Report from an Individual Simultaneous Consultation on the Centers for Disease Control and Prevention's Immunization Safety Office Research Agenda

May 10 and 11, 2007, Atlanta, GA

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Table of Contents

Executive Summary: Individual Simultaneous Consultation on the Immunization Safety Office Research Agenda

Background

- In response to an Institute of Medicine (IOM) recommendation and as part of its strategic planning, the Centers for Disease Control and Prevention's (CDC) Immunization Safety Office (ISO) is developing an ISO research agenda that includes, but is not limited to, the Vaccine Safety Datalink (VSD) project. This research agenda will have a 3-to-5 year horizon and is being developed with extensive partner and expert input.
- After the initial phase of the process, the National Vaccine Advisory Committee (NVAC) will conduct a scientific review of a draft ISO research agenda and provide feedback to CDC.
- To initiate the process of developing the ISO research agenda and to inform its development, ISO convened an individual simultaneous consultation with seven peer-recommended external scientists in Atlanta, GA on May 10 and 11, 2007.
- One scientist served as the moderator for discussions during the meeting. The scientists represented the fields of pediatric infectious diseases, adult infectious diseases, obstetrics and gynecology, immunology, genomics, and epidemiology.

Charge to Individual Consultants:

- To identify vaccine safety topics and gaps in knowledge that will be important for public health and could be studied by ISO.
- To advise on prioritization of the topics.
- To propose potential approaches to study the topics.

Approach

- During the meeting, several brainstorming discussions were held to generate ideas. The discussion sessions were based on 1) five life stages (i.e., infant, child, non-pregnant adolescent, non-pregnant adult, and pregnant women), and 2) cross-cutting areas (i.e., vaccine safety public perception; adjuvants, other non-antigen vaccine components, and new vaccine technologies; surveillance; and clinical outcomes that occur years after vaccination)
- Consultants completed feedback worksheets for each of these sessions. In addition, six consultants gave oral presentations of their individual recommendations.
- An ISO medical officer reviewed consultant input from the discussions, presentations, and worksheets and summarized the suggestions into scientifically relevant categories.
- This report:
    - Expresses ideas that represent the individual opinions of consultants; no attempt was made to achieve consensus.
    - Does not necessarily depict the topics or prioritization of topics that will be included on the ISO research agenda; some suggestions from consultants may not be relevant to the ISO research agenda because they are underway or have been adequately addressed, are outside the scope of ISO's mission, or are not research areas.

Findings

Overall, the key vaccine safety research areas identified during the individual simultaneous consultation were:

- Vaccine-specific
  - Safety monitoring for new vaccines or vaccines with new indications; *examples are: rotavirus vaccine, live, attenuated influenza vaccine (LAIV), human papillomavirus (HPV) vaccine, and zoster vaccine.*
  - Safety of vaccines when used for a purpose different from one of the indications for which the product is approved by the Food and Drug Administration (FDA) (i.e., "off label" use): *examples include use of rotavirus vaccine in infants outside the FDA-approved age-range; the use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine (Tdap) in older persons; and LAIV use in persons with chronic medical conditions.*
  - Safety of combination vaccines
  - Safety of annual influenza vaccines across the life stages
  - Safety of pandemic influenza vaccines across the life stages

- Host factors which might predispose an individual to vaccine adverse events (VAEs)
  - Demographic factors; *examples are gender and race*
  - Underlying medical conditions; *examples are inborn errors of metabolism, prematurity, asthma, and diabetes.*
  - Genetic factors; *an example is identifying genetic polymorphisms associated with VAEs through the use of genome-wide association studies.*

- Clinical outcomes
  - VAEs potentially associated with particular vaccines; *examples are intussusception after rotavirus vaccine and wheezing after LAIV.*
  - Outcomes reported or alleged to occur after a variety of vaccines; *examples include demyelinating disorders, autoimmune diseases, and neurodevelopmental disorders.*
  - Background rates of health conditions that occur during particular life-stages that could be helpful to assess risk for VAEs in these life stages; *examples are cardiac disorders in older adults and thromboembolic events in adolescents using oral contraceptives.*

- Immune pathophysiologic mechanisms which may lead to VAEs; *an example is characterizing the development of the immune system at different stages of life, including pregnancy, and how these changes may relate to risk for VAEs.*

- Safety of various adjuvants and non-antigen components of vaccines; *examples include, new adjuvants that contain Toll-like receptor agonists, conjugate proteins, and exipients.*

- Epidemiologic research and surveillance areas; *examples are use of signal detection algorithms to detect potential adverse events, approach(es) for rapid signal assessment, design and validation of more specific case definitions, assessment of sources for rapid unbiased case ascertainment, selection of appropriate comparison groups, and data analysis approaches regarding association of an outcome with a vaccine.*

- Risk perception; *examples include tracking public perception of vaccine safety issues and identifying effective strategies to communicate accurate risk information with the public, clinicians and media. Autism was identified as one example of a perceived vaccine safety concern.*

Background

CDC's Immunization Safety Office (ISO) is responding to a recommendation from the 2005 Institute of Medicine (IOM) report, "Vaccine Safety Research, Data Access and Public Trust."[1] The IOM recommended that a subcommittee of the National Vaccine Advisory Committee (NVAC) review and provide advice on the Vaccine Safety Datalink (VSD) project research plan. In addition, ISO has begun a strategic planning process and it was recognized that an ISO research agenda would be an important component of this plan. Because effective research requires collaboration among all the ISO research and surveillance components, ISO is developing a comprehensive scientifically robust research agenda with extensive partner and expert input. This agenda will include, but is not limited to, the VSD project, and it will have a 3-to-5 year horizon. A draft ISO research agenda will be shared with the NVAC Subcommittee on Vaccine Safety for its scientific review. NVAC will provide input about the draft ISO research agenda to CDC and CDC/ISO will seriously consider this advice as it finalizes the research agenda.

To initiate the process of developing the ISO research agenda and to inform its development, ISO convened a meeting of individual expert scientists in Atlanta, GA on May 10 and 11, 2007 (Appendices A and B). Seven peer-recommended scientists representing the fields of pediatric infectious diseases, adult infectious diseases, obstetrics and gynecology, immunology, genomics, and epidemiology provided individual simultaneous consultation. One of these scientists served as the moderator for discussions during the meeting. In addition, seven liaison representatives from federal agencies, advisory committees, ISO research collaborations, and several staff persons from CDC's Immunization Safety Office and the Office of the Chief Science Officer participated (Appendix C).

Charge

The charge to each external consultant was to: 1) identify emerging vaccine safety questions and gaps in knowledge that will be important for public health and could be studied by ISO, 2) advise on prioritization of the topics and 3) propose some potential approaches to study the topics.

Approach

Before the meeting consultants received briefing materials about the ISO program, including lists of research studies underway or planned (Appendix D). They were asked to prepare presentations describing important areas for vaccine safety research in their areas of expertise and provide ideas on a framework for discussion during the meeting (Appendix G). On the basis of input from teleconferences before the meeting, the meeting included nine group brainstorming sessions. Five covered life stages: infants aged <1 year, children aged 1-10 years, non-pregnant adolescents aged 11-18 years, non-pregnant adults aged ≥19 years, and pregnant women of all ages. Four were cross-cutting

[1] Vaccine Safety Research, Data Access, and Public Trust**,** available at http://www.nap.edu/catalog/11234.html, accessed 1/16/08.

sessions on: the role of public perception of vaccine safety in shaping the research agenda, new vaccine technologies and non-antigen vaccine constituents, vaccine safety surveillance, and vaccine adverse events (VAEs) that occur years after vaccination. For each brainstorming session, participants heard relevant background information, focusing on vaccines recommended for routine use in the civilian population by the Advisory Committee on Immunization Practices (ACIP).[2] The moderator then facilitated group discussion about the topics. At the end of each brainstorming session, each consultant completed a feedback worksheet asking about key research topics, prioritization, and some feasible approaches to study the research topics (Appendix E). Liaisons and CDC participants did not complete worksheets. In addition, six consultants presented their individual recommendations by discipline during the meeting (Appendix G). A detailed administrative summary of the meeting is provided in Appendix A.

An ISO medical officer reviewed consultant input from the discussions, presentations, and worksheets and summarized the suggestions into scientifically relevant categories. This report provides a summary of the full spectrum of individual input from the individual consultants to ISO. It also contains the general themes that emerged during discussions among all meeting participants. No attempt was made to achieve consensus among the consultants; however, for ease of presentation in some sections suggestions from two or more of the consultants are referred to collectively as those from the "consultants." In practice, during the meeting consultants thought broadly about vaccine safety issues, without consideration of funding or program infrastructure or the ISO research activities already underway. Some of the ideas expressed in this report may not be relevant to the future ISO research agenda for the following reasons: 1) they have already been adequately addressed or are underway in ISO, 2) they are outside the scope of the ISO mission and would be better studied by another program or agency, or 3) they are not research activities.

Summary of Key Input from the Brainstorming Sessions

In each section, we present a summary of the key themes that emerged during the brainstorming sessions. For the life stages, consultant input is categorized into five areas: 1) vaccine-specific, 2) host factors which might predispose an individual to VAEs, 3) clinical outcomes, 4) other research areas and 5) non-research areas. Clinical outcomes include VAEs that have been reported or alleged to occur after a particular vaccine or a variety of vaccines. The terms "vaccine adverse event (VAE)" and "adverse event following immunizations (AEFI)" are used interchangeably in this report and appendices and do not necessarily imply that a particular clinical condition has been causally linked with a vaccine exposure. If at least one consultant indicated the topic was a high priority, it is marked with an **asterisk*** in the list of suggestions from each brainstorming session. Not all five areas were addressed in each session. Ideas that were discussed in more than one brainstorming section or in the consultant presentations are listed in the most relevant session or cross-referenced. For each topic, consultants were asked to suggest

[2] The 2007 ACIP immunization schedule for persons aged 0-18 years is available at http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5551a7.htm?s_cid=mm5551a7_e; the 2006 ACIP adult immunization schedule is available at http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5540a10.htm?s_cid=mm5540a10_e., accessed 10-20-07.

approaches that could be used: large-linked database study, other epidemiologic study with or without biological specimens, clinical trials and other study designs (Appendix E). For most research topics, multiple approaches were suggested. For some areas, basic science or behavioral research methods were recommended.

1. Life Stage: Infants aged <1 year

A. Background:

In May 2007, the following inactivated vaccines were routinely recommended by the ACIP for infants aged <1 year: diphtheria and tetanus toxoids and acellular pertussis (DTaP), *Haemophilus influenza* type b (Hib), pneumococcal conjugate vaccine (PCV7), inactivated polio vaccine (IPV), hepatitis B, and trivalent inactivated influenza vaccine (TIV) (for persons aged ≥6 months). In addition, DTaP-Hepatitis B- IPV is currently licensed and a biologics license application (BLA) has been submitted for DTaP-IPV-Hib. Rotavirus vaccine was the only live vaccine routinely recommended by ACIP for infants in the United States.

B. Consultant Input: (see also Summary of Input from Individual Consultant Presentations: Pediatric Infectious Diseases, page 16)
Vaccine-specific: Safety monitoring is needed for all newly licensed infant vaccines.* Specific suggested research areas are:

- Rotavirus vaccine:* Consultants highlighted rotavirus vaccine safety as an important research area. The main clinical outcome of concern is intussusception (IS) which was associated with receipt of an earlier rotavirus vaccine that is no longer in use in the United States. A particular issue of concern is use of the vaccine outside the recommended age groups (e.g., administration of dose one after 12 weeks of age). Both large- linked databases and other epidemiologic study methods could be used to assess risk for IS after rotavirus vaccine; case control studies in populations larger than the VSD may be needed. Consultants noted that another rotavirus vaccine (human attenuated formulation) would be submitted for a BLA in the near future (it was submitted in 6/2007[3]); comparing safety profiles between two rotavirus vaccines, if this second rotavirus vaccine is licensed, would be important. Other suggestions were to evaluate the effect of maternal rotavirus antibody concentrations on risk for infant reactogenicity after rotavirus vaccination and the extent of viral shedding in rotavirus vaccine recipients.
- Influenza vaccines:* Influenza vaccine safety (TIV and live, attenuated influenza vaccine [LAIV]) is important for annual vaccination programs and pandemic preparedness. Consultants suggested researching the safety of LAIV in infants, an off-label population[4]. A specific concern is risk for wheezing events, including reactive airway disease and asthma. Multiple approaches could be used to study

[3] Redbook Online: Status of Licensure and Recommendations for New Vaccines. http://aapredbook.aappublications.org/news/vaccstatus.shtml, accessed 10/20/07.
[4] "Off label" use occurs when a vaccine is used for a purpose different from one of the indications for which the product is approved by the Food and Drug Administration (FDA).

Life Stage: Infants (continued)

influenza vaccine safety. Consultants commented that there are no data on safety of pandemic influenza vaccines in this population.

- Combination vaccines:* Consultants emphasized the need to study the safety of combination vaccines before and after licensure in infants. One could assess if risk for VAEs were higher after combination vaccines or after the individual vaccines, using multiple methods. It was noted that combination vaccines might be more reactogenic than the individual vaccines, administered simultaneously. Specific clinical outcomes of concern were not described. It is important to figure out which component of a combination vaccine is associated with a particular VAE. It was noted that several new combination vaccines are in the pipeline, including a Hib/meningococcal vaccine.
- Bioterrorism vaccines:*: VAEs after administration of vaccines for bioterrorism preparedness or response has generally not been evaluated in infants.

Host factors which might predispose an individual to VAEs:

- Premature infants:* There is a paucity of data on vaccine safety in premature and low birth weight infant populations. Both of these populations have been increasing in size in recent years in the United States. It was suggested that premature infants may have increased rates VAEs after vaccination. A consultant asked if risk for apnea and bradycardia might be increased in this population after vaccination. Another suggestion was to evaluate the effect of maternal antibody on risk for reactogenicity after vaccination in premature infants.
- Low birth weight infants:* Similar principles as described for premature infants apply. Very low birth weight infants were a population of particular concern.
- Infants with genetic and metabolic disorders:* Similar principles as described for premature infants apply. A consultant raised concern that fever following vaccination in this population may be clinically important.
- Genetic risk factors: * (see Summary of Input from Individual Consultant Presentations: Genomics, pages 18-19)

Clinical outcomes:

- Consultants suggested establishing baseline rates of clinical conditions that have been reported as VAEs so that accurate assessment of any potential risk can be determined. In particular, they suggested assessing baseline rates of neurodevelopmental disorders. One consultant advised that establishing baseline rates in isolation is a not useful activity (see also Summary of Input from Individual Consultant Presentations: Epidemiology, pages 19-20).

Other research areas: Multiple approaches, including basic science and genomics research, could be used to study the following areas:

- Responses to vaccine adjuvants* (see Cross-cutting Sessions: Non-antigen Vaccine Constituents and New Vaccine Technologies, page 14)
- Simultaneous administration of multiple vaccines
- Public acceptance of vaccines (see Cross Cutting Sessions: Role of Public Perception in Shaping the Research Agenda, pages 13-14))
- Effect of mode of delivery on adverse events, e.g. oral route

Life Stage: Infants (continued)

- Characterization of immunological immaturity and development of immune response to understand and possibly predict the risk for a VAE.*
- Impact of vaccination on human indigenous flora and heterologous disease (most important age group to assess), and the role of indigenous microbiota in determining the nature of the host response to vaccines.
- Environmental risk factors which may influence the occurrence of VAEs.*
- Recognition of VAEs: A consultant asked how well we are able to recognize VAEs in the infant age group.

2. Life Stage: Children aged 1–10 years (see also Summary of Input from Individual Consultant Presentations: Pediatric Infectious Diseases, page 16)

A. Background

In May 2007, excluding catch-up vaccination, ACIP recommended several inactivated vaccines for children aged 1-10 years: DTaP, IPV, hepatitis A, PCV7, Hib, and TIV (aged <5 years and children with high-risk indications). Meningococcal polysaccharide vaccine (MPS4) and pneumococcal polysaccharide vaccine (PPV23) were recommended for certain high-risk children. Biologics license applications (BLA) had been submitted for DTaP-IPV-Hib and meningococcal conjugate vaccine (MCV4) (licensed for use in children aged 2-10 years 10/07). Four live vaccines were used in children: measles, mumps, rubella (MMR), varicella, MMRV (combination MMR and varicella), and live, attenuated influenza vaccine (LAIV). Recently ACIP recommended that a second dose of varicella vaccine be administered to children aged 4-6 years. In May 2007, LAIV was licensed for persons aged >=5 years and a biologics license application had been submitted to revise the license to included children aged 12-59 months (LAIV was licensed for use in children aged 24-59 months in September 2007).

B. Consultant Input

Vaccine-specific: New vaccines are an area of interest.

- Influenza vaccines safety:* The principles from the infant life stage section of the report apply (see also Summary of Key Input from Brainstorming Sessions [infant life stage], page 7). A specific area of interest is risk for wheezing, reactive airway disease, and asthma after LAIV. In addition to short-term wheezing events, risk for long-term pulmonary consequences should be studied. Researching the safety LAIV in children with chronic diseases, such as diabetes also was suggested. Because studies have suggested that LAIV, may have greater efficacy than TIV in children, studies comparing the risk/benefit profiles of LAIV and TIV may be useful.
- Combination vaccines: The same principles described in the infant life stage section of the report apply (see also Summary of Key Input from Brainstorming Sessions [infant life stage], page 8).

Host factors which might predispose an individual to VAEs:

- Chronic disease*: Consultants emphasized that inadequate safety data are available at the time of licensure for children with underlying medical conditions. Risk for VAEs should be assessed in children with chronic conditions. Specific

Life Stage: Children

underlying conditions mentioned were diabetes type 1 and 2 and reactive airways disease and asthma.

- Premature birth:* The same principles described in the infant life stage apply (see also Summary of Key Input from Brainstorming Sessions [infant life stage], page 8).
- Gender: Consultants suggested assessing the influence of gender on VAEs.

Clinical outcomes

- Autism and other neurodevelopmental disorders:* Consultants suggested establishing baseline rates of neurodevelopmental disorders, including autism. A goal is to improve objective diagnostics for cases definitions. Comprehensive studies, including genetic studies are needed to define the etiology of these conditions.
- Establishing baseline rates of other conditions reported as VAEs* including inflammatory bowel disease, multiple sclerosis and Guillain-Barré Syndrome (GBS) was suggested. One consultant advised that establishing baseline rates in isolation is a not useful activity (see also Summary of Input from Individual Consultant Presentations: Epidemiology, pages 19-20).
- Diabetes types 1 and 2: At least one consultant suggested assessing whether vaccines play any role in the development of diabetes.

Other Research Areas: Multiple approaches, including basic science research and genomics, could be used to study the following areas:

- Impact of immunization on human indigenous microbiota and the role of indigenous microbiota in determining the nature of the host response to vaccines
- Long-term sequelae of adverse events (see Cross-cutting Session on Adverse Events that Occur Years after Vaccination, p 15).

3. Life Stage: Adolescents aged 11–18 years (non-pregnant)

A. Background:

During 2005 and 2006, ACIP recommended three new vaccines for adolescents: tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap, two products), tetravalent meningococcal conjugate vaccine (MCV4), and quadrivalent human papillomavirus (HPV) vaccine (females only). In May 2007, influenza vaccine, pneumococcal polysaccharide vaccine (PPV23) and hepatitis A vaccines were recommended for certain high-risk populations. In addition, a second dose of varicella vaccine has been recommended for adolescents without a history of varicella disease.

B. Consultant Input:

Vaccine-specific

HPV vaccine:* Safety monitoring is needed for the HPV vaccine – a vaccine that one consultant described as a "sensitive" vaccine. Studies should assess for rare adverse events. Optimal timing of booster doses should also be explored. Consultants suggested studying safety in the younger group of girls recommended for vaccination (e.g., aged 9 to 15 years). A BLA has been submitted for a bivalent HPV vaccine. It contains a novel adjuvant ASO4 (contains aluminum hydroxide and 3-deacylated monophosphoryl lipid A). Post-licensure safety monitoring will be important if this HPV vaccine is licensed. It

Life Stage: Adolescents (continued)

was mentioned that HPV vaccine might be licensed for use in males in the future (see also Summary of Input from Individual Consultant Presentations: Obstetrics and Gynecology, pages 17-18).

- Td-to-Tdap interval:* Consultants suggested assessing the safety of short intervals between these two tetanus and diphtheria toxoid-containing vaccines using large-linked databases or other epidemiologic methods.
- Varicella: Studying safety of the second dose in adolescents was suggested

Clinical outcomes

- Guillain-Barré Syndrome (GBS) and demyelinating disorders:* Establishing baseline rates of GBS and other demyelinating disorders was suggested for males and females. Research should address mechanisms and risk factors, including genetic risk factors, for development of GBS. National Institutes of Health (NIH) involvement might be useful.
- Other autoimmune disorders: The same principles as described for GBS apply.
- Baseline rates of other conditions: Because many vaccinees may also be using oral contraceptives, establishing baseline rates for adverse events associated with oral contraceptive use would be useful to help interpret signals after vaccination (e.g., rates of thromboembolic events). Also consultants suggested establish baseline rates of adolescent psychiatric diseases* and conditions, including suicide. One consultant advised that establishing baseline rates in isolation is not a useful activity (see also Summary of Input from Individual Consultant Presentations: Epidemiology, pages 19-20

Other research areas

- Adolescent perceptions: Explore adolescent perceptions of vaccine safety and the influence of these beliefs on uptake of adolescent vaccines*
- Monitoring for HPV serotype replacement

4. Life Stage: Adults aged ≥19 years (non-pregnant)

A. Background

In May 2007, ACIP recommended that adults receive Td boosters, annual influenza vaccine if aged >=50 years, and PPV23 if >=65 years. In 2006, ACIP had provisionally recommended the first live vaccine for routine use in older adults: zoster vaccine. Also a single dose of Tdap is recommended for adults aged <65 years to replace a dose of Td. In addition, it is recommended that adults with medical or social risk factors receive certain other vaccines, including biodefense and travel vaccines.

B. Consultant Input: Consultants recommended studying safety of vaccines used in persons who were not included in the licensed or recommended groups (i.e., off label use of vaccine) (see also Summary of Input from Individual Consultant Presentations: Adult Infectious Diseases, page 17).

Vaccine-specific

- Zoster:* The safety of zoster vaccine should be assessed in the recommended population of adults in persons in groups that are not recommended for vaccination, including those with certain medical conditions and persons aged <60 years. An additional interest is safety of the vaccine in persons with a history of zoster.

Life Stage: Adults (continued)

- Influenza:* The principles from the infants and children life stages sessions apply; a continuing concern is to understand the association between TIV and GBS. Consultants also suggested that LAIV safety should be studied in adults not currently recommended for vaccination, including older adults and those with chronic conditions that put them at risk for influenza disease. At least one consultant suggested that a risk-benefit analysis be conducted in older adults for LAIV and TIV use. Safety of new influenza vaccine adjuvants should be studied.
- Tdap: Safe Td-to-Tdap intervals and off-label use in persons aged ≥65 years should be studied.

Host factors which might predispose an individual to VAEs:

- Older persons:* Immune function may decline with age in older persons and this phenomenon may impact risk for VAEs and should be studied.
- Gender differences in vaccine AEs are an important area to study since rates and etiology of the adverse event may differ by gender. A specific concern is the influence of gender on risk for local reactions and arthritis after vaccination.

Clinical Outcomes:

- Adult chronic diseases:* Assessing associations between vaccines and VAEs and establishing baseline rates of various chronic diseases in adults were suggested. The following conditions were emphasized: cardiac, rheumatologic and autoimmune diseases, and chronic fatigue syndrome. One consultant advised that establishing baseline rates in isolation is not a useful activity (see also Summary of Input from Individual Consultant Presentations: Epidemiology, pages 19-20).

Other Research Areas

- Vaccine acceptance:* Explore adult perceptions of vaccine safety and the influence of these beliefs on uptake of adult vaccines.
- Reporting issues for VAEs in adults:* Underreporting of VAEs in adults may be greater than in younger age groups. It is important to understand reporting practices among vaccine providers for adults and adult vaccinees
- Therapeutic vaccines safety: Research issues may not be the same for therapeutic vaccines as they are for preventive vaccines. Therapeutic vaccines may be used for infectious or non-infectious diseases.

Non-research Area:

- Reporting practices: It is important to educate adult healthcare providers and vaccinees about the need to report VAEs to the Vaccine Adverse Events Reporting System (VAERS).

5. Life Stage: Pregnant women

Background

In May 2007, the only vaccine routinely recommended for pregnant women were TIV and Td. Live vaccines are generally contraindicated during pregnancy. Vaccines to prevent type 2 herpes virus infections are being studied in clinical trials.[5]

Consultant Input: (see also Summary of Input from Individual Consultant Presentations: Obstetrics and Gynecology, pages 17-18)

Vaccine-specific

- TIV: The safety of TIV use during pregnancy, particularly during the first trimester should be studied. It was noted that only a minority of obstetricians administer influenza vaccine to pregnant women, even though the vaccine is routinely recommended for pregnant women.*
- Tdap: The safety of Tdap use during pregnancy should be studied.* A particular concern is whether maternal vaccination with Tdap interferes with the infant response to pertussis antigens in pediatric DTaP. *
- HPV vaccine: Safety in pregnant women should be studied through large-linked database studies or clinical trials.
- Herpes simplex virus (HSV) vaccine: At least one consultant suggested that the safety of HSV vaccine in pregnant women should be studied in clinical trials. It was not specified if these studies should occur before or after potential licensure for this vaccine.

Other Research Issues

- Pregnancy registries: These should be used to study the safety of vaccines administered during pregnancy, including vaccines inadvertently administered.*
- Infant follow-up: Infants should be followed long-term after maternal vaccination; specific putative VAEs were not described.
- Immune response: The nature of immune function changes during pregnancy and should be studied.

Non-research.

- Liability: At least one consultant noted that liability issues related to use of vaccines in pregnancy women should be addressed.*

6. Cross-cutting: Role of Public Perception in Shaping the Vaccine Safety Research Agenda

Consultants commented that understanding public perceptions is important (see summary of consultant presentations). They highlighted three main areas that should be addressed: 1) defining the general etiology of autism and neurodevelopment disorders, 2) conducting behavioral research related to vaccine safety perceptions and communication, and 3) enhancing non-research communication activities related to vaccine safety issues.

[5] Information available at http://clinicaltrials.gov/, accessed on December 8, 2007; at time of access no trials for preventive vaccination with HSV vaccine were enrolling pregnant women.

Cross-cutting: Role of Public Perception in Shaping the Vaccine Safety Research Agenda (continued)

Specific suggestions were:

Tracking public perceptions of vaccine safety:* Consultants noted that questions from the public about vaccine safety persist and proliferate to a greater degree than do questions about other aspects of public health. Messages from the federal government about vaccine safety information may not be reaching the public.

- Activities to assess and enhance the effectiveness of vaccine safety communication messages to the public, healthcare professionals and media:* A particular area of concern was communication around autism issues. Focus groups could be used to improve the effectiveness of messages. Consultants suggested that messages provide clear information about autism services, the lack of association between vaccines and autism, and current efforts to understand the etiologies of autism. They should also describe the positive benefits of vaccination. It was suggested that ISO needs to advocate for clear communication of all vaccine safety information. A consultant suggested identifying media relations strategies that work to communicate risk information accurately.
- Public Involvement: At least one consultant believed that communication issues should drive the research agenda and that the public should provide input for this research agenda.
- Research to define the pathogenesis and biological basis of autism:* Consultants suggested studying the etiologies of autism. At least one consultant believed this issue needed to be studied in a broad interagency manner, including evaluation of genetic factors. A consultant suggested conducting systematic reviews of existing data (see consultant presentation summaries)
- VAE reporting: At least one consultant suggested involving the public to enhance rates of VAE reporting.* One consultant did not believe that the juice was "worth the squeeze" and suggested not focusing efforts on this non-research activity.

7. Cross-cutting: Non-antigen Vaccine Constituents and New Vaccine Technologies

Research areas:

- New adjuvants in vaccines:* Understanding the safety of new adjuvants in vaccines was highlighted as an important research area throughout the consultation meeting. In the future it is anticipated that a larger number of vaccines will contain adjuvants, many of which will be new. The safety of adjuvants which are agonists of Toll-like receptors is a particularly important issue. An example of this type of novel adjuvant is ASO4 (aluminum hydroxide and 3-deacylated monophosphoryl lipid A). ASO4 is in the bivalent HPV vaccine (submitted for BLA); it induces an enhanced antibody response to HPV virus-like particles. ASO4 is currently used in hepatitis B vaccines in Europe. Future influenza vaccines will also contain new adjuvants. Defining mechanisms of immunopotentiation from new adjuvants is important. Improved assays for adjuvant responses would be useful. Understanding how new adjutants perform in the different age groups was suggested.

Cross-cutting: Non-antigen Vaccine Constituents and New Vaccine Technologies (continued)

- Other areas: Assessing safety of other non-antigen components of vaccines (e.g., aluminum, conjugate proteins like diphtheria toxoid, exipients and adventitious agents) was suggested. In the future, assessing safety of DNA vaccines may be important.

Non-research area:

- Roles: Defining ISO's role in addition to FDA's and NIH's role for vaccine safety research related to adjuvants and non-antigen components is important.

8. Cross-cutting: Surveillance Considerations for Vaccine Safety Research and Adverse Events that Occur Years after Vaccination:[6] (see also Summary of Input from Individual Consultant Presentations: Epidemiology, pages 19-20 and Summary of Key Input from Brainstorming Sessions: Life Stages, pages 6-13)

Research Areas

- Case definitions:* Use standardized nomenclature for reported vaccine AEs; use case definitions with greater specificity. Examples of long-term clinical outcomes of interest include autoimmune diseases, cancer, diabetes, and neurodevelopmental disorders*
- Databases:* Large-linked databases which can be rapidly accessed are needed. Obtain standardized sets of clinical data from vaccinees and controls, including information on gender. Consultants suggested expanding VSD; one consultant suggested that location of the sites should be more representative of the nation's population distribution. Consultants suggested improving systems to validate and standardize information from large-linked databases
- Background rates for clinical outcomes reported as VAEs should be characterized; improve surveillance protocols and databases to assess rates of chronic conditions reported after vaccination (see also Summary of Input from Individual Consultant Presentations: Epidemiology, pages 19-20).
- Response protocol: Standardize protocols for rapid collection of specimens and data after signals emerge; develop response protocols in the event that adventitious virus agents are identified in vaccines
- Genetic studies: Conduct genome-wide analyses to examine host susceptibility to VAEs; characterize genetic risk factors for reported AEs after vaccination

Non-research Area

- Phase 4 studies: Consider ISO's role in Phase 4 studies. At least one consultant suggested formal CDC participation in Phase 4 studies. This consultant noted that expertise to do these studies is more likely to be with CDC vaccine subject matter experts, outside ISO, than within ISO. ISO might serve as a "neutral broker" and perhaps manage funding from vaccine manufacturers in an independent manner.

[6] Information from these two brainstorming sessions overlapped and has been consolidated for this report.

Summary of Input from the Individual Consultant Presentations

The following section presents a summary of presentations from each of six consultants, representing six disciplines. Please see Appendix G for the complete presentations, in their original form.

Pediatric Infectious Diseases

Dr. Dennehy described eight key areas for research in order of importance. She informally collected information from several sources to prepare her presentation, including colleagues in pediatric infectious diseases through the American Academy of Pediatrics (AAP) Committee on Infectious Diseases (COID), practicing general pediatricians, and parents.

The suggested vaccine safety research areas, in order of importance were (#1 highest):

- #1 Misperception of vaccine risks by parents and the media: The most pressing concern is about vaccines and the development of neurodevelopmental disorders, including autism. She identified 3 areas of research. First is the need to understand why thimerosal continues to be an issue. She speculates it is due to a misperception of risks by parents and the media and because thimerosal is a "convenient scapegoat" for autism, a devastating diseases. Second, the cause(s) of autism must be identified. Third, one needs to examine how best to communicate information about thimerosal and other vaccine safety issues to parents, healthcare providers and the media.
- #2 Risk of intussusception (IS) after rotavirus vaccination: Risk of IS after rotavirus vaccine among infants vaccinated outside the recommended age ranges (6 weeks to 32 weeks) is an area of concern. Because this practice is not uncommon, she suggested review of existing large-linked databases. She also acknowledged the importance of post-licensure surveillance for the risk of IS after rotavirus vaccine that is ongoing.
- #3 Guillain-Barré Syndrome (GBS) and demyelinating disorders after vaccination: She suggested assessing baseline rates of GBS and other demyelinating disorders to compare with rates after vaccination.
- #4 Adverse events after live, attenuated influenza vaccine (LAIV): A specific concern is the risk for wheezing after vaccination. A review of post-licensure data in VSD using a self-control case series approach may be useful. Another area of interest is safety of LAIV administered to children with underlying diseases such as diabetes; LAIV is not currently recommended for persons with chronic conditions.
- #5 Adverse events following immunization (AEFI) in premature and low birth weight infants
- #6 AEFI in children with genetic and metabolic diseases
- #7 AEFI with combination vaccines
- #8 Safety of pandemic influenza vaccines and bioterrorism vaccines

Adult Infectious Diseases

Dr. Schaffner described several areas of research for the adult life stage (non-pregnant). He informally conducted a "mini-survey" of colleagues to prepare his presentation. He noted that data from other developed countries might also inform the research agenda. He recommended post-licensure surveillance for US-licensed vaccines and off label use of these vaccines, emphasizing specific concerns and gaps in knowledge for four adult vaccines. Some of these areas are related to use of the vaccines in a manner that is not consistent with licensure or ACIP recommendations. The vaccine-specific areas are:

- Zoster vaccine: The safety of zoster in the following groups was not studied before licensure: persons with underlying conditions, particularly subtle immunocompromise, persons with a history of previous zoster, and persons aged <60 years with different degrees of immune function.
- Tdap: The safe interval from Td-to-Tdap (two diphtheria and tetanus toxoid-containing vaccines).
- TIV: The risk of GBS after TIV
- LAIV: Use of LAIV in persons aged >=50 years and in persons aged 5 to 49 years with chronic conditions (e.g., diabetes)

Dr. Schaffner believes that the importance of vaccine safety research is measured by the following criteria: questions raised by parents, the media, and the ACIP; legislation proposed by state legislators; and lawsuits filed. He considers the most important current vaccine safety issue in the United States to be in the area of "thimerosal and autism." He highlighted other perceived associations as well (e.g., hepatitis B vaccine and multiple sclerosis). He asked questions about the criteria that should be used for selecting areas of public concern for the ISO research agenda. He also asked which institutions should assume responsibility for addressing these concerns (e.g., CDC, FDA, NIH, vaccine manufacturers). Dr. Schaffner proposed that rigorous evidence-based reviews be conducted for all major vaccine safety questions raised by the public and emphasized the importance of effective communication around vaccine safety issues.[7]

Obstetrics and Gynecology

Dr. Ault discussed vaccine safety areas related to general women's health and those specific to pregnant women. He suggested that HPV vaccine is an important research area. The quadrivalent HPV vaccine is recommended for females aged 9-26 years. A BLA was submitted to the FDA for a bivalent vaccine, with a novel ASO4 adjuvant that includes a monophosphorylated form of lipid A of *Salmonella*. A suggested research need is to study the safety of HPV vaccine in the youngest cohort of girls, aged 9-15 years. He acknowledged the importance of researching other impacts of HPV vaccine including the effect of HPV vaccine recommendations on cervical cancer screening practices and on serotype replacement. Dr. Ault also noted that herpes simplex virus type 2 (HSV-2) vaccine trials are underway.

[7] In May 2004, the IOM published a report titled, "Immunization Safety Review: Vaccines and Autism." The IOM Immunization Safety Review Committee concluded that "the evidence favors rejection of a causal relationship between thimerosal-containing vaccines and autism " and that "the evidence favors rejection of a causal relationship between MMR vaccine and autism." Executive summary available at http://www.iom.edu/?ID=4705, accessed on December 8, 2007.

Obstetrics and Gynecology (continued)

Physiologic and immunologic changes during pregnancy affect the mother and fetus. Pregnant women may be more susceptible to vaccine-preventable diseases; influenza is a prime example. Pathogens that are only mildly pathogenic to most persons may be highly pathogenic to the fetus, such as cytomegalovirus (CMV). Of the licensed vaccines, Dr. Ault noted that pregnant women may benefit from influenza vaccine, HPV vaccine, Tdap, and tetanus vaccine. They may also benefit from vaccines under development, including vaccines to prevent Group B streptococcal, HSV, CMV and respiratory syncytial virus (RSV) infections. For Tdap, research should focus on the benefit of vaccination to the mother and fetus, as well as compliance. For influenza, he suggested research is needed to assess safety of influenza vaccine during early pregnancy and to assess provider and patient perceptions of influenza vaccine safety.

Immunology

Dr. Wilson reviewed immunological mechanisms of adverse events following immunization. These include: bystander injury, autoimmunity, and impeding the development of protective immunity to the infectious disease for which a vaccine was designed to prevent (e.g., aberrant immune response and tolerance). He also reviewed the "hygiene hypothesis," which states that vaccines contribute to the rising prevalence of allergic and autoimmune diseases in the developed world. Three broad factors affect risk for adverse events following immunization: developmental (especially at beginning and end of the life stages), environmental, and genetic.

He suggested that greater understanding of each of these areas is needed. In addition, he recommended that efforts focus on identifying the genetic and environmental factors associated with autism and other insidious diseases to address public perceptions that vaccines may contribute to risk for these conditions. For autism, the study design could be a large prospective cohort. Archived DNA (anonymous or coded) could be obtained for genetic testing. In addition demographic and clinical data could be obtained. He suggests VSD and CISA could collaborate with NIH (e.g., through the National Children's Study[8]) to conduct this study.

Genomics

Dr. Relman described two goals of vaccine safety research: 1) to identify features of the host that help predict vaccine efficacy, as well as host susceptibility to vaccine-preventable diseases and to VAEs, and 2) to identify features of vaccines and approaches for vaccine development that enhance vaccine efficacy and minimize VAEs. Features of the host that might help predict susceptibilities, efficacy, and adverse events are: host genotype, patterns of host gene and protein expression, and patterns of diversity among the indigenous microbiota.

Genomics enables novel assessments of host vulnerabilities (to disease, to adverse events) and enhanced vaccine design. It offers the possibility of early, post-immunization prediction of adverse events (or of continued good health) and early detection of chronic insidious adverse conditions. Genome-based patterns of host response may yield new insights into the mechanism of VAEs. He outlined the following challenges for the use of genomic approaches for vaccine safety research: timely specimen collection and

[8] Information about the National Children's Study is available at http://www.nationalchildrensstudy.gov/about/mission/index.cfm, accessed on December 8, 2007.

Genomics (continued)
appropriate storage; sufficient number of appropriate specimens, including controls; ethical, social and legal implications; and data analysis

Epidemiology

Dr. Broome described epidemiology as a "cross-cutting discipline." When a vaccine safety signal is detected (e.g., from VAERS), epidemiology provides the approach to assess whether it is real, causal, and determine the magnitude of risk compared with the benefit of the vaccine. Epidemiologic approaches are listed below:

- Design and validation of case definitions
- Estimation of expected rate (i.e., background rate, clustering post-vaccination receipt)
- Selection of the appropriate comparison group
- Data analysis regarding association with vaccine

Dr. Broome suggested the following research areas:

- Signal detection: Automated aberration detection algorithms in electronic databases could be used to detect increases in various diagnostic categories. One could investigate collaborative systems for aberration detection as similar approaches could be used to detect vaccine or drug adverse events, toxic exposures or new diseases. This could take advantage of the investment in bioterrorism event detection algorithms.
- Design and validation of case definition: New diagnostic tests focused on increased specificity rather than sensitivity could be used (e.g., could PET scans be useful for defining autistic spectrum disorders?).
- Unbiased case ascertainment: One could investigate feasibility and utility of population based linked electronic health records (EHR) for case ascertainment, in collaboration with VSD.
- Estimation of expected rate: The EHR approach could be used to assess the expected rate of conditions of interest in the population, adjusted for age, gender, race, seasonality, secular trends, etc.
- Selection of the appropriate comparison group: Explore options for obtaining data of population frequency of risk factors, including behaviors. Data from the Behavioral Risk Factor Surveillance Survey (BRFSS) and National Health Interview Survey (NHIS) and clinical information systems may be useful. Availability of these data may determine whether cohort or case control approaches are feasible or necessary.
- Data analysis regarding association with vaccine: Creative approaches to evaluate alleged associations between vaccines and chronic diseases are needed. Two additional research areas are: 1) statistical and modeling techniques to address conditions with multiple causes, such as GBS; and risk factors with multi-collinearity and 2) development of criteria and approaches for a "rapid screen" of an alleged association to assess need to proceed to full study.

Epidemiology (continued)

During and after the meeting Dr. Broome commented on the lack of usefulness of "establishing baseline rates" in advance of identifying a potential VAE. Dr. Broome explained that baseline rates in isolation are generally not useful. To establish a comparable "baseline rate" one needs to address seasonality, secular trends, and adjustment for age, race, gender, etc. One also needs to use comparable case definitions with appropriate specificity for the adverse event and to address likely confounders. For example, a confounder for GBS is co-existent circulating infections. Rather than focusing on baseline rate, Dr. Broome suggested that the goal be to be able to select appropriate comparison groups when needed to address specific concerns about VAEs. To achieve this goal, ISO should continue to expand the large-linked database capacity and refine its rapid accessibility and flexibility.

List of Abbreviations

ACIP	Advisory Committee on Immunization Practices
AEFI	adverse events following immunization
BLA	Biologics License Application
CDC	Centers for Disease Control and Prevention
CISA	Clinical Immunization Safety Assessment
EHR	electronic health record
FDA	Food and Drug Administration
GBS	Guillain-Barré Syndrome
Hib	*Haemophilus influenza* type b
HPV	quadrivalent human papillomavirus
IOM	Institute of Medicine
IPV	inactivated polio vaccine
IS	intussusception
ISO	Immunization Safety Office
LAIV	live, attenuated influenza vaccine
MCV4	tetravelent meningococcal conjugate vaccine
MMR (V)	measles, mumps, rubella (and varicella) vaccine
NIH	National Institutes of Health
NVAC	National Vaccine Advisory Committee
NVPO	National Vaccine Program Office
OCSO	Office of the Chief Science Officer
PCV7	pneumococcal conjugate vaccine
PPV23	pneumococcal polysaccharide vaccine
Td	adult tetanus and diphtheria toxoids vaccine
Tdap	tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine
TIV	trivalent inactivated influenza vaccine
VAE	vaccine adverse event
VAERS	Vaccine Adverse Event Reporting System
VSD	Vaccine Safety Datalink
*	An asterisks is used to designate that at least one consultant indicated that the topic was a high priority.

List of Appendices

Appendix A: Administrative Summary from an individual simultaneous consultation on CDC's Immunization Safety Office Research Agenda
Appendix B: Meeting agenda
Appendix C: Meeting participants: consultants and liaisons
Appendix D: Table of contents from briefing materials
Appendix E: Brainstorming feedback worksheet (template)
Appendix F: Endorsement from consultants that report represents individual input
Appendix G: Presentations from six consultants (in original form)

Appendix A:
Administrative Summary from an Individual Simultaneous Consultation on CDC's Immunization Safety Office Research Agenda

On May 10 and 11, 2007 CDC's Immunization Safety Office (ISO) hosted an individual simultaneous consultation to obtain input on the future ISO research agenda. The meeting occurred in Atlanta, on CDC's Roybal campus. The meeting followed the general organization listed in the meeting agenda (Appendix B), except small modifications were made to accommodate consultant schedules. The three main agenda items were: presentations from ISO/Office of the Chief Science Officer (OCSO) staff and a keynote speaker for information; consultant brainstorming sessions based on life stages or cross-cutting topics; and presentations from individual consultants, followed by discussion.

Seven invited individual consultants, representing six different disciplines, attended the meeting (Appendix C). One consultant, Dr. Peter, served as the moderator for the discussion sessions of the meeting. The disciplines were: pediatric infectious diseases, adult infectious diseases, obstetrics and gynecology, epidemiology, immunology and genomics. Dr. Schaffner, representing adult infectious diseases, only attended on the first day and Dr. Ault, representing obstetrics and gynecology, missed several hours of the first day due to schedule conflicts; the other 5 consultants participated in all sessions during both days. Seven invited liaison representatives from Federal advisory committees and agencies and two ISO research networks (VSD and CISA) also attended the full meeting (Appendix C). Dr. Walt Orenstein, director of the Emory Program for Vaccine Policy and Development, Emory University School of Medicine and former director of the National Immunization Program, CDC delivered a keynote speech during the information session; he did not attend the discussion parts of the meeting. CDC staff on the ISO research agenda development team and meeting organizers were invited to participate in the full meeting (see below). Other ISO staff persons were invited to hear the opening background presentations, but did not attend the discussion sessions.

On May 10, 2007, the meeting convened at about 8:00 am. Dr. Iskander, Acting Co-director, ISO and Dr. Popovic, Chief Science Officer, CDC each welcomed the consultants and provided background information. After these remarks, Dr. Broder read the following information to consultants, *"the charge to each consultant is to identify emerging vaccine safety research questions that will be important for public health and could be studied by ISO but are not currently being addressed. We will not be seeking a consensus of the gathered experts, but rather will be seeking each person's individual expert advice. If during the meeting a consultant does not have time to express his/her individual input, we will be happy to follow-up with that person after the meeting to obtain his/her input."* The rest of the morning generally followed the agenda and the group adjourned for lunch at about 12:10 pm.

At approximately 1:00 pm, Dr. Broder reviewed procedures for brainstorming; a slide noted "*individual input desired, not seeking consensus*" Following this presentation, Dr. Broder verbally summarized information about potential real or perceived conflicts of interests from each of the seven consultants, based on information voluntarily provided

before the meeting. Mr. Malone, representing CDC's Office of the General Counsel attended this session.

After these procedural issues were discussed, the consultant discussion portion of the meeting commenced. The remainder of the afternoon followed the meeting agenda, except the order of the last two presentations was switched (presentation from Dr. Schaffner occurred before discussion of the role of public perception in shaping the research agenda). Dr. Peter moderated these discussion sessions in a manner that allowed for each consultant to provide individual input. The main discussion occurred among consultants; however, liaisons and ISO/OCSO staff participated at the discretion of Dr. Peter when their input was felt to be useful. The first day of the meeting adjourned at about 5:00 pm.

On May 11, 2007 at about 8:00 am the meeting resumed. Following brief administrative updates, consultant presentations and group brainstorming sessions occurred. Dr. Peter continued to moderate these discussions. The topics followed the meeting agenda, except the brainstorming discussion about the life-stage of pregnancy followed, rather than preceded, Dr. Ault's presentation. At about 12:30 pm, the meeting adjourned.

During both days of the meeting, each consultant completed feedback worksheets at the end of each brainstorming session he/she attended. Liaisons and ISO/OCSO participants did not complete worksheets. The discussion framework and scientific ideas generated during these brainstorming discussions are presented in the body of this report.

A list of participating consultants and liaisons is provided in Appendix C. The following persons from ISO/OCSO attended some or part of the scientific discussion sessions:

- Dixie Snider, MD, MPH, Senior Advisor, OCSO, CDC
- James Stephens, PhD, Associate Director for Science, OCSO, CDC
- John Iskander, MD, MPH, Acting Co-director, ISO, OCSO, CDC
- Kristin Pope, MEd, Acting Co-director, ISO, OCSO, CDC
- Brigid Batten, MPH, Orise Fellow, ISO, OCSO, CDC
- Karen R. Broder, MD, Senior Medical Advisor, ISO, OCSO, CDC
- Jae Duncan, Program Coordinator, ISO, OCSO, CDC
- Paul Gargiullo, PhD, Acting Team Leader, Vaccine Safety Datalink (VSD) Project, ISO, OCSO, CDC
- Jane Gidudu, MD, MPH, Acting Team Leader, The Brighton Collaboration, ISO, OCSO, CDC
- Laura Leidel, RN, FNP-C, MPH, Epidemiologist, ISO, OCSO, CDC
- Nancy Levine, PhD, Policy Analyst, ISO, OCSO, CDC
- Claudia Vellozzi, MD, MPH, Acting Team Leader, Clinical Immunization Safety Assessment (CISA) Network, ISO, OCSO, CDC

Appendix B: Meeting Agenda

Immunization Safety Office (ISO) External Scientific Consultancy Meeting

Centers for Disease Control and Prevention
1600 Clifton Road, Atlanta GA
Roybal Campus
Building 19, Room 247 and 248

Final Agenda*

Day 1: Thursday May 10

Time	Agenda Item	Purpose	Presenter(s)
8:00-12:00	**Presentations about the Immunization Safety Office (ISO)**		
8:00-8:10	Welcome from ISO	Information	Dr. Iskander, Acting Co-director, Immunization Safety Office (ISO)
8:10-8:25	Welcome from Office of the Chief Science Officer	Information	Dr. Popovic, Chief Science Officer, CDC
8:25-8:35	Organization of Meeting and Compliance with Requirement for Individual Simultaneous Consultation	Information	Dr. Broder, Senior Medical Advisor, ISO
8:35-8:45	Introductions	Information	Dr. Broder and meeting participants
8:45-9:00	Immunization Safety Office Program Overview	Information	Dr. Iskander
9:00-9:15	CDC's Immunization Safety Office Development of a Research Agenda	Information	Dr. Broder
9:15-9:45	Vaccine Safety Monitoring – Perspectives from a Former Immunization Program Director	Keynote speaker presentation	Dr. Orenstein, Professor of Medicine and Pediatrics Director, Emory Vaccine Policy and Development Associate Director, Emory Vaccine Center
9:45-10:00	Break		

* Some minor modifications in the order of events occurred to accommodate consultant schedules (10/13/07)

Time	Agenda Item	Purpose	Presenter(s)
10:00-10:20	Summary of the Institute of Medicine Immunization Safety Reviews: 2001-2004	Information	Dr. Broder
10:20-10:35	Clinical Immunization Safety Assessment (CISA) network	Information	Dr. Vellozzi, Acting CISA Team Lead
10:35-10:50	Clinical Immunization Safety Assessment (CISA) network	Questions and Answers	Dr. Vellozzi and Dr. Dekker, CISA Principal Investigator, Stanford University School of Medicine
10:50-11:10	Vaccine Safety Datalink (VSD) project	Information	Dr. Gargiullo, Acting VSD Team Lead
11:10-11:30	Vaccine Safety Datalink (VSD) project	Questions and Answers	Dr. Gargiullo and Dr. Jackson, VSD PI, Group Health Center for Health Statistics, Seattle, WA (VSD PI)
11:30-11:40	Vaccine Adverse Event Reporting System	Presentation	Dr. Iskander
11:40-11:50	Brighton Collaboration	Presentation	Dr. Gidudu (Acting Brighton Collaboration Team Lead)
11:50-12:00	Vaccine Adverse Event Reporting System (VAERS) and the Brighton Collaboration	Questions and Answers	Drs. Iskander and Gidudu
12:00-12:50	**Lunch**		Ms. Duncan to coordinate in Room 256

Time	Agenda Item	Purpose	Presenter(s)
12:50-5:00	**Brainstorming Sessions**		
12:50-1:00	Procedures for Brainstorming Sessions	Information	Dr. Broder and Dr. Peter, Professor Emeritus, the Warren Alpert Medical School of Brown University
1:00-1:10	Disclosure of Consultant Vaccine-related Interests	Information and Discussion	Dr. Broder
1:10-1:50	Life Stage 1: Infant Aged <12 Months of Age	Discussion among consultants	Dr. Peter moderates Dr. Broder presents information Dr. Vellozzi takes notes during discussion for all to see
1:50-2:30	Life Stage 2: Child 1-10 Years of Age	Discussion among consultants	Drs. Peter moderates Drs. Broder and Vellozzi facilitate
2:30-2:40	Break		
2:40-3:20	Life Stage 3: Adolescents 11-18 Years of Age	Discussion among consultants	Drs. Peter moderates Drs. Broder and Vellozzi facilitate
3:20-4:00	Life Stage 4: Adults ≥19 years of Age	Discussion among consultants	Drs. Peter moderates Drs. Broder and Vellozzi facilitate
4:00-4:40	Across the Life Stages A: Role of Public Perception in Shaping the Immunization Safety Research Agenda	Discussion among consultants	Drs. Peter moderates Drs. Broder and Vellozzi facilitate
4:40-5:00	**Presentation from Consultant:** Adult Infectious Diseases	Information	Dr. Schaffner, Vanderbilt University School of Medicine
5:00	Adjourn Day 1		
7:00-9:00	Dinner Top Spice 3007 North Druid Hills Road, Atlanta, GA 404-728-0588		Ms. Leidel to coordinate

Day 2: Friday May 11

Time	Agenda Item	Purpose	Presenter(s)
8:00-8:35	**Brainstorming Session:** Life Stage 5: Pregnancy	Discussion among consultants	Drs. Peter moderates Drs. Broder and Vellozzi facilitate
8:35-10:30	**Presentations from Consultants**		
8:35-8:55	Pediatric Infectious Diseases	Information and Questions and Answers	Dr. Dennehy, The Warren Alpert Medical School of Brown University
8:55-9:15	Obstetrics and Gynecology	Information and Questions and Answers	Dr. Ault, Emory University School of Medicine
9:15-9:35	Immunology	Information and Questions and Answers	Dr. Wilson, University of Washington School of Medicine
9:35-9:55	Genomics	Information and Questions and Answers	Dr. Relman, Stanford University School of Medicine
9:55-10:15	Epidemiology	Information and Questions and Answers	Dr. Broome, Rollins School of Public Health, Emory University
10:15-10:30	Break		
10:30-12:00	**Brainstorming Sessions: Across the Life Stages**		
10:30-11:00	Across the Life Stages B: Considerations for Vaccine Safety Surveillance		Drs. Peter moderates Drs. Broder and Vellozzi facilitate
11:00-11:30	Across the Life Stages C: Safety of Non-antigen Vaccine Constituents and New Vaccine Technologies		Drs. Peter moderates Drs. Broder and Vellozzi facilitate
11:30-12:00	Across the Life Stages D: Adverse Events that Occur Years after Vaccination		Drs. Peter moderates Drs. Broder and Vellozzi facilitate

Time	Agenda Item	Purpose	Presenter(s)
12:00-12:15	Plans for Completing Report and Closing Remarks	Information	Drs. Broder and Peter
12:15-12:30	Shuttle pick up to Emory Conference Center		
12:30-2:00	Lunch at Le Giverny Bistro Emory Inn 1615 Clifton Road 404-325-7252		Ms. Leidel to coordinate
2:00pm*	Adjourn Day 2		

* Guests should try to schedule flights after 5:00 pm EDT.

Appendix C: ISO EXTERNAL SCIENTIFIC CONSULTANCY PARTICIPANT LIST OF CONSULTANTS AND LIAISONS					
Name	**Degree**	**Title/Affiliation**	**Role**	**Email Address**	**Phone Number**
AULT, Kevin	MD	Associate Professor of Gynecology and Obstetrics, Emory University School of Medicine, Atlanta, GA	Invited Independent Consultant for Obstetrics and Gynecology	kevin.ault@emory.edu	1.404.616.5419 -Office 1.404.521.3589 -Fax
BART, Kenneth	MD, MPH, MSHPM	Consultant, National Vaccine Program Office (NVPO), HHS, Washington DC	Invited Liaison, NVPO Representative	Kbart@hhs.gov	1.202.205.0076 -Office 1.202.260.1165 -Fax
BROOME, Claire	MD MPH	Adjunct Professor Rollins School of Public Health, Emory University (retired CDC, Berkeley, CA)	Invited Independent Consultant for Epidemiology	cvbroome@gmail.com	1.510.248.4095 -Home 1.510.219.9629 -Cell
DEKKER, Cornelia	MD	Associate Professor, Pediatrics, Medical Director, Stanford-LPCH Vaccine Program, Stanford University School of Medicine, Stanford, CA	Invited Liaison, CISA Network Principal Investigator Representative	cdekker@stanford.edu	1.650.724.4437 -Office 1.650.724.3088 -Fax
DENNEHY, Penelope	MD	Warren Alpert Medical School of Brown University, Director of Pediatric Infectious Diseases, Hasbro Children's Hospital, Providence, RI	Invited Independent Consultant for Pediatrics/Pediatric Infectious Diseases	Pdennehy@lifespan.org	1.401.444.8360 -Office 1.401.444.5650 -Fax
DEVILLE, Jaimie	MD	Associate Clinical Professor of Infectious Disease, Department of Pediatrics, David Geffen School of Medicine, University of CA, Los Angeles	Invited Liaison, Advisory Commission on Childhood Vaccines (ACCV) Representative	jdeville@mednet.ucla.edu	1.310.825.9660 -Office 1.310.825.9175 -Fax
EVANS, Geoffrey	MD	Compensation Program (VICP), Health Resources and Services Administration (HRSA) , Rockville, MD	Invited Liaison, VICP Representative	GEvans@HRSA.GOV	301-443-6593 -Office 301-443-4198 -Fax
JACKSON, Lisa	MD MPH	Senior Investigator, Group Health Cooperative, Seattle, WA	Invited Liaison, VSD Project Principal Investigator Representative	Jackson.L@ghc.org	1.206.442.5216 -Office 1.206.287.4677 -Fax

Name	Degree	Title/Affiliation	Role	Email Address	Phone Number
PAVIA, Andrew	MD	Presidential Professor and Chief, Division of Pediatric Infectious Diseases, University of Utah, Salt Lake City, UT	Invited Liaison, National Vaccine Advisory Committee Representative, Chair Subcommittee on Vaccine Safety	Andy.pavia@hsc.utah.edu	1.801.581.6791 -Office 1.801.560.4607 -Cell
PETER, Georges	MD	Professor Emeritus of Pediatrics, The Warren Alpert Medical School of Brown University, Providence, RI (Brookline, MA)	Invited Independent Consultant, External Leader	gpeter@lifespan.org	1.617.277.1090 -Office 1.617.277.1129 -Fax
RELMAN, David	MD	Associate Professor of Microbiology & Immunology and of Medicine, Stanford University School of Medicine, Palo Alto, CA	Invited Independent Consultant for Genomics	relman@stanford.edu	1.650.852.3308 -Office 1.650.852.3291 -Fax
SCHAFFNER, William	MD	Professor and Chair, Department of Preventive Medicine, Vanderbilt University School of Medicine, Nashville, TN	Invited Independent Consultant for Internal Medicine/Adult Infectious Diseases	william.schaffner@vanderbilt.edu	1.615.322.2037 -Office 1.615.343.8722 -Fax
SMITH, Jean Claire	MD	Immunization Policy, Immunization Services Division, National Center for Immunization and Respiratory	Invited Liaison, Advisory Committee on Immunization Practices, Executive Secretary Representative	jis6@CDC.GOV	1.404.639.6227 -Office 1.404.639.8905 -Fax
WILSON, Christopher	MD	Professor and Chairman, Department of Immunology, University of Washington School of Medicine, Seattle, WA	Invited Independent Consultant for Immunology	cbwilson@u.washington.edu	1.206.685.3956 -Office 1.206.616.4561 -Fax

Appendix D-1:
Table of Contents
Scientific Consultancy Briefing Materials

Appendix D-2:
Immunization Safety Office External Scientific Consultancy Meeting
Atlanta, Georgia, May 10 and 11, 2007

Late-breaking Materials

Item	Category	Document
1	Administrative	
1-A		Final Meeting Agenda
1-B		Updated Meeting Participant List
1-C		Hotel and Meal Information
2	Updated Presentation for Opening Session on the Immunization (ISO), CDC	
2-A		Immunization Safety Office Overview Presentation (Dr. Iskander)
3	Additional Presentations for Opening Session on ISO, CDC	
3-A		Vaccine Safety Monitoring – Perspectives from a Former Immunization Program Director (Dr. Orenstein)
3-B		Summary of the Institute of Medicine Immunization Safety Reviews, 2001−2004 (Dr. Broder)
3-C		Updates from the Clinical Immunization Safety Assessment Network Annual Meeting (Drs. Dekker and Vellozzi)
3-D		Updates from the Vaccine Safety Datalink Project Annual Meeting (Drs. Jackson and Gargiullo)
4	Materials for Brainstorming Sessions	
4-A		Immunization Safety Office External Scientific Consultancy Meeting: Brainstorming Session Procedures (Drs. Broder and Peter)
4-B		Immunization Safety Office External Scientific Consultancy Meeting: Brainstorming Session Background (Dr. Broder)
4-C		Vaccines by Life Stage Table (Dr. Broder)
4-D		Consultant Feedback Worksheets

Appendix E: Sample Brainstorming Worksheet

Date:
Name of consultant:

Life stage 1: Infant <12 months of age

For this session, please list what you believe to be the 5 most important research topics?
For each topic, please address 3 specific questions, using the codes below.

Question 1: Why is the topic important (note all that apply)
□1. Burden of health risk associated with vaccine preventable disease in the absence of vaccination?
□2. Burden of health risk associated with the adverse event following vaccination?
□3. Perceived intensity of public or professional concern? □4. Other (specify)

Question 2: Using a scale of 1–5 (highest), what is the overall priority score for the topic?

Question 3: What are some feasible approaches to study the topic (check all that apply)
□1. Large-linked database study □2. Other epidemiological study
□3. Epidemiological study involving collection of biological specimens □4. Clinical trial □ 5. Other approach (specify)

	Vaccine Safety Research Topic	1) Why is the topic important? (choices 1−5; list all that apply)	2) Priority score 1−5 (5 is highest)?	3) Approaches to study the topic? (choices 1−5; list all that apply)
1				
2				
3				
4				
5				

Comments:

Appendix F:
Endorsement from Consultants that Report Represents Individual Input

Each consultant was asked to respond to the following statement:

I have reviewed the 10/21/2007 Draft "Report from an Individual Simultaneous Consultation on the Centers for Disease Control and Prevention's Immunization Safety Office Research Agenda: May 10 and 11, 2007, Atlanta, GA."

This document accurately reflects my individual comments and the events as they transpired on May 10 and 11, 2007 during the portions of the meeting that I attended.

1. I agree with this statement and have no additional comments related to content (exclude minor comments related to grammar, spelling and writing style) ___

2. I agree with this statement but have additional comments related to content (describe below) ___

3. I do not agree with this statement (describe below) ___

Of the seven consultants, four checked box 1 and three checked box 2. Comments from the individuals who checked box 2 have been incorporated into the final document.

Appendix G
Independent Consultant Presentations

1. Immunization Safety Office Scientific Consultancy: the Pediatric Infectious Disease Perspective, presented by Penelope H. Dennehy, MD
2. Immunization Safety Issues: Results of a Mini-Survey of Colleagues, presented by William Schaffner, MD
3. Vaccines and Women's Health, presented by Kevin A. Ault, MD
4. Immunologic Mechanisms of Vaccine Adverse Events, presented by Christopher Wilson, MD
5. Genetics and Emerging Vaccine Safety Issues, presented by David Relman, MD
6. Immunization Safety Office: Epidemiology and the Research Agenda, presented by Claire Broome, MD, MPH

Immunization Safety Office Scientific Consultancy

The Pediatric Infectious Diseases Perspective

Penelope H. Dennehy, M.D.
Director, Division of Pediatric Infectious Diseases
Hasbro Children's Hospital
Professor of Pediatrics
The Warren Alpert School of Medicine of Brown University

Vaccine Safety Issues: The Pediatric Infectious Disease Perspective

- Sources of data
  - Querying COID members
  - Referred calls to AAP
  - Questions from community physicians
  - Work with state AAP chapter on anti-thimerosol legislation
  - Conversations with parents

Pediatric ID Perspective: Important Vaccine Safety Research Areas

- Ranked in order of importance
- #1 Misperception of vaccine risks by parents and the media
  - Thimerosol mentioned as most important by all
  - Vaccines and the development of neurodevelopmental disorders including autism

Pediatric ID Perspective: Important Vaccine Safety Research Areas

- #2 Rotavirus vaccine and intussusception
  - Use of RV vaccine outside of the recommended age ranges
  - Post-licensure evaluation of risk of IS
- #3 GBS and other demyelinating disease after vaccination

Pediatric ID Perspective: Important Vaccine Safety Research Areas

- #4 AEs with LAIV
  - Risk of wheezing
  - Use of LAIV in children with underlying diseases such as diabetes
- #5 AEFI in premature and LBW infants

Pediatric ID Perspective: Important Vaccine Safety Research Areas

- #6 AEFI in children with genetic and metabolic diseases
- #7 AEs with combination vaccines
- #8 Safety of pandemic flu and BT vaccines

Pedi ID Suggested Research Areas

- RV vaccine and risk of intussusception addressed by current ongoing surveillance
- Use of RV vaccine outside the recommended age range could be addressed by review of existing LLDBs since rate of out of age use is significant

Pedi ID Suggested Research Areas

- Need to assess baseline rates of GBS and other demyelinating disease to compare with rates after vaccination
- Risk of wheezing after receipt of LAIV
  - Review of post-licensure data in VSD cohort
  - Self control case series approach may be useful here

Thimerosol – "The issue that refuses to die"

- Most important concern of pediatricians
- Need to understand why thimerosol continues to be an issue
  - Underlying reason seems to be misperception of vaccine risks by parents and the media
  - Also thimerosol is a convenient scapegoat for a frustrating and devastating disease

Thimerosol – "The issue that refuses to die"

- Need to address question of what causes autism
- Need to examine how to communicate our concern to parents but redirect them to more productive areas of research

Thimerosol – "The issue that refuses to die"

- Need to address how to help PCPs communicate risks associated with thimerosol and other vaccine safety issues to parents
- Need to develop messages that are credible and provide understandable information for both parents and the media

CDC
Immunization Safety Office
External Scientific Consultancy
May 10, 2007

Adult Immunization Safety Issues

Results of a Mini-Survey of Colleagues

William Schaffner, MD

Vanderbilt University School of Medicine

Vaccine Safety
Life Stage: Adult (non-pregnant)

- Licensed Vaccines: Post-licensure surveillance
  - Zoster
    Will be given to many persons with underlying conditions who were excluded from clinical trials, particularly with subtle immunocompromise
    Persons with previous zoster
  - Tdap
    Interval since prior Td
  - TIV
    Guillain-Barré syndrome

Vaccine Safety
Life Stage: Adult (non-pregnant)

- Licensed Vaccines: Off-label use

  Off-label use where the principal issue seems to be safety, not efficacy
  - Tdap
    Persons ≥65 years
  - LAIV
    Persons 5 to 49 years with diabetes, CHF, hypertension, COPD, etc.
    Persons ≥50 years
  - Zoster
    Persons <60 years with intact immunity
    Persons <60 years anticipating immunocompromise
    Persons <60 years with mild immunocompromise

Vaccine Safety

Across Life Stages ⟶

- Use of data from other developed countries including (but not restricted to) Canada, the U.K., European Union, Australia, New Zealand

Vaccine Safety

Across Life Stages ⟶

- What is the most important vaccine safety issue in the United States today?

Vaccine Safety

Across Life Stages ⟶

- What is the most important vaccine safety issue in the United States today?

  Importance measured by:
  - Questions parents ask
  - News reports in newspapers, TV, books
  - State legislators submitting bills
  - Lawsuits filed
  - Questions asked at ACIP meetings

Vaccine Safety

Across Life Stages ⟶

- What is the most important vaccine safety issue in the United States today?

Importance measured by:
- Questions parents ask
- News reports in newspapers, TV, books
- State legislators submitting bills
- Lawsuits filed
- Questions asked at ACIP meetings

Thimerosal and Autism

Similar Issues

- Thimerosal ……..Autism
- Measles Vaccine ……Inflammatory bowel disease
- Vaccine sequence …. …….Type I diabetes
- Hepatitis B vaccine ……Multiple sclerosis
- Multiple immunizations … Weakened immune system

These issues have been raised by the public
- anecdotes, provocative stories
- temporal sequence

At what point do these questions acquire "standing" to require scientific investigation?

Which institutions should assume responsibility?
- CDC, FDA, NIH, Vaccine Manufacturers

Another Type of Research

- Systematic, evidence-based reviews based on rigorous methods synthesizing existing scientific information

to address

All questions raised by the public

Thimerosal:
- Mercury chemistry
- In vitro toxicology
- Clinical toxicology
- Epidemiology

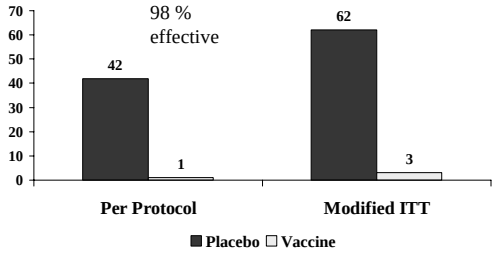
- Effective communication

Vaccines and Women's Health

Kevin A. Ault, MD
Department of Gynecology and Obstetrics
Emory University School of Medicine
Atlanta GA

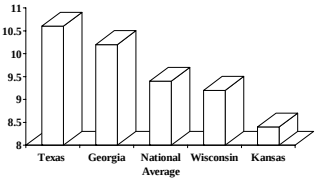
EMORY UNIVERSITY

Quadrivalent HPV – Phase III Results for CIN 2/3 at 36 months



Presented at Advisory Committee on Immunization Practices 2-2007

Cervical Cancer in the USA – 1998 to 2002



From Saraiya *et al* '07

HPV Vaccine

- Quadrivalent Vaccine recommended for adolescents and women ages 9 – 26 yo
- Bivalent vaccine at FDA March 2007
- Some suggested research needs
  - Safety in youngest cohort (9-15 yo)
  - Effect on screening
  - Type replacement

Bivalent HPV Vaccine

- GSK has AS04 in their version of the vaccine
  - contains a 3 deacylated form of monophosphorylated form of lipid A of *Salmonella*
- Commercial version of hepatitis B with AS04 available in Europe, more immunogenic
- In a recent abstract, higher anti-VLP antibodies observed in HPV VLP vaccine with AS04

HSV Vaccine

- Phase III trial underway
- Problem - HSV-1 and HSV-2 'double negative' women
- Best age for vaccination?
- Burden of disease?
- HIV-HSV interaction?

Pregnancy

- Physiological and immunological changes
- Maybe more susceptible to various vaccine preventable disease (varicella, flu)
- Fetus may develop disease from "mildly" pathogenic microbe (toxo, CMV)
- Pregnant women may benefit from the following vaccines – tetanus, Tdap, HPV, HSV, Group B Strep, flu, RSV

Pertussis Vaccine and Pregnancy

Recommendations for use of Td and Tdap in Pregnant Women (adolescents 11-18 years and adults 19-64 years of age) who previously have not received Tdap

Routine post-partum Tdap: Pregnant women who previously have not received a dose of Tdap (including women who are breastfeeding) should receive Tdap after delivery, before discharge from the hospital or birthing center, if 2 years or more have elapsed since the last Td; shorter intervals can be used

Suggested research – compliance? Benefit?

See MMWR 12-15-06, final recommendations pending

Flu Vaccine and Pregnancy

- Recommended for ten years, now during all trimesters
- 95 % of obstetricians recommend vaccine during pregnancy but 36 % do not give vaccine in their practice
- Suggested research needs
  - Safety during early pregnancy
  - Provider and patient perceptions

See MMWR 10-21-2005

Chris Wilson, Professor and Chairman, Department of Immunology, University of Washington School of Medicine, Seattle, WA

Immunological Mechanisms of Vaccine Adverse Events

Vaccines may incite

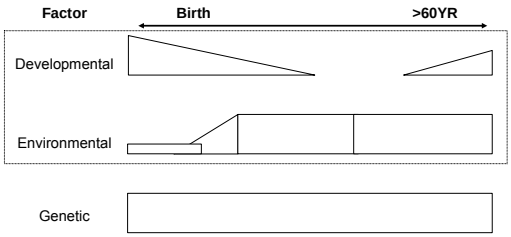
- Bystander injury – vaccine antigen induces
  - allergic response (IgE/Th2-mediated)
  - immune complex disease (IgG-mediated)
- Autoimmunity – vaccine incites immune-mediated attack against self antigens
  - Bystander activation – vaccine activates innate immunity and this overrides self-tolerance
  - Molecular mimicry – vaccine antigen mimics self antigen and activates cross-reactive T/B cells that attack self

Immunological Mechanisms of Vaccine Adverse Events

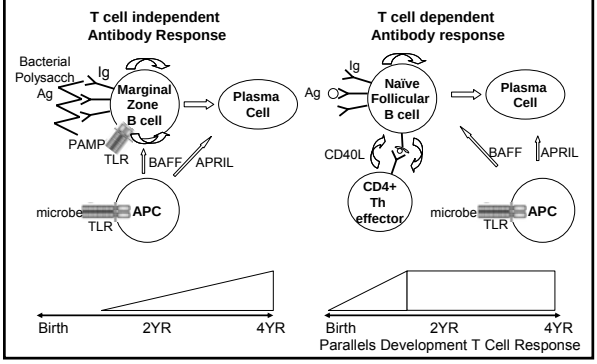
Vaccines may impede

- Protective immunity to the infectious disease it was designed to prevent
  - aberrant immune responses (e.g., inactivated measles and RSV vaccines)
  - tolerance to vaccine antigens (PRP-OMPC in neonates)
- Self-tolerance induced by infections they are designed to prevent, i.e., the 'Hygiene Hypothesis', which states that vaccines contribute to rising prevalence of allergic and autoimmune diseases in developed world – theoretical only

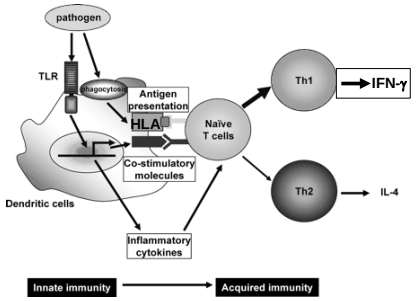
Factors Affecting Risk for Vaccine Adverse Events



Ontogeny of Antigen-Specific B cell and Antibody Responses in Humans



TLRs and Dendritic Cells – Gatekeepers of Antigen-specific Immunity & Th1/Th2 Bias



Developmental Issues: Limited environmental exposure to microbes?
Diminished/selectively different responses by neonatal dendritic cells?

Modified from Takeda and Akira 2005

Implications of Inherent and Intentional Incorporation of Microbial TLR Agonists as Vaccine Adjuvants

Inherent: Live or inactivated bacteria or viruses

Intentional: New adjuvants to enhance immunogenicity: Example, MPL/alum in GSK hepatitis B (Europe), HPV and HSV vaccines

Such microbial adjuvants should be more immunogenic but will they be for all?

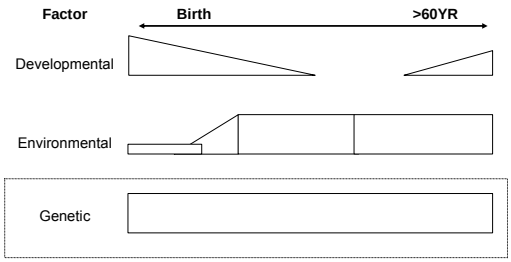
Genetic and Developmental Differences

Chris Wilson, Professor and Chairman, Department of Immunology, University of Washington School of Medicine, Seattle, WA

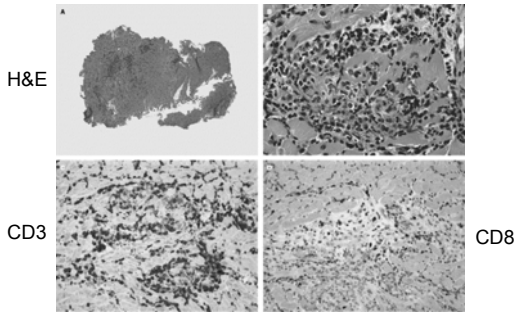
Caution! Regarding Immunization with Non-Live Vaccines Containing TLR Ligands in Early Life

- PRP-OMPC vaccine - Hib PRP conjugated to OMPC, a TLR2>>4 agonist
- Given at 2 mo age → protective T cell-dependent Ab response with a single dose while other PRP conjugates require 2-3 doses to induce protection
- Given at birth → B cell/antibody tolerance throughout infancy (Ward, Keyserling), although these infants respond normally at 18 mo to HbOC booster (Ward)
- Similar but less consistent data for DTwP
- Why?
- We do not know!

Factors Affecting Risk for Vaccine Adverse Events



Histopathology – Smallpox Vaccine-Associated Myocarditis

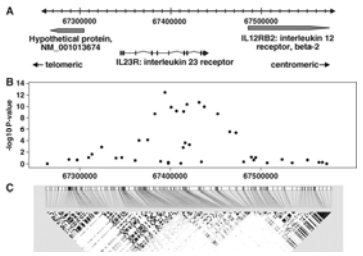


Murphy et al. Lancet 2003:362:1378

Smallpox Vaccine Associated Myocarditis

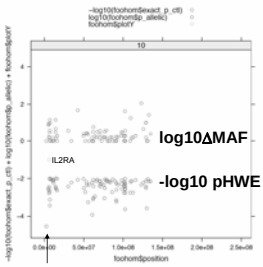
- Overt smallpox vaccine-associated myopericarditis is rare (~1:5-10,000), predominantly affects individuals of European ancestry (RR3.4, p=0.001), and is characterized by a CD4 T cell infiltrate in the myocardium in the absence of vaccinia virus
- Mechanistic Hypothesis
  - Autoimmune myocarditis triggered by vaccinia virus
- Genetic Hypothesis
  - The risk allele(s) is of relatively recent, European origin
  - One or two alleles/extended haplotypes, are associated with ≥80% of the attributable risk

Whole Genome Scanning To Define Genetic Risk Factors For Autoimmunity



Unbiased Whole Genome-Wide Association Study Identifies IL23R Arg381Gln with OR= 0.26 for Crohn's disease $p=6.6\times10^{-19}$
Duerr et al Science 2006;314:1461

Smallpox Vaccine Associated Myocarditis Preliminary Hit by Whole Genome Scan Chromosome 10 - IL2RA



- Direct hit
  - IL2RA: 6.1M
  - Cluster: 5.3M-7.0M
- Case MAF: 82%
- Control MAF: 32%

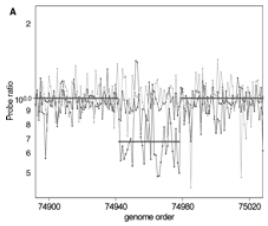
Chris Wilson, Professor and Chairman, Department of Immunology, University of Washington School of Medicine, Seattle, WA

Whole Genome P-value Forecasts

- IL2RA: 32% control, 82% case
  - 24 cases v 22 controls: p = 0.0001
  - 48 cases v 132 controls: p = 2×10^{-9}
- HLA: 5% control, 28% case
  - 24 cases v 22 controls: p = 0.0035
  - 48 cases v 132 controls: p = 8×10^{-10}

Modified from C Carlson

Identify the Real Genetic and Environmental Factors Associated with Autism (and other insidious diseases)



1.1 Mb Deletion encompassing the gene encoding Oxtyocin in a child with Asperger Syndrome
Sebat et al Science 2007;316:445

Identify the Real Genetic and Environmental Factors Associated with Autism (and other insidious diseases) as Preemptive Approach

- Accrue large cohorts of prospectively followed individuals with
  - Anonymous or coded, archived DNA and broad consent for genetic testing for studies
  - Personal infection and immunization history
  - Family history
  - Gender and race/ethnicity (the latter is moot with whole genome studies)
- Stronger links VSD $\rightarrow$ CISA $\rightarrow$ NIH to support these studies (National Child Study)

Genomics and emerging vaccine safety issues

Immunization Safety Office, CDC
May 11, 2007
David A. Relman, Stanford University

Genomics and emerging vaccine safety issues

- Goals, questions
- Approaches
- Issues

Genomics and emerging vaccine safety issues

- Goals, questions
  - Elucidate features of the host that help predict susceptibilities, efficacy, effects
  - Elucidate features of the vaccine that enhance efficacy, minimize adverse effects

Genomics and emerging vaccine safety issues

- Goals, questions
  - Elucidate features of the host that help predict susceptibilities, efficacy, effects
  - Elucidate features of the vaccine that enhance efficacy, minimize adverse effects

Features of the host that might help predict susceptibilities, efficacy, adverse reactions

- host genotype
- host RNA (transcript) profile
  - mRNA
  - miRNA, etc
- host protein profiles
- patterns of diversity among indigenous microbiota

A Role for Genetics in the Immune Response to the Varicella Vaccine

Nicola P. Klein, MD, PhD,† Bruce Fireman, MA,* Andrea Enright, MD,† Paula Ray, MPH,* Steven Black, MD,* and Cornelia L. Dekker, MD,† for the Clinical Immunization Safety Assessment (CISA) Network*

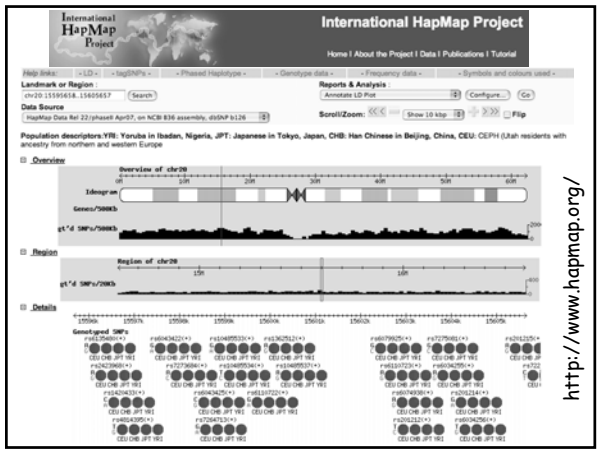
Ped Inf Dis J 2007; 26:300-305

Available online at www.sciencedirect.com
ScienceDirect
Vaccine
ELSEVIER
Vaccine 25 (2007) 306–313
www.elsevier.com/locate/vaccine

Impact of genetic variants in IL-4, IL-4 RA and IL-13 on the anti-pneumococcal antibody response

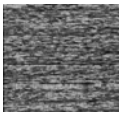
Selma P. Wiertsema[a,b,1], Gareth Baynam[b,1], Siew-Kim Khoo[b,1], Reinier H. Veenhoven[c], Niels van Heerbeek[d], Guicheng Zhang[b], Ingrid A. Laing[b], Ger T. Rijkers[a,e], Jack Goldblatt[b,f], Elisabeth A.M. Sanders[c], Peter N. Le Souëf[b,*]

[a] Department of Paediatric Immunology, Wilhelmina Children's Hospital, University Medical Center Utrecht, 3584 EA Utrecht, The Netherlands
[b] School of Paediatrics and Child Health, University of Western Australia, Perth, 6008 WA, Australia
[c] Department of Paediatrics, Spaarne Hospital, Hoofddorp, The Netherlands
[d] Department of Otorhinolaryngology, Radboud University Nijmegen Medical Centre, The Netherlands
[e] Department of Medical Microbiology and Immunology, St. Antonius Hospital, Nieuwegein, The Netherlands
[f] Genetic Services of Western Australia, Perth, 6008 WA, Australia



High throughput genotyping

- Newer sequencing technologies, e.g., sequencing by extension (pyrosequencing)
- Mass spectrometry
- Allele-specific PCR
- Single nucleotide primer extension
- Oligonucleotide ligation
- High density oligonucleotide microarray



Sciencexpress Report

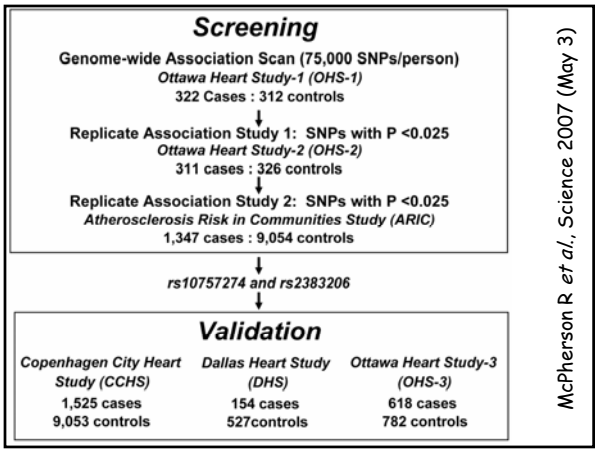
A Common Allele on Chromosome 9 Associated with Coronary Heart Disease

Ruth McPherson,[1*†] Alexander Pertsemlidis,[2*] Nihan Kavaslar,[1] Alexandre Stewart,[1] Robert Roberts,[1] David R. Cox,[3] David A. Hinds,[3] Len A. Pennacchio,[4] Anne Tybjaerg-Hansen,[5] Aaron R. Folsom,[6] Eric Boerwinkle,[7] Helen H. Hobbs,[2,9] Jonathan C. Cohen[2,8†]

[1]Division of Cardiology, University of Ottawa Heart Institute, Ottawa K1Y4W7, Canada. [2]Donald W. Reynolds Cardiovascular Clinical Research Center and the Eugene McDermott Center for Human Growth and Development, University of Texas Southwestern Medical Center, Dallas, TX 75390, USA. [3]Perlegen Sciences, Mountain View, CA 94043; USA. [4]Genomics Division, Lawrence Berkeley National Laboratory, Berkeley, CA 94720, USA & U.S. Department of Energy Joint Genome Institute, Walnut Creek, CA 94598, USA. [5]Department of Clinical Biochemistry, Rigshospitalet, Copenhagen University Hospital, Copenhagen DK-2100, Denmark. [6]Division of Epidemiology and Community Health, University of Minnesota, Minneapolis, MN 55454, USA. [7]Human Genetics Center and Institute for Molecular Medicine, University of Texas Health Science Center, Houston, TX 77030, USA. [8]Center for Human Nutrition and the [9]Howard Hughes Medical Institute at the University of Texas Southwestern Medical Center, Dallas, TX 75390, USA.

Coronary heart disease (CHD) is a major cause of death in Western countries. Here we used genome-wide association scanning to identify a 58 kilobase interval on chromosome 9p21 that was consistently associated with CHD in six independent samples (n > 23,000 participants) from four Caucasian populations. This interval, which is located near the *CDKN2A* and *CDKN2B* genes, contains no annotated genes and is not associated with established CHD risk factors such as plasma lipoproteins, hypertension or diabetes. Homozygotes for the risk allele comprise 20-25% of Caucasians and have a ~30-40% increased risk of CHD.

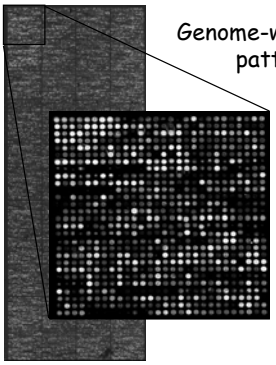
Science 2007 (May 3)



McPherson R *et al.*, Science 2007 (May 3)

Features of the host that might help predict susceptibilities, efficacy, adverse reactions

- host genotype
- host RNA (transcript) profile
  - mRNA
  - miRNA, etc
- host protein profiles
- patterns of diversity among indigenous microbiota



Genome-wide transcript abundance patterns:

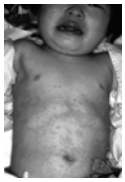
One lens through which to examine biological programs of host and pathogen, and the interplay between them

Are there patterns early after immunization that predict subsequent adverse reactions, or…the absence of such?

Pattern Recognition

- Unsupervised (class discovery)
  - Clustering (agglomerative, hierarchical, n-cut), SOM, SVD (PCA), ICA
- Supervised (class prediction)
  - SAM, support vector machines, t/f-test (DLDA, ANOVA), discriminative margin clustering, modeling (waveform, periodicity)

SOM = self-organizing maps; SVD = singular value decomposition; PCA = principal component analysis; ICA = independent component analysis; SAM = significance analysis of microarrays; DLDA = diagonal linear discriminant analysis; ANOVA = analysis of variance.

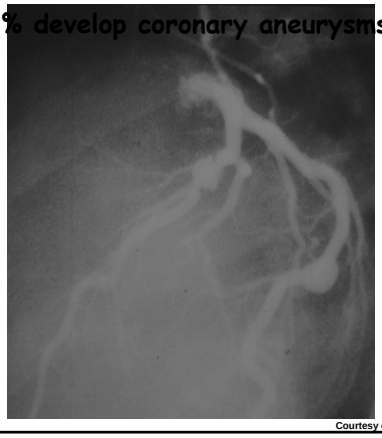


Kawasaki syndrome

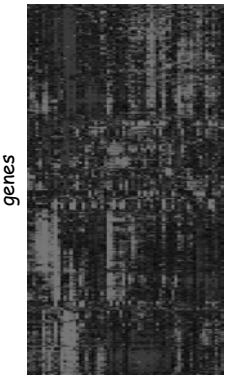
- Vasculitis of unknown etiology (infection?)
- 90/100,000/yr Jap <5 yr old
- 6-11/100,000/yr USA <5 yr old
- Winter-Spring
- Siblings w/in 10 days

http://www.mars.dti.ne.jp/~maachan/Kawasaki1.JPG

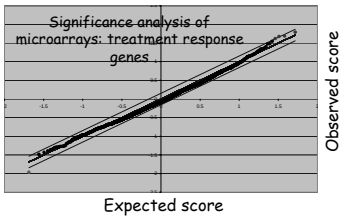
20-25% develop coronary aneurysms



Courtesy of Jane Burns, UCSD

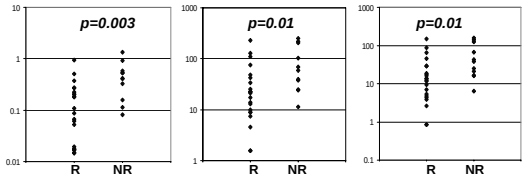


Patterns of gene expression in whole blood samples from 64 patients with acute phase Kawasaki Disease



SNK, FKBP5, VAMP5, ACTB, CEACAM1

Association of pre-treatment CEACAM1 mRNA abundance (RT-PCR) with subsequent treatment response in independent group of 33 patients



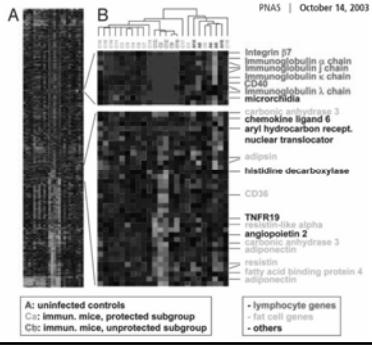
L-form of CEACAM1 S-form of CEACAM1

Protective immunity against *Helicobacter* is characterized by a unique transcriptional signature

Anne Mueller*†, Jani O'Rourke‡, Pauline Chu§, Charles C. Kim*, Philip Sutton¶‖, Adrian Lee‡, and Stanley Falkow*

Departments of *Microbiology and Immunology and §Comparative Medicine, Stanford University School of Medicine, Stanford, CA 94305-5402; and ¶School of Biotechnology and Biomolecular Sciences, University of New South Wales, Sydney NSW 2052, Australia

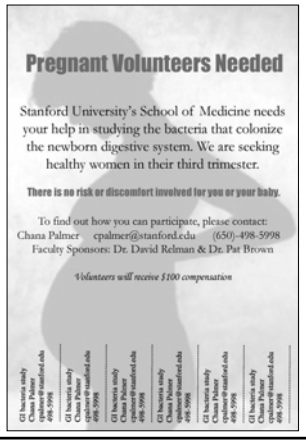
PNAS | October 14, 2003 | vol. 100 | no. 21 | 12289–12294



- oral *H. felis* vaccine
- oral challenge
  2 mo later
- examine stomach
  22 mo later

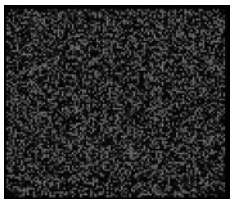
Features of the host that might help predict susceptibilities, efficacy, adverse reactions

- host genotype
- host RNA (transcript) profile
  - mRNA
  - miRNA, etc
- host protein profiles
- patterns of diversity among indigenous microbiota



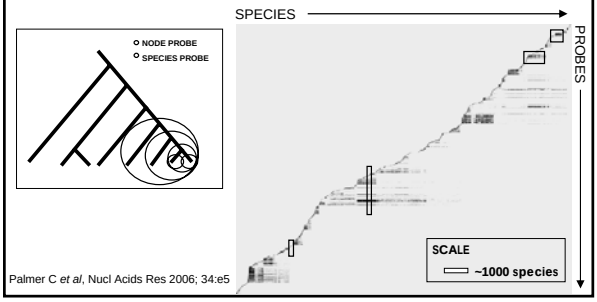
We are born ~100% human, but die >90% bacterial…

What are the features of early microbial colonization in the human body?



Array Design

- Database: 15765 bacterial + 672 archaeal ssu rDNA seqs ("prokMSA", DeSantis, 2003)
- BLAST was used to identify "node" and species-specific 40nt sequences
  - Node probe subsets were selected for optimal coverage of all species
  - Species specific probes were selected to represent "interesting" microbes



Palmer C *et al*, Nucl Acids Res 2006; 34:e5

Study Overview

	Samples
BABY	
Days 0 -14	15
Weeks 3-12	10
Months 4-6	3
Year 1	1
TOTAL PER BABY	**29**

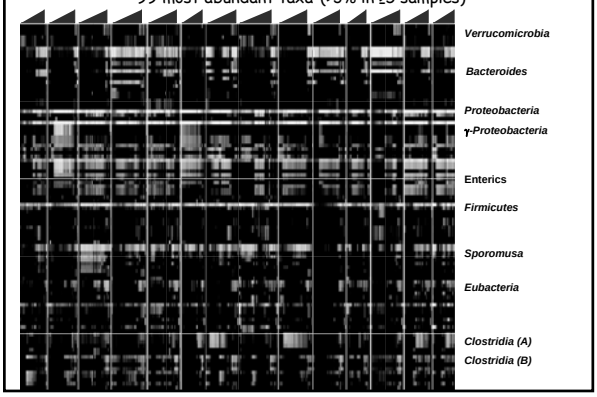
	Samples
MOM	
Vaginal swab	1
Stool (Day 0, Month 6, Year 1)	3
Breast milk	1
OTHER	
Dad stool (Year 1)	1
Sibling stool (Year 1)	1
TOTAL PER MOM/BABY	7

Baby Stats (n=14):
- 5 C-section & 9 vaginal
- All breast fed (+ formula)
- All full term

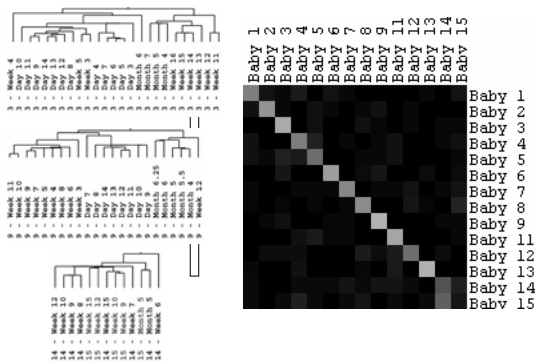
TOTAL SPECIMENS: 430

A year in the life of 14 babies

99 most abundant taxa (>3% in ≥5 samples)



Within- and between-baby similarity



Genomics and emerging vaccine safety issues

- Goals, questions
  - Elucidate features of the host that help predict susceptibilities, efficacy, effects
  - Elucidate features of the vaccine that enhance efficacy, minimize adverse effects

REPORTS

Identification of Vaccine Candidates Against Serogroup B Meningococcus by Whole-Genome Sequencing

Mariagrazia Pizza,[1*] Vincenzo Scarlato,[1*] Vega Masignani,[1] Marzia Monica Giuliani,[1] Beatrice Aricò,[1] Maurizio Comanducci,[1] Gary T. Jennings,[1] Lucia Baldi,[1] Erika Bartolini,[1] Barbara Capecchi,[1] Cesira L. Galeotti,[1] Enrico Luzzi,[1] Roberto Manetti,[1] Elisa Marchetti,[1] Marirosa Mora,[1] Sandra Nuti,[1] Giulio Ratti,[1] Laura Santini,[1] Silvana Savino,[1] Maria Scarselli,[1] Elisa Storni,[1] Peijun Zuo,[1] Michael Broeker,[2] Erika Hundt,[2] Bernard Knapp,[2] Eric Blair,[3] Tanya Mason,[3] Hervé Tettelin,[3] Derek W. Hood,[4] Alex C. Jeffries,[4] Nigel J. Saunders,[4] Dan M. Granoff,[5] J. Craig Venter,[3] E. Richard Moxon,[4] Guido Grandi,[1] Rino Rappuoli[1†]

Science 2000; 287:1816-20

GENOMIC MEDICINE

VIEWPOINT

Reverse Vaccinology and Genomics

Rino Rappuoli and Antonello Covacci

The genomic revolution has had a dramatic effect on our ability to find new vaccine targets and develop effective vaccines.

based on a grid of superco
major scientific institutions

Science 2003; 302:602

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Vaccine

Vaccine 23 (2005) 3016–3025

www.elsevier.com/locate/vaccine

Screening the whole genome of a pathogen in vivo for individual protective antigens

Katherine Stemke-Hale[a], Bernhard Kaltenboeck[b], Fred J. DeGraves[b], Kathryn F. Sykes[a], Jin Huang[b], Chun-hui Bu[a], Stephen Albert Johnston[a,*]

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[b] Department of Pathobiology, College of Veterinary Medicine, 270 Greene Hall, Auburn University, Auburn, AL 36849-5519, USA

PNAS PNAS PNAS

Genome analysis of multiple pathogenic isolates of *Streptococcus agalactiae*: Implications for the microbial "pan-genome"

Hervé Tettelin[a,b], Vega Masignani[b,c], Michael J. Cieslewicz[b,d,e], Claudio Donati[c], Duccio Medini[c], Naomi L. Ward[a,f], Samuel V. Angiuoli[a], Jonathan Crabtree[a], Amanda L. Jones[g], A. Scott Durkin[a], Robert T. DeBoy[a], Tanja M. Davidsen[a], Marirosa Mora[c], Maria Scarselli[c], Immaculada Margarit y Ros[c], Jeremy D. Peterson[a], Christopher R. Hauser[g], Jaideep P. Sundaram[g], William C. Nelson[a], Ramana Madupu[a], Lauren M. Brinkac[a], Robert J. Dodson[a], Mary J. Rosovitz[a], Steven A. Sullivan[a], Sean C. Daugherty[a], Daniel H. Haft[a], Jeremy Selengut[a], Michelle L. Gwinn[a], Liwei Zhou[a], Nikhat Zafar[a], Hoda Khouri[a], Diana Radune[a], George Dimitrov[a], Kisha Watkins[a], Kevin J. B. O'Connor[h], Shannon Smith[i], Teresa R. Utterback[i], Owen White[a], Craig E. Rubens[g], Guido Grandi[c], Lawrence C. Madoff[d,j], Dennis L. Kasper[e,j], John L. Telford[c], Michael R. Wessels[d,e], Rino Rappuoli[c,k,l], and Claire M. Fraser[a,b,k,m,n]

Contributed by Rino Rappuoli, August 5, 2005

The development of efficient and inexpensive genome sequencing methods has revolutionized the study of human bacterial pathogens and improved vaccine design. Unfortunately, the sequence of a single genome does not reflect how genetic variability drives pathogenesis within a bacterial species and also limits genome-wide screens for vaccine candidates or for antimicrobial targets. We have generated the genomic sequence of six strains representing the five major disease-causing serotypes of *Streptococcus agalactiae*, the main cause of neonatal infection in humans. Analysis of these genomes and those available in databases showed that the *S. agalactiae* species can be described by a pan-genome consisting of a core genome shared by all isolates, accounting for ~80% of any single genome, plus a dispensable genome consisting of partially shared and strain-specific genes. Mathematical extrapolation of the data suggests that the gene reservoir available for inclusion in the *S. agalactiae* pan-genome is vast and that unique genes will continue to be identified even after sequencing hundreds of genomes.

PNAS 2005; 102:13950-55

Genomics and emerging vaccine safety issues

- Goals, questions
- Approaches
- Issues

Considerations in the use of genomic approaches for vaccine assessment

- Specimen collection
  - Anatomic compartment
  - Timing
  - Clinical metadata
  - Standardized methods
- Numbers of necessary specimens
- Data analysis

Conclusions

• Genomics enables novel assessments of host vulnerabilities (to disease, to adverse events), and of vaccine design

• Possibilities for early, post-immunization prediction of adverse events (or of continued health); detection of chronic, insidious adverse conditions

• Genome-based patterns of host response may yield new insights into mechanisms of adverse events

Immunization safety office: epidemiology and research agenda

Claire Broome, M.D.
Atlanta, Georgia
May 11, 2007

Epidemiology as cross-cutting discipline

- "signal detection" from VAERS, CISA, lab observations, genetic hypotheses, etc
- Epidemiology gives us the systematic approach to address:
  - Is it real?
  - Is it causal?
  - What is magnitude of risk compared to benefit of vaccine?

Epidemiologic approaches:

- Design and validation of case definition
  - Objective measures? Applied in blinded method?
- Unbiased case ascertainment
  - Pre-press? Representative population?
- Estimation of expected rate
  - Background data? Clustering post vax receipt?
- Design of appropriate comparison group
  - Address key risk factors, confounders; controls vs cohort
- Data analysis re association with vaccine
  - Control for relevant variables, stratify; Dose response; other analyses

Research areas

- **signal detection:** Automated aberration detection algorythms, in electronic clinical databases to detect increases in various diagnostic categories. (take advantage of investment in bioterrorism event detection)
  - Investigate collaborative systems for aberration detection—related principles for vax, drug AE's; toxic exposures (EMS), new diseases (TSS)
- **Design and validation of case definition:** new diagnostic tests, focused on increased specificity, rather than sensitivity—eg could PET scans be useful for defining Autism Spectrum Disorders?

Research areas, continued…

- **Unbiased case ascertainment:** investigate feasibility/utility of population based linked electronic health records (EHR) for case ascertainment; could be validated, then more broadly extended in collaboration with VSD investigators
- **Estimation of expected rate:** above EHR approach, used to assess expected rate in population

Research areas, continued…

- **Design of appropriate comparison group:** research on options for obtaining data on population frequency of risk factors, including behaviours—could explore utilization of surveys such as BRFS or NHIS; opportunities to include risk factors in clinical information systems. (Availability of such data may determine whether cohort or case control approach is feasible/necessary)

Research areas, continued…

- **Data analysis re association with vaccine:**
  - research in statistical and modelling techniques, eg to address conditions with multiple causes (GBS); risk factors with multi-collinearity
  - Research in developing criteria/approach for a "rapid screen" to assess need to proceed to full study
  - Creative approaches to evaluate alleged associations with chronic diseases