurodevelopmental disorders (including other than thimerosal-containing vaccines and MMR; assess causes)[1]
- Risk perception
  - Risk perception and communication (particular around autism)
  - Perception of causality of neural disease in infants through 3 years[2]
  - Reasons for delay in immunization[2]

Session 1: Infants and Children (continued)

- Other related to vaccine safety research
  - Collect control samples for specimens collected via CISA[1]
  - Background rates for childhood medical events (< 5 years)
  - Is immunization compliance associated with wellness?[2]
- Other not related to vaccine safety research
  - Surveillance for serotype replacement for pneumoccocal disease
  - Vaccine effectiveness in low birth weight populations

Session 2: Adolescents (non-pregnant) Aged 11-18 Years

- Vaccines
  - Newly licensed vaccines[1]
  - HPV, especially new vaccine with novel adjuvant; suggest broad look for adverse events; assess risk in persons with chronic conditions, including HIV (noted HPV also licensed for girls aged 9 and 10 years)[1,2]
  - MCV4, especially risk for Guillain-Barre syndrome (GBS)[1]
  - Tdap
  - Varicella
  - Travel vaccines, including use with regular vaccines
  - Combination vaccine
- Vaccination practices
  - Simultaneous vaccination[1,2]
  - Vaccination of persons immune (problems with incomplete immunization history)
  - Clinical guidelines for medical exemptions, outcomes rechallenges
  - Clinical guidelines for adverse event causality assessment
- Non-antigen components
  - Diphtheria toxoid (multiple doses), including risk for GBS[1]
  - Adjuvants, especially new adjuvant in HPV (BLA)
- Host:
  - Gender
  - Immunocompromised, particular for live viral vaccines
  - Chronic conditions (including HIV and immunocompromised – especially live vaccines)
  - Genetic risk factors
  - Sports (effect of strenuous exercise on AEFI)

Session 2: Adolescents (non-pregnant) Aged 11-18 Years

- Reported adverse event following immunization (AEFI)
  - Establish baseline rates for adverse events that could be perceived as AEFI[1]
  - GBS and other demyelinating diseases (especially with MCV4, influenza vaccine or hepatitis vaccine)[2]
  - Autoimmune diseases
  - Baseline rates for adolescent health conditions, including gynecologic, acne, psychiatric, especially with HPV[2]
  - Sexual initiation, especially with HPV[1]
  - Risk perception and communications
  - Overall communication for safety
- Other not related to vaccine safety research
  - HPV serotype replacement
  - Improve methods for risk benefit assessment, especially for vaccines preventing rare diseases
  - Consent issues for adolescents

Session 3: Adults Aged ≥19 Years and Pregnant Women

- Vaccines
  - Newly licensed vaccines[1]
  - Live vaccine safety in older persons
  - Multiple pneumococcal polysaccharide vaccines; how many doses is it safety to receive as an older adult?[2]
  - Zoster vaccine, including immunosenescence[1]
  - Influenza vaccine and association with neurologic and rare AEFI, other than GBS (e.g., vasculitis)
  - Travel and deployment vaccines (e.g., anthrax, smallpox), in conjunction with regular vaccines and medications (suggested use of DoD cohort)[2]
  - Influenza vaccine in pregnant women[1]
  - Tdap vaccine in pregnant women[1]
- Vaccination practices
  - Simultaneous and near-simultaneous vaccination
  - Off label use of vaccines (e.g., Zoster, Tdap, HPV)[1]
  - Clinical guidelines for medical exemptions, outcomes rechallenges[2]
  - Clinical guidelines for adverse event causality assessment[1]

Session 3: Adults Aged ≥19 Years and Pregnant Women (continued)

- Non-antigen components
  - Total adjuvant content received with multiple vaccines; dose response
  - Aluminum (exposure from multiple vaccines; component of smallpox and Anthrax vaccines)
  - Adjuvants - pre-licensure trials need 3 arms to assess safety in adjuvant-only recipients[1]
  - Adjuvants in multiple vaccines and combination vaccines (e.g., role of adjuvants and autism)[2]
  - Adjuvant risk in different populations (e.g, across age, race and gender groups; autoimmunity in older persons)
  - Adjuvants in pandemic and pre-pandemic vaccines
  - Effects of cumulative levels of components in vaccines[2]
  - Thimerosal and risk for AEFIs in pregnant women[1]
- Host:
  - Gender differences for AEFIs, including serious adverse events
  - Interactions with other medications, particularly in older adults[1]
  - Chronic conditions[1]
  - Older age, immunosenescence[1,2]
  - Ethnicity
  - Genetic risk factors
  - Pregnancy (suggestions for single maternal registry, pregnancy outcome database)[1,2]
  - Increased fetal inflammatory mediators affecting neonatal outcome such as low birth weight
- Reported adverse event following immunization (AEFI)
  - Establish baseline rates for adverse events that could be perceived as AEFI, adjusting for gender, race and age
  - Demyelinating diseases[1]
  - Chronic diseases, with onset in older adults[2]
  - Chronic fatigue syndrome[2]
  - Common AEFIs with ranges of severity, including syncope, injection site reactions and more severe events
  - Disability outcomes
  - Autoimmune diseases (e.g., multiple sclerosis, hepatitis)
  - AEFIs in pregnant women (VSD case series)
- Other related to vaccine safety research
  - Live vaccine transmission studies
  - Break adult age-group into sub-groups
  - Therapeutic vaccine safety, including cancer vaccines
- Other not related to vaccine safety research
  - Vaccine immunogenicity studies in the elderly[2]
  - Affect of demographic factors (e.g., ethnicity) on vaccine effectiveness
  - Vaccine effectiveness studies in pregnant women
  - Elective termination of pregnancy practices after vaccine

Session 4: Vaccine Adjuvants, Other Non-antigen Vaccine Components and New Vaccine Technologies

Related topics were also identified during the life-stage sessions, described above.

- Identify non-antigen components in each vaccine and assess safety profile of these components; consider other biological and environmental exposures (suggestion that ISO is not the lead) [1]
- Association of adjuvants and AEFI (and effectiveness); look at effect of single and multiple adjuvants administered once or multiple times[1]
- Cytokine responses to new adjuvants; cell-based safety [1]
- Identify potential adverse events in phase 3 trials for which number of subject was too small to fully assess risk; ensure information is communicated to ISO[1]
- Long-term risk of repeated exposure to adjuvant vaccines in older persons, particularly for autoimmune diseases[2]
- Assess if vaccines with same ingredients are associated with similar AEFI[2]
- Exposure to aluminum in multiple vaccines
- Cumulative exposures to proteins (e.g., diphtheria toxoid, CRM, tetanus toxoid)
- Surveillance for adjuvant safety (suggest large surveillance evaluation)
    - Across product classes and age-groups
    - Long-term AEFIs, including cancer (suggest collaboration with NCI SEER)
- Identify specific AEFI of interest for new adjuvant vaccines, by age, gender and race; assess background rates
- Evaluate for cardiotoxicity with novel pox virus vector vaccines
- Pre-exisiting immunity with recombinant viral vectors and reactogenicity (e.g., adenovirus 5)
- Investigate AEFI (and effectiveness) in sub-populations of older persons to determine if additional or fewer doses are needed.

Appendix B: Abbreviations

Abbreviation	Definition
ADEM	acute disseminated encephalomyelitis
AEFI	adverse event following immunization
BLA	biologics license application
CDC	Centers for Disease Control and Prevention
CISA	Clinical Immunization Safety Assessment Network
DoD	Department of Defense
FDA	Food and Drug Administration
GBS	Guillain-Barre syndrome
HPV	human papillomavirus vaccine
HRSA	Health Resources and Services Administration
ISO	Immunization Safety Office
LAIV	live, attenuated influenza vaccine
MCV4	meningococcal conjugate vaccine
MMR	measles, mumps and rubella vaccine
MMRV	measles, mumps, rubella and varicella vaccine (combined)
NCI	National Cancer Institute
NIH	National Institutes of Health
NVPO	National Vaccine Program Office
SEER	Surveillance, Epidemiology, and End Results
Tdap	tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine
VSD	Vaccine Safety Datalink