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Conference Overview

The remarkable growth of vaccine biotechnology continues apace in basic science discovery, product development, market introduction, and adoption into immunization programs. New cytokines are identified, innate and induced immune regulatory pathways unraveled, novel adjuvants and antigen constructs prove effective, and recently-licensed products achieve high coverage, already yielding noticeable decreases in disease incidence. One can envision a growing number of challenging maladies – including chronic, non-infectious, and neoplastic – that may become vaccine-preventable or vaccine treatable in the years ahead.

The Annual Conference on Vaccine Research (ACVR) provides high-quality, up-to-date reports of such scientific progress in its unique mix of invited presentations by acknowledged international experts in symposia of topical interest and its sessions and posters of peer-reviewed submitted abstracts. The ACVR encourages the participation of all the disparate fields of vaccinology in both its human and veterinary domains in order to facilitate valuable cross-fertilization of ideas and approaches among researchers often narrowly focused on their specific diseases or methods.

The 16th ACVR is an unique scientific meeting devoted exclusively to research on vaccines and associated technologies for disease prevention and treatment through immunization. It is a premier venue for cutting-edge learning, effective data-sharing, and convenient networking for scientific collaboration.

The conference organizers invite you to participate in the audience discussions, poster presentations, Meet the Expert breakfast sessions, special luncheon lecture, and evening reception, and to provide the helpful feedback essential for further evolution and improvement.

Conference Objectives

Overall Conference Objectives
At the conclusion of this conference, participants will be able to:

- Discuss recent scientific advances contributing to progress in the development of vaccines
- Identify research opportunities and scientific challenges associated with vaccine development, production, and distribution

Symposia Objectives
At the conclusion of each symposium, participants will be able to:

Keynote I: Mary Lou Clements-Mann Memorial Lecture in Vaccine Sciences:
Eradication of Disease through Vaccination: The 35th Anniversary of the Last Case of Smallpox
- Understand the factors that were responsible for the eradication of smallpox and the relevance of the most salient, current, and contemplated initiatives for the eradication of other infectious diseases
Symposium 1: Challenges for Future Disease Eradication by Vaccination

- Evaluate the biologic feasibility of measles and rubella eradication by reviewing current elimination and control of these diseases, and identify the major barriers to achieving eradication
- Review the polio eradication program short- and long-term challenges and possible solutions
- Explain the molecular, biological, and clinical characteristics and ideal vaccine profile for controlling and eradicating foot-and-mouth disease

Symposium 2: Malaria Vaccines-Current and Future

- Understand the particularities and challenges of malaria vaccine clinical development
- Understand the rationale for the principal antigen targets chosen for malaria vaccine development and the potential effects on malaria infection/disease/transmission that such vaccines may confer
- Obtain an adequate knowledge of current development of the most advanced malaria candidate vaccine RTS,S
- Review the recent World Health Organization (WHO)-sponsored update to the Malaria Vaccine Technology Roadmap and status of malaria vaccine development and findings
- Understand the worldwide impact of malaria in 2013 and review the role of whole organism P. falciparum Sporozoite vaccines

Keynote II: Decade of Vaccines

- Discuss the goals of the Decade of Vaccines and how the Global Vaccine Action Plan will be used to achieve these goals

Symposium 3: Prevention of Infant Infections and Maternal Immunization

- Understand the disease burden of influenza and pertussis and the safety and efficacy of these vaccines to prevent these infections in pregnant women and young infants
- Implement the current guidelines for use of influenza, tetanus and diphtheria toxoid, and acellular pertussis (Tdap) vaccines during pregnancy
- Describe three recent changes in Tdap immunization recommendations designed to protect infants from pertussis and review the evidence supporting waning immunity from pertussis vaccines
- Summarize the effectiveness of antenatal influenza immunization and epidemiology in North American and tropical populations
- Describe the need for a group B streptococcal vaccine based upon the current group B streptococcal disease burden in the US and globally
- Understand the rationale for potential group B streptococcal glycoconjugate vaccine constructs
- Discuss the evidence base supporting the potential efficacy of a group B streptococcal conjugate vaccine

Symposium 4: New and Emerging Vaccines for Respiratory Infections

- Review the phenomenon of vaccine-associated enhanced respiratory disease described in swine to identify consistent predisposing factors associated with the disease
- Describe the consistent pathologic features and immune response associated with vaccine-associated enhanced respiratory disease in pigs following
Influenza A virus challenge to identify possible similarities to other Influenza A virus hosts

- Compare whole inactivated virus to LAIV in naïve and pigs with passively acquired immunity for efficacy against heterologous Influenza A virus challenge to understand the impact of prior immune status on vaccination
- Describe the types of respiratory syncytial virus vaccines currently in development, and their utility in various target populations, and obstacles to vaccine development
- Review the Department of Defense’s development, use, and loss of adenovirus vaccine, followed by reemergence of adenovirus disease and the successful development and deployment of a new adenovirus vaccine
- Understand the complex epidemiology and mechanism of influenza viruses and review developments in universal influenza vaccines

Symposium 5: Prospects for New Tuberculosis Vaccines

- Review information on the current status of live mycobacterial vaccines for tuberculosis undergoing clinical assessment
- Understand the scientific rationale for the design of tuberculosis subunit vaccine development and review recent progress in the development of novel post-exposure vaccines for latently infected individuals
- Review status of tuberculosis studies to delineate correlates of risk and analyze assays used in clinical tuberculosis vaccine trials

Symposium 6: Vaccine Discovery and New Technologies

- Understand the current status of veterinary tuberculosis vaccine research for cattle and wildlife and their potential applications for development of human TB vaccines
- Understand the characteristics of HPV pseudovirions as gene transfer agents and the immune responses they induce so they can be appropriately applied to mucosal vaccine applications
- Recognize the differences in the ability of systemic versus local mucosal immunization strategies to induce long-lived tissue resident CD8+ T-cells in a mucosal epithelium
- Review data from diverse vaccines showing that higher immune responses in females compared with males are well conserved across diverse antigens, and examine whether genes and/or sex hormones, including estrogens and androgens, influence immune responses to vaccines
- Discuss how the new field of Synthetic Genomics will catalyze the expansion of vaccine science by enabling researchers to rapidly and inexpensively create new vaccines using synthetic DNA
- Understand and describe the two major mechanisms of influenza evolution (antigenic drift and antigenic shift) that are critical to vaccine development and how genetically engineering vaccines differs
Acknowledgments (as of April 8, 2013)
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BD Diagnostics
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• Peter Palese (invited speaker) is employed by Mount Sinai Medical School which has filed several patent applications in the area of universal influenza virus vaccines.

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The Conference Information Desk is located in the foyer area outside the Constellation Ballroom in the Hyatt Regency Inner Harbor. NFID staff will be available at the desk throughout the conference.

CONFERENCE LANGUAGE
The official language for the conference is English.

CONFERENCE LOCATION
All sessions of the conference will be held at:

Hyatt Regency Inner Harbor
300 Light Street
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DR. RICHARD J. DUMA MEET THE EXPERTS BREAKFAST SESSIONS
Named in honor of one of NFID’s founders, the Dr. Richard J. Duma Meet the Experts breakfast sessions are conducted in a small group format focusing on interaction between invited experts and attendees.

The format is conducive to informal discussion led by introductory remarks from the expert and followed by questions and answers from the participants. The sessions are open to all attendees; however, seating capacity is limited and is available on a first-come, first-served
basis. Please be sure to take advantage of this networking opportunity for a thoughtful exchange of ideas among peers, mentors, and colleagues.

The breakfast sessions are scheduled for Tuesday, April 23 and Wednesday, April 24 from 7:00-7:45 am, in Constellation Ballroom, Salon F.

**TUESDAY, APRIL 23**

The New WHO Recommendations for the Global Use of Influenza Vaccines  
Jon S. Abramson, MD  
Wake Forest University School of Medicine  
Winston-Salem, NC

Immunization of Pregnant Women: Two for One Protection  
Carol J. Baker, MD  
Baylor College of Medicine  
Houston, TX

Advisory Committee on Immunization Practices Update  
Ruth A. Karron, MD  
Johns Hopkins Bloomberg School of Public Health  
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Universal Influenza Virus Vaccine and Durability of Vaccines  
Peter Palese, MD  
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**WEDNESDAY, APRIL 24**

Polio Eradication: Is it in the Future?  
Walter A. Orenstein, MD  
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Pertussis Strategies  
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University of California San Diego  
San Diego, CA

One Health Approaches from a Veterinary Perspective  
W. Ray Waters, DVM, PhD  
Agricultural Research Services  
US Department of Agriculture  
Ames, IA

Synthetic Genomic Vaccine Technologies  
David E. Wentworth, PhD  
The J. Craig Venter Institute  
Rockville, MD

**GREEN INITIATIVES**

NFID is committed to implementing sustainability practices that will lessen the impact of its events on the planet. This includes working with the conference hotel, suppliers, and attendees to find ways to reduce our environmental impact. NFID actions include:

- Printing meeting materials on recycled paper, using environmentally friendly ink. To reduce the amount of paper used, presentations will be made available online before and after the conference.
- Encouraging attendees to reduce, reuse, and recycle paper, metal, plastic, and glass. Recycle your badge before you leave—look for the boxes as you exit the main ballroom. In addition to paper, cans, or bottles, you can recycle your poster as well, as long as they aren’t laminated.
• Using reusable servicewear such as cups, mugs, plates, and cutlery when possible. Attendees are encouraged to bring a reusable water bottle to the meeting-water stations are available throughout the conference hotel.
• Attendees are asked to turn off lights and other electronics when not in use; to participate in the Hyatt linen reuse program for towels and bed linens; and to take advantage of the many public transportation options throughout the city. We encourage you to walk around town or explore the area using the city’s buses or light rail to discover Baltimore.

MESSAGES
All sleeping rooms in the hotel are equipped with a voice mail system. This system is accessible via the hotel operator using a house phone. In case of emergencies requiring immediate attention, your party should call the general hotel number and instruct the switchboard to deliver a message to Sharon Cooper-Kerr at the NFID Conference Information Desk in the foyer area outside of the Constellation Ballroom.

NO SMOKING POLICY
The Hyatt Regency Inner Harbor is a non-smoking facility. No smoking is allowed in any of the session rooms, break areas, or sleeping rooms.

POSTER SESSIONS
Posters will be on display from 5:00 pm on Monday, April 22 until 12:00 pm on Wednesday, April 24 in the Atrium of the hotel. Presenters will be at their boards to answer questions and discuss their research during the welcome reception scheduled for Monday, April 22, at 5:00 pm and during the poster session scheduled for Tuesday, April 23, from 7:30–8:30 am.

PRESENTATIONS
With the permission of each presenter, final presentation slides will be posted online for a limited time following the conference. Registered attendees will be notified by email when the slides are available.

PROGRAM AND ABSTRACTS
The registration fee includes one copy of the Program Agenda and Abstract Book for each registered participant. Additional copies, if available, may be purchased for $25 US each. Orders for additional copies will be taken at the Conference Information Desk beginning on Tuesday, April 23, 2013 and after the conference by e-mail to vaccine@nfid.org.

PLEASE NOTE THAT NFID IS UNABLE TO REPLACE LOST OR STOLEN ABSTRACT BOOKS.

REGISTRATION FEES AND HOURS
The full registration fee includes a program/abstract book, continental breakfasts, all scheduled coffee breaks, welcome reception on Monday evening, and luncheon on Tuesday. Accommodations and additional meals are not included.

VERIFICATION OF ATTENDANCE
International attendees may obtain a letter of attendance verification from the NFID staff at the Conference Information Desk during registration hours.
NFID Luncheon
April 23, 2013
12:00–1:15 pm

Opening Remarks and Introductions
Bruce G. Weniger, MD, MPH

Robert Austrian Memorial Lecture
Richard Malley, MD

Presentation of Dr. Charles Mérieux Award
Susan J. Rehm, MD

Dr. Charles Mérieux Award Acceptance
Robert G. Webster, PhD

Presentation of Maurice R. Hilleman Early-Stage Career Investigator Award
(Recipient To Be Announced)
Bruce G. Weniger, MD, MPH

Richard Malley, MD
2013 Robert Austrian Memorial Lecturer
Associate Professor of Pediatrics, Children’s Hospital Boston, Boston, MA

Dr. Malley is the Kenneth McIntosh Chair in Pediatric Infectious Diseases at Children’s Hospital Boston and an Associate Professor of Pediatrics at Harvard Medical School. Dr. Malley runs a research laboratory at Boston Children’s Hospital, focusing on innate and acquired immune responses to pneumococci. In collaboration with PATH and the ongoing participation of Dr. Porter Anderson, Dr. Malley is leading an international effort for the development and manufacture of a whole-cell killed pneumococcal vaccine for use in developing countries. A Phase I trial of the whole-cell vaccine was completed in 2012 in the US, with plans to pursue additional clinical trials of this vaccine in Africa and Asia.

Robert G. Webster, PhD
2013 Dr. Charles Mérieux Award Recipient
Rose Marie Thomas Chair, Division of Virology, Department of Infectious Diseases, St. Jude Children’s Research Hospital, Memphis, TN

Dr. Webster’s interests include the emergence and control of influenza viruses, viral immunology, the structure and function of influenza virus proteins, and the development of new vaccines and antivirals. Together with Graeme Laver, he developed one of the first subunit vaccines for influenza that is still being produced in Australia. The major focus of his research is the importance of influenza viruses in wild aquatic birds as a major reservoir and their role in the evolution of new pandemic strains for humans and lower animals. He contributed to the establishment of the Center of Excellence for Influenza Research at the University of Hong Kong and to the Center of Excellence for Influenza Research and Surveillance at St. Jude Children’s Research Hospital. His work has influenced current understanding of the continuing evolution and control of H5N1 influenza viruses. His is the author of over 650 original articles and reviews on influenza viruses and has trained many scientists who now contribute to our understanding of the evolution and pathogenesis of influenza.
Robert Austrian Memorial Lecture

The Robert Austrian Memorial Lecture honors the late Robert Austrian, MD, a University of Pennsylvania researcher who developed the first multivalent vaccine against pneumococcal bacteria. Dr. Austrian received his Doctor of Medicine degree from Johns Hopkins University and completed fellowships in infectious diseases at Johns Hopkins and New York University. He went on to found the infectious diseases division and fellowship program at the University of Pennsylvania and was chairman of the department of research medicine there from 1962 to 1986. Among his many honors, Dr. Austrian received the NFID’s Maxwell Finland Award for Scientific Achievement in 2001.

Dr. Charles Mérieux Award

Dr. Charles Mérieux was a French scientist, humanist, and entrepreneur, who devoted his life to the prevention of infectious diseases. At the age of 30, he took over the family laboratory founded by his father in 1897, and turned it into one of the leading vaccine manufacturing companies in the world, known today as sanofi pasteur. His work and vision laid important foundations for the vaccine industry and the worldwide fight to control and eliminate infectious diseases through immunization. This Award is presented to an individual who demonstrates a commitment to science-based medicine and research in infectious diseases, shows excellence in clinical and research activities, and has an unsurpassed dedication to improving public health.

Maurice R. Hilleman Early-Stage Career Investigator Award

The Maurice R. Hilleman Early Stage Career Investigator Award memorializes the lifetime achievements of the late Maurice R. Hilleman, PhD in the field of vaccinology. Dr. Hilleman was a long-serving member of the National Foundation for Infectious Diseases’ Board of Directors and Board of Trustees and was the 1998 recipient of NFID’s Maxwell Finland Award for Scientific Achievement. This award recognizes promising scientists in the early stages of their careers in any field of vaccinology, from basic research, through pre-clinical and clinical studies, manufacturing, and production, to related research in public health, agriculture, health delivery, policy, and regulatory matters.

This session is supported by grants from Merck & Co., Inc. and sanofi pasteur.
MARY LOU CLEMENTS-MANN MEMORIAL LECTURE IN VACCINE SCIENCES

D.A. Henderson, MD, MPH, Resident Scholar at the Center for Biosecurity (Baltimore) and Professor of Medicine and Public Health, University of Pittsburgh, will present the 2013 Mary Lou Clements-Mann Memorial Lecture, “Eradication of Disease through Vaccination: The 35th Anniversary of the Last Case of Smallpox” on Monday, April 22, 2013 at 8:30 am

Abstract on page 49.

The Mary Lou Clements-Mann Memorial Lecture in Vaccine Sciences was initiated at the Second Annual Conference on Vaccine Research in 1999 to honor and remember a prolific, compassionate, and courageous vaccinologist. Dr. Clements-Mann was a professor in the John Hopkins University School of Hygiene and Public Health, where she worked starting in 1985, founding and directing its Center for Immunization Research. Her career in vaccine science began in 1979, when she joined the Center for Vaccine Development at the University of Maryland School of Medicine as assistant professor of medicine. Dr. Clements-Mann was internationally recognized for her clinical research and leadership on viral vaccines of public health importance. Her bibliography includes more than 100 papers indexed to vaccination for influenza (37), HIV (31), cholera (6), hepatitis B (5), respiratory syncytial virus (4), parainfluenza (4), Rocky Mountain spotted fever (4), rotavirus (3), E. coli (3), and typhoid (1).

Raised on a Texas ranch, Mary Lou Clements entered Texas Tech University intending to become a veterinarian, but her interests soon changed to human disease, and upon graduation she attended the University of Texas Southwestern Medical School. After completing an internship and residency at Temple University in Philadelphia, she obtained a diploma at the London School of Tropical Medicine and Hygiene in 1975. At that time, the frontlines of public health were in the global program to eradicate smallpox, and she went to India to work for the World Health Organization (WHO) for the final years of vaccination and surveillance. After returning in 1977, she moved to Baltimore to earn her MPH degree at Hopkins.

It was quite early in the AIDS pandemic when Dr. Clements-Mann founded the Center for Immunization Research, but she recognized the threat of this new disease and made it a major focus of her research. She became a dominant figure in the multi-center networks established by the National Institutes of Health to conduct phase I and II clinical trials of AIDS vaccines. She also consulted for WHO and the joint United Nations Programme on AIDS to help prepare for essential AIDS vaccine trials in developing countries. Her great contributions to these efforts arose from her broad experience testing vaccines for other diseases, and her vision for how to move forward the development process.

In 1996, she married Dr. Jonathan Mann, founder of the Global Programme on AIDS at WHO, an international authority on the pandemic, and an eloquent advocate for human rights and compassion in controlling it. In the final years of their lives, they became increasingly frustrated with impediments to AIDS vaccine development not faced by other vaccines, and began crusading – despite the risk to her peer-reviewed research grants – for a reinvented Federal AIDS vaccine effort. This was the theme of Dr. Clements-Mann's invited lecture before the First Annual Conference on Vaccine Research on May 30, 1998. On September 2 of that year the couple perished in the crash of Swissair flight 111 off the coast of Nova Scotia, Canada.
PROGRAM AGENDA

SUNDAY, APRIL 21, 2013
4:00–6:30 pm  Registration  Constellation Ballroom

MONDAY, APRIL 22, 2013
7:30 am–5:00 pm  Registration  Constellation Ballroom Foyer
7:30 am   Poster Set-Up  Atrium
7:45 am   Continental Breakfast  Atrium
8:15 am   Welcome and Introductions  Susan J. Rehm, MD  National Foundation for Infectious Diseases  Bethesda, MD

8:30 am  Keynote I: Mary Lou Clements-Mann  CE  Constellation Ballroom, Salon A & B
Memory Lecture in Vaccine Sciences
Moderator:  Bruce G. Weniger, MD  Chiang Mai University  Atlanta, GA

1  Eradication of Disease through Vaccination: The 35th Anniversary of the Last Case of Smallpox  D.A. Henderson, MD, MPH  Johns Hopkins Bloomberg School of Public Health  Center for Biosecurity of University of Pittsburgh Medical Center  Baltimore, MD

9:15 am   Questions and Answers
9:30 am   Coffee Break

Symposium 1:  Challenges for Future Disease & Eradication by Vaccination  CE  Constellation Ballroom, Salon A
Moderator:  Gregory A. Poland, MD  Mayo Clinic and Foundation  Rochester, MN

9:45 am  2  Measles and Rubella–Will They Ever be Eradicated?  Walter A. Orenstein, MD  Emory Vaccine Center  Emory University  Atlanta, GA
# PROGRAM AGENDA

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Speaker</th>
<th>Institution/Location</th>
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<tbody>
<tr>
<td>10:20 am</td>
<td><strong>3</strong> Polio Eradication</td>
<td>Philip D. Minor, PhD</td>
<td>National Institute for Biological Standards and Control, Hertfordshire, UK</td>
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<tr>
<td>10:55 am</td>
<td><strong>4</strong> Development of Vaccines Toward the Global Control and Eradication of Foot-and-Mouth Disease</td>
<td>Cyril G. Gay, DVM, PhD</td>
<td>Agricultural Research Service, US Department of Agriculture, Beltsville, MD</td>
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<tr>
<td>11:30 am</td>
<td><strong>Panel Discussion on Disease Eradication</strong></td>
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<tr>
<td>12:00 pm</td>
<td>Lunch (on your own)</td>
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<td>1:00 pm</td>
<td><strong>Symposium 2:</strong> Malaria Vaccines—Current and Future</td>
<td>Myron M. Levine, MD, DTPH</td>
<td>Center for Vaccine Development, University of Maryland School of Medicine, Baltimore, MD</td>
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<td><em>CE</em></td>
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<td></td>
<td><strong>Moderator:</strong> Myron M. Levine, MD, DTPH</td>
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<td><strong>Constellation Ballroom, Salon A &amp; B</strong></td>
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<td>1:00 pm</td>
<td><strong>5</strong> RTS,S</td>
<td>Pedro L. Alonso, PhD</td>
<td>Barcelona Centre for International Health Research (CRESIB), Barcelona, Spain</td>
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<td>1:30 pm</td>
<td><strong>6</strong> Vaccines that Interfere with Transmission</td>
<td>David C. Kaslow, MD</td>
<td>PATH Malaria Vaccine Initiative, Washington, DC</td>
</tr>
<tr>
<td>2:00 pm</td>
<td><strong>7</strong> The Whole Organism, <em>P. falciparum</em> Sporozoite, Vaccine Approach</td>
<td>Kirsten E. Lyke, MD</td>
<td>Center for Vaccine Development, University of Maryland School of Medicine, Baltimore, MD</td>
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<tr>
<td>2:30 pm</td>
<td>Questions and Answers</td>
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<tr>
<td>3:00 pm</td>
<td><strong>Coffee Break</strong></td>
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Submitted
Presentations 1A: Immunologic Science and Immune Response

***Constellation Ballroom, Salon A***

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<tr>
<th>Time</th>
<th>Session</th>
<th>Title</th>
<th>Presenters</th>
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<tbody>
<tr>
<td>3:30 pm</td>
<td>S1</td>
<td>Vaccine-Associated Enhanced Respiratory Disease following Heterologous Influenza Vaccination is Associated with Cross-Reactive Anti-HA2 Antibodies with Virus Fusion Enhancing Activity</td>
<td>S. Khurana¹, C. L. Loving², A. L. Vincent³, H. Golding³ ¹FDA, Bethesda, MD, ²USDA, Ames, IA</td>
</tr>
<tr>
<td>3:45 pm</td>
<td>S2</td>
<td>IL18R1 and IL18 Gene Polymorphisms are Associated with Immune Responses to Smallpox Vaccine</td>
<td>I. G. Ovsyannikova, I. H. Haralambieva, R. B. Kennedy, M. M. O’Byrne, V. S. Pankratz, G. A. Poland, Mayo Clinic Vaccine Research Group, Mayo Clinic and Foundation, Rochester, MN</td>
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<tr>
<td>4:00 pm</td>
<td>S3</td>
<td>Influence of Maternal Murine Immunization with <em>Neisseria meningitidis</em> Outer Membrane Antigens on the Immune Response in Offspring</td>
<td>E. N. De Gaspari, Immunology, Adolfo Lutz, São Paulo, Brazil</td>
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<tr>
<td>4:15 pm</td>
<td>S4</td>
<td>Vaccination with Human Hookworm Vaccine “<em>Necator americanus</em> Aspartic Protease-1 M74” Generates Neutralizing Antibodies and a Potent Immune Response in BALB/c Mice</td>
<td>A. R. Jariwala¹, X. Chen¹, M. S. Pearson³, B. Keegan³, J. B. Brelsford¹, J. L. Plieskat¹, A. Loukas¹, B. Zhan¹, P. J. Hotez³, J. M. Bethony¹ ¹The Department of Microbiology, Immunology, and Tropical Medicine, The George Washington University, Washington, DC, ³Center for Bio-discovery and Molecular Development of Therapeutics, James Cook University, Cairns, Australia, ²Department of Pediatrics and Molecular Virology and Microbiology, National School of Tropical Medicine, Baylor College of Medicine, Houston, TX</td>
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<tr>
<td>4:30 pm</td>
<td>S5</td>
<td>Design of Vaccine Adjuvants through Regulated Induction of Programmed Necrosis</td>
<td>L. S. Jacobson, M. Goldberg, H. Lima, F. Diaz-Griffero, K. Chandran, J. Brojatsch, Microbiology and Immunology, Albert Einstein College of Medicine, Bronx, NY</td>
</tr>
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</table>
4:45 pm  S6  **Comparison of the Live Attenuated Yellow Fever Vaccine 17D-204 to its Virulent Parental Strain Asibi by Deep Sequencing**  
A. Beck¹, R. Tesh¹, T. Wood², S. Widen², K. Ryman³, A. D. Barrett⁴  
¹Pathology, University of Texas Medical Branch, Galveston, TX, ²Molecular Genomics Core Facility, University of Texas Medical Branch, Galveston, TX, ³Center for Vaccine Research, University of Pittsburgh, Pittsburgh, PA, ⁴Sealy Center for Vaccine Development, University of Texas Medical Branch, Galveston, TX

**Submitted Presentations 1B**  
**Vaccine Safety**  
**Constellation Ballroom, Salon B**  
**Moderator:** CAPT Rebecca L. Sheets, PhD  
National Institute of Allergy and Infectious Diseases  
National Institutes of Health  
Bethesda, MD

3:30 pm  S7  **Outcome-Based Vaccine Safety Surveillance**  
R. Baxter, E. Lewis, B. Fireman, J. McDonald, N. Klein  
Kaiser Permanente Vaccine Study Center, Oakland, CA

3:45 pm  S8  **Guillain-Barré Syndrome and Pneumonia and Influenza Hospitalizations: An Ecologic Overview**  
S. Iqbal, R. Li, C. Vellozzi  
OID/NCEZID/DHQP/ISO, Centers for Disease Control and Prevention, Atlanta, GA

4:00 pm  S9  **Adverse Events after Fluzone Intradermal® Vaccine Reported to the Vaccine Adverse Event Reporting System, 2011-13**  
P. L. Moro¹, T. Harrington¹, T. Shimabukuro¹, M. Cano¹, O. I. Museru¹, D. Menschik², K. Broder¹  
¹Immunization Safety Office, Centers for Disease Control and Prevention, Atlanta, GA, ²Center for Biologics Evaluation and Research, Food and Drug Administration, Rockville, MD
PROGRAM AGENDA

4:15 pm  S10  Use of Live-Attenuated Influenza Vaccine in Children and Adolescents with Cystic Fibrosis
  C. Quach¹, M. A. Lefebvre¹, L. C. Lands², F. D. Boucher³, B. Tapiero⁴, E. Toth⁵,
  P. Daignault⁶, J. E. Marcotte⁷, G. De Serres⁸
  ¹Paediatrics Infectious Diseases, McGill University, The Montreal Children’s Hospital, Montreal, QC, Canada, ²Paediatric Respiratory Medicine, McGill University, The Montreal Children’s Hospital, Montreal, QC, Canada, ³Paediatric Infectious Diseases, Chul, Quebec, QC, Canada, ⁴Paediatric Infectious Diseases, Chu Sainte-Justine, Montreal, QC, Canada, ⁵Quebec Ministry of Health, Montreal, QC, Canada, ⁶Pediatric Respiratory Medicine, Chul, Quebec, QC, Canada, ⁷Pediatric Respiratory Medicine, Chu Sainte-Justine, Montreal, QC, Canada, ⁸Institut national de santé publique du Quebec, Quebec, QC, Canada

4:30 pm  S11  Birth Outcomes Following H1N1 Immunization
  A. Eaton, N. Lewis, B. Fireman, J. Hansen, R. Baxter, N. Klein
  Vaccine Study Center, Kaiser Permanente, Oakland, CA

4:45 pm  S12  Chance Associations are Lopsided in Unbalanced Studies of Infrequent Events in Vaccine Safety
  R. Baxter, B. Fireman, N. Klein
  Kaiser Permanente Vaccine Study Center, Oakland, CA

5:00–6:00 pm  Welcome Reception & Poster Presentations  Atrium
TUESDAY, APRIL 23, 2013

7:00 am–5:00 pm  Registration  Constellation Ballroom Foyer

7:00–7:45 am  Dr. Richard J. Duma Meet the Experts Breakfast Session  Constellation Ballroom, Salon F

The New WHO Recommendations for the Global Use of Influenza Vaccines
Jon S. Abramson, MD
Wake Forest University School of Medicine
Winston-Salem, NC

Immunization of Pregnant Women: Two for One Protection
Carol J. Baker, MD
Baylor College of Medicine
Houston, TX

Advisory Committee on Immunization Practices Update
Ruth A. Karron, MD
Johns Hopkins Bloomberg School of Public Health
Baltimore, MD

Universal Influenza Virus Vaccine and Durability of Vaccines
Peter Palese, MD
Mount Sinai School of Medicine
New York, NY

7:30–8:30 am  Continental Breakfast/Poster Presentations  Atrium

8:30 am  Keynote II  CE  Constellation Ballroom, Salon A & B
Moderator:  Alison C. Mawle, PhD
Centers for Disease Control and Prevention
Atlanta, GA

8  Decade of Vaccines
Jon S. Abramson, MD
Wake Forest University School of Medicine
Winston-Salem, NC

9:15 am  Questions and Answers

9:30 am  Coffee Break
Symposium 3: Prevention of Infant Infections and Maternal Immunization  

Constellation Ballroom, Salon A & B

Moderator: Georges Peter, MD  
Warren Alpert Medical School of Brown University  
Providence, RI

9:45 am  9  Maternal Immunizations: An Overview  
Carol J. Baker, MD  
Baylor College of Medicine  
Houston, TX

10:10 am  10  Pertussis Strategies  
Mark H. Sawyer, MD  
University of California San Diego  
San Diego, CA

10:35 am  11  Prenatal Influenza Immunization: A Global Strategy  
Mark C. Steinhoff, MD  
Cincinnati Children’s Hospital and Medical Center  
Cincinnati, OH

11:00 am  12  Group B Streptococcal Vaccine Developments  
Morven S. Edwards, MD  
Baylor College of Medicine  
Houston, TX

11:30 am  Questions and Answers

12:00 pm  NFID Luncheon  
Constellation Ballroom, Salon C-F

Robert Austrian Memorial Lecture by Richard Malley, MD  
Associate Professor of Pediatrics, Children’s Hospital Boston, Boston, MA

Charles Mérieux Award Presentation to Robert G. Webster, PhD  
Rose Marie Thomas Chair, Division of Virology, Department of Infectious Diseases,  
St. Jude Children’s Research Hospital, Memphis, TN

Maurice R. Hilleman Early-Stage Career Investigator Award Presentation
## Symposium 4: New and Emerging Vaccines for Respiratory Infections

**Constellation Ballroom, Salon A & B**

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<tr>
<th>Time</th>
<th>Session Details</th>
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| 1:30 pm| **13** LAIV Provides Protection from Heterologous Influenza A Virus Infection without Inducing Vaccine-Associated Enhanced Respiratory Disease  
Amy L. Vincent, DVM, PhD  
Agricultural Research Service  
US Department of Agriculture  
Ames, IA |
| 1:50 pm| **14** Vaccines for Respiratory Syncytial Virus  
Ruth A. Karron, MD  
Johns Hopkins Bloomberg School of Public Health  
Baltimore, MD |
| 2:10 pm| **15** Adenovirus: Lessons Learned from the Department of Defense  
Ret. COL Charles H. Hoke, Jr., MD  
US Army Medical Materiel Development Activity  
Ft. Detrick, MD |
| 2:30 pm| **16** Novel Influenza Vaccines  
Peter Palese, PhD  
Mount Sinai School of Medicine  
New York, NY |
| 3:00 pm| Questions and Answers |
| 3:30 pm| **Coffee Break** |
Submitted
Presentations 2A: Epidemiology and Burden of Disease

Moderator: Cyril G. Gay, DVM, PhD
US Department of Agriculture
Agricultural Research Service
Beltsville, MD

(Concurrent Sessions)

4:00 pm S13 Logistical Implications of Implementing a Universal Rotavirus Program in Canada
1School of Nursing, Dalhousie University, Halifax, NS, Canada, 2Canadian Center for Vaccinology, St. Francis Xavier University, Antigonish, NS, Canada, 3Health and Wellness, Charlottetown, PE, Canada, 4Health and Wellness, Halifax, NS, Canada, 5Canadian Center for Vaccinology, Halifax, NS, Canada, 6Pediatrics, Dalhousie University, Halifax, NS, Canada, 7Capital District Health Authority, Halifax, NS, Canada, 8Dalhousie University, Pediatrics, Halifax, NS, Canada

4:15 pm S14 Trends in RSV-Associated Hospitalizations among Children and Adults in the United States, 2005-10
C. Archer, P. Kilgore, E. Martin, T. Taylor
Wayne State University, Detroit, MI

4:30 pm S15 Epidemiology of Herpes Zoster in Ontario, Canada, 1992-2011
A. E. Wormsbecker1, J. Wang4, L. C. Rosella4, J. C. Kwong4, C. Seo4, S. L. Deeks1
1Immunization and Vaccine Preventable Diseases, Public Health Ontario, Toronto, ON, Canada, 2Analytical Services, Public Health Ontario, Toronto, ON, Canada, 3Public Health Sciences, Public Health Ontario, Toronto, ON, Canada, 4Institute for Clinical Evaluative Sciences, Toronto, ON, Canada

4:45 pm S16 Invasive Pneumococcal Disease in Adults During the Age of Prevnar®
R. Baxter, A. Yee, T. Ray
Kaiser Permanente Vaccine Study Center, Oakland, CA
Submitted
Presentations 2B: Antigen Design and Development  

(Concurrent Sessions)  Moderator:  Hana Golding, PhD
Center for Biologics Evaluation and Research
US Food and Drug Administration
Bethesda, MD

4:00 pm  S17  A Universal Influenza Virus Vaccine Based on the Stalk Domain of the Hemagglutinin
F. Krammer, I. Margine, N. Pica, R. Hai, P. Palese
Department of Microbiology, Mount Sinai School of Medicine, New York, NY

4:15 pm  S18  CD4+ T-Cell Responses to Cross-Reactive Influenza H1N1 T-Cell Epitopes Identified by Immunoinformatic Methods
L. Moise, C. Boyle, M. Ardito, F. Terry, H. Latimer, R. Tassone, M. Cote, W. Martin,
A. S. De Groot
EpiVax, Inc., Providence, RI

4:30 pm  S19  Phylogenetic Considerations in Designing a Broadly Protective Multimeric L2 Vaccine
S. Jagu1, K. Kwak1, J. T. Schiller2, D. R. Lowy3, H. Kleanthous4, K. Kalnin5, H. Wang6,
L. T. Chow7, W. K. Huh7, K. S. Jaganathan8, S. V. Chivukula9, R. B. Roden1
1Pathology, Johns Hopkins University, Baltimore, MD, 2NCI, NIH, Bethesda, MD,
3Sanofi Pasteur, Boston, MA, 4Departments of Biochemistry and Molecular Genetics, University of Alabama at Birmingham, Birmingham, AL,
5Departments of Gynecologic Oncology, University of Alabama at Birmingham, Birmingham, AL,
6Shantha Biotechnics Limited, Hyderabad, India

4:45 pm  S20  Norovirus Consensus GII.4 Virus-like Particles in Monovalent and Bivalent Vaccine Formulations Provide Broad Immunogenicity and Cross-Reactivity
G. I. Parra1, K. Bok1, R. Taylor2, J. R. Haynes2, R. F. Bargetze3, S. V. Sosnovtsev4,
C. Richardson5, K. Y. Green1
1Calicivirus Section, LID, NIAID, NIH, Bethesda, MD, 2LigoCyte/Takeda Pharmaceutical, Bozeman, MT

5:00 pm  S21  Immunogenicity and Protective Efficacy of a Multi-Epitope Vaccine Composed of Ebola Virus and Venezuelan Equine Encephalitis Virus HLA Class II T-Cell Epitopes in HLA Transgenic Mice
L. C. Dupuy1, D. Mitchell1, M. J. Richards1, C. Bounds1, M. Ardito2, E. McClaine3,
L. Moise2, W. Martin2, A. S. De Groot2, C. S. Schmaljohn1
1USAMRIID, Fort Detrick, MD, 2EpiVax, Inc., Providence, RI
PROGRAM AGENDA

WEDNESDAY, APRIL 24, 2013

7:00 am–12:00 pm  Registration  Constellation Ballroom Foyer

7:00–7:45 am  Dr. Richard J. Duma Meet the Experts Breakfast Session  Constellation Ballroom, Salon F

Polio Eradication: Is it in the Future?
Walter A. Orenstein, MD
Emory Vaccine Center
Emory University
Atlanta, GA

Pertussis Strategies
Mark H. Sawyer, MD
University of California San Diego
San Diego, CA

One Health Approaches from a Veterinary Perspective
W. Ray Waters, DVM, PhD
Agricultural Research Services
US Department of Agriculture
Ames, IA

Synthetic Genomic Vaccine Technologies
David E. Wentworth, PhD
The J. Craig Venter Institute
Rockville, MD

7:30 am  Continental Breakfast  Atrium

Submitted
Presentations 3A: Immunization Programs and Vaccine Delivery  CE

(Concurrent Sessions)  Moderator:  Susan J. Rehm, MD
National Foundation for Infectious Diseases
Bethesda, MD

8:00 am  S22  Evaluation of Canadian Workplace Policies Used to Promote Influenza Vaccination among Healthcare Personnel
D. M. MacDougall1, B. Halperin2, L. Crowe3, P. Lam4, H. Ramsey5, A. McCarthy6
1Canadian Center for Vaccinology, St. Francis Xavier University, Antigonish, NS, Canada, 2Canadian Center for Vaccinology, Dalhousie University, Halifax, NS, Canada, 3Bruyere Research Institute, Ottawa, ON, Canada, 4University of Toronto, Toronto, ON, Canada, 5Ottawa Hospital Research Institute, Bruyere Research Institute, Ottawa, ON, Canada
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<th>Time</th>
<th>Session</th>
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<td>8:15 am</td>
<td>S23</td>
<td>2011/2012 Immunization Coverage from Ontario, Canada: Uptake and Exemptions</td>
<td>S. Wilson, G. H. Lim, J. Fediurek, M. A. McIntyre, S. L. Deeks Immunization and VPD, Public Health Ontario, Toronto, ON, Canada</td>
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</table>
| 8:30 am  | S24     | Building HPV Vaccine Acceptance: A Case Study of Social Media Potential | C. Zhang¹, M. Gotsis², M. Jordan-Marsh³  
¹Mork Family Department of Chemical Engineering and Materials Science, University of Southern California, Los Angeles, CA, ²Creative Media & Behavioral Health Center, Interactive Media Division, University of Southern California, Los Angeles, CA, ³School of Social Work, University of Southern California, Los Angeles, CA |
| 8:45 am  | S25     | The Use of a Massively Open Online Course (MOOC) for Global Vaccine Trial Education | K. R. Charron¹, A. B. Cox², A. J. Feller², I. E. Gooding³  
¹International Health and Center for Teaching and Learning, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, ²International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, ³Center for Teaching and Learning, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD |
| 9:00 am  | S26     | Jet Injection for Influenza: A Randomized Controlled Clinical Trial to Demonstrate Non-Inferiority of Jet Injection vs. Needle and Syringe for Administration of TIV Influenza Vaccine (Afluria® Season 2012-13) | L. McAllister¹, K. Copeland¹, K. Werth¹, D. Plant¹, N. Le Cam Bouveret², D. K. Cobb³  
¹PharmaJet, Inc, Golden, CO, ²CSL Biotherapies, Parkville, Victoria, Australia, ³Medical Center of the Rockies, Loveland, CO |
| 9:15 am  | S27     | A Novel Vaccine Presentation to Address the Challenges of Vaccine Delivery in Low-Resource Settings | D. Chen, M. Lal  
Vaccine Technologies, PATH, Seattle, WA |
Submitted Presentations 3B: Vaccine Candidates: Preclinical and Clinical Studies

**Constellation Ballroom, Salon B**

(Concurrent Sessions)  

**Moderator:** Kathleen M. Neuzil, MD, MPH  
Program for Appropriate Technology in Health (PATH)  
Seattle, WA

**8:00 am**  
**S28**  
**A Novel Intramuscular W80SEC Nanoemulsion Adjuvanted Respiratory Syncytial Virus Vaccine Protects Cotton Rats against RSV Challenge**  
T. Hamouda¹, V. Bitko¹, J. K. Simmon¹, P. E. Makidon², D. M. Smith², A. Fattom¹, J. R. Baker, Jr.¹  
¹NanoBio Corp, Ann Arbor, MI, ²University of Michigan, Ann Arbor, MI

**8:15 am**  
**S29**  
**Development of a Multi-Valent Chimeric OspA Vaccine to Prevent Lyme Disease**  
P. N. Barrett¹, B. Luft², A. Loew-Baselli³, N. Wressnigg³, E. M. Poellabauer³, S. Fritsch⁴, B. A. Crowe¹, I. Livey¹, B. Schmitt⁵, M. Zeitlinger⁶, H. Kollaritsch⁶, P. G. Kremser⁶, M. Esen⁷, H. J. Ehrlich⁸, G. Aichinger³  
¹Vaccine R&D, Baxter Bioscience, Orth/Donau, Austria, ²Stony Brook University Medical Center, New York, NY, ³Vaccine R&D, Baxter Bioscience, Vienna, Austria, ⁴Global R&D, Baxter Bioscience, Vienna, Austria, ⁵Health Center Mainz, Mainz, Germany, ⁶Medical University of Vienna, Vienna, Austria, ⁷University of Tuebingen, Tuebingen, Germany

**8:30 am**  
**S30**  
**Reduced Effectiveness of Pertussis Vaccine without an 18 Month Booster**  
R. Menzies, H. Quinn, P. McIntyre  
National Centre for Immunisation Research and Surveillance, Sydney, NSW, Australia

**8:45 am**  
**S31**  
**Immunogenicity of Heterologous H5N1 Influenza Booster Vaccination 6 or 18 Months after Primary Vaccination in Adults**  
J. M. Langley¹, L. Frenette², R. Jeanfreau³, S. A. Halperin⁴, M. Kyle⁵, L. Chu⁶, S. McNeil⁴, M. Dramé⁶, S. Phay Tran⁶, T. Ollinger¹⁰, K. X. Walravens¹⁰, L. Fries¹¹, D. Vaughn⁸  
¹Pediatrics and Community Health and Epidemiology, Canadian Center for Vaccinology, Dalhousie University, Halifax, NS, Canada, ²QT Research, Sherbrooke, QC, Canada, ³Benchmark Research Metairie, Metairie, LA, Canada, ⁴Pediatrics, Canadian Center for Vaccinology, Dalhousie University, Halifax, NS, Canada, ⁵Benchmark Research, Austin, TX, ⁶Radiant Research, Chicago, IL, ⁷Canadian Center for Vaccinology, Dalhousie University, IWK Health Centre and Capital Health District, Dalhousie University, Halifax, NS, Canada, ⁸GlaxoSmithKline Biologicals, King of Prussia, PA, ⁹GSK Vaccines, Canada, Laval, QC, Canada, ¹⁰GlaxoSmithKline Biologicals, Rixenstart, Belgium, ¹¹Novavax, Rockville, MD
9:00 am  S32  Sabin-IPV Clinical Studies and Continued Process Optimization for Cost-Price Reduction and Technology Transfer Purposes  
W. A. Bakker, Y. E. Thomassen, A. G. van ‘t Oever, J. Westdijk, A. Hamidi, M. G. van Oijen, P. Verdijk, L. A. van der Pol  
Institute for Translational Vaccinology, Bilthoven, Netherlands

9:15 am  S33  Randomized Trial of Human Papillomavirus Vaccination Schedules among College Age Males  
R. Zimmerman  
Family Medicine & Clinical Epidemiology, University of Pittsburgh, Pittsburgh, PA

9:30 am  Coffee Break

Symposium 5:  Prospects for New Tuberculosis Vaccines  
Constellation Ballroom, Salon A & B

Moderator:  Bruce G. Weniger, MD  
Chiang Mai University  
Atlanta, GA

10:00 am  17  Progress Towards Live Vaccines for Tuberculosis  
Stefan H.E. Kaufmann, PhD  
Max Planck Institute for Infection Biology  
Berlin, Germany

10:30 am  18  Prospects for Subunit Vaccines Targeting Tuberculosis Latency  
Peter L. Andersen, DVM, DMS  
Statens Serum Institut  
Copenhagen, Denmark

11:00 am  19  Biomarkers for Assessing Immunity to Tuberculosis  
Willem Hanekom, MBChB, DCH  
South African Tuberculosis Vaccine Initiative  
University of Cape Town  
Cape Town, South Africa

11:30 am  20  One Health/Veterinary Links Associated with Tuberculosis Vaccines  
W. Ray Waters, DVM, PhD  
Agricultural Research Service  
US Department of Agriculture  
Ames, IA

12:00 pm  Questions and Answers

12:30 pm  Lunch (on your own)
**Symposium 6: Vaccine Discovery and New Technologies**

*Constellation Ballroom, Salon A & B*

**Moderator:** Cyril G. Gay, DVM, PhD  
Agricultural Research Service  
US Department of Agriculture  
Beltsville, MD

1:30 pm  
**21 Induction of Vaginal Intraepithelial CD8+ T-Cells by HPV Vector Vaccination**  
John T. Schiller, PhD  
National Cancer Institute  
National Institutes of Health  
Bethesda, MD

1:55 pm  
**22 Gender-Based Differences in Vaccine Response**  
Sabra L. Klein, PhD  
Johns Hopkins Bloomberg School of Public Health  
Baltimore, MD

2:20 pm  
**23 Synthetic Genomics Vaccines for Human Health**  
John I. Glass, PhD  
The J. Craig Venter Institute  
Rockville, MD

2:45 pm  
**24 Using Synthetic Genomics to Create Influenza Vaccine**  
David E. Wentworth, PhD  
The J. Craig Venter Institute  
Rockville, MD

3:10 pm  
Questions and Answers

3:30 pm  
**Adjourn**
POSTER SESSIONS
GENERAL POSTERS (P1-P28)

P1  Identification of EHEC Specific Protective Antigens Using Whole Genome Approach  
A. Kalita1, V. A. Garcia-Angulo1, M. K. Kalita2, A. G. Torres1  
1Microbiology & Immunology, UTMB, Galveston, TX, 2Internal Medicine, UTMB, Galveston, TX

P2  Process Development for a Live-Attenuated Respiratory Syncytial Virus Vaccine  
Y. E. Thomassen, J. E. van der Welle, C. J. Smitsman, W. A. Bakker  
Process Development, InTraVacc, Bilthoven, Netherlands

P3  Helicobacter pylori Vaccine Development by Reverse Vaccinology  
1EpiVax, Inc., Providence, RI, 2Department of Medicine, Rhode Island Hospital/Warren Alpert Medical School of Brown University, Providence, RI, 3Institute for Immunology & Informatics, University of Rhode Island, Providence, RI

P4  Evaluation of Immune Response against Neisseria meningitidis B Using DDA-BF as Adjuvant  
F. M. Rinaldi1, E. B. Gaspar2, N. Lincopan3, E. N. De Gaspari1  
1Immunology, Adolfo Lutz Institute, São Paulo, Brazil, 2Animal Husbandry, Embrapa Southern Region, Bagé/RS, Brazil, 3Department of Microbiology, University of São Paulo, São Paulo, Brazil

P5  Delayed-Type Hypersensitivity Response is a Predictor of Cell Immunity after Immunization with Neisseria meningitidis Outer Membrane Antigens  
1Immunology, Adolfo Lutz Institute, São Paulo, Brazil, 2Department of Pathology, Adolfo Lutz, São Paulo, Brazil, 3Department of Immunology, Adolfo Lutz, São Paulo, Brazil, 4Animal Husbandry, Embrapa Southern Region, Bagé/RS, Brazil, 5Microbiology, University of São Paulo, São Paulo, Brazil

P6  Serum Levels of Th1 and Th2 Cytokines Produced in Nigerian Children with Measles Vaccine Failure in Measles Outbreak in Ogun State Nigeria  
A. A. Adeiga, O. B. Awoderu, A. Faneye, G. B. Akintunde, J. Onyewuche  
Microbiology, Nigeria Institute Of Medical Research Yaba, Lagos, Nigeria

P7  Oral DNA Vaccination Encoding Turkey Coronavirus Spike Protein Containing Neutralizing Epitope Delivered by Attenuated Salmonella Elicits Protective Immune Responses in Turkeys  
Y. Chen1, T. Lin2  
1Biosciences Technology, Chung Yuan Christian University, Chung Li, Taiwan, 2Comparative Pathobiology, Purdue University, West Lafayette, IN
POSTER SESSIONS

P8  Aerosol Vaccination against Ebola Virus
M. Meyer¹, T. Garron¹, T. Geisbert², G. Olinger³, P. Collins⁴, A. Bukreyev¹
¹Pathology, University of Texas Medical Branch, Galveston, TX, ²Microbiology & Immunology, University of Texas Medical Branch, Galveston, TX, ³Viral Pathogenesis and Immunology Branch, United States Army Institute for Infectious Diseases, Frederick, MD, ⁴RNA Viruses Section, National Institute of Allergy and Infectious Diseases, Bethesda, MD

P9  Immunogenicity Assessment of In Silico-Selected T-Cell Epitopes for a Burkholderia Biodefense Vaccine
R. Liu, J. Desrosiers, B. Martin, L. Moise, A. S. De Groot
Institute for Immunology and Informatics, University of Rhode Island, Providence, RI

P10 Human Papillomavirus Vaccine Uptake among 18-26 Year Old Low-Income, Multiethnic Women
A. B. Berenson, E. Male, A. Lee, M. Rahman
Ob-Gyn, University of Texas Medical Branch, Galveston, TX

P11  WITHDRAWN

P12  Efficacy of Live-Attenuated Influenza Vaccine against Moderate to Severe Influenza Illness Compared with Efficacy against Mild Influenza Illness in Children
C. S. Ambrose², X. Wu¹, R. B. Belshe¹
¹MedImmune, LLC, Gaithersburg, MD, ²Saint Louis University Medical Center, St. Louis, MO

P13  The Development of Serum Bactericidal Assays to Evaluate Salmonella Vaccines
Center for Vaccine Development, University of Maryland, School of Medicine, Baltimore, MD

P14  Cross-Reactive, Linear B-Cell Epitopes in the Influenza Virus Matrix Protein 1
K. Lin¹, A. L. Vincent², J. A. Roth³, M. Kehrli³, K. M. Lager², S. Ramamoorthy⁴
¹Veterinary Diagnostic and Production Animal Medicine, College of Veterinary Medicine, Iowa State University, Ames, IA, ²Virus and Prion Diseases Research Unit, National Animal Disease Center, USDA-ARS, Ames, IA, ³Veterinary Microbiology and Preventive Medicine, Iowa State University, Ames, IA, ⁴Veterinary and Microbiological Sciences, N. Dakota State University, Fargo, ND

P15  Construction of a Candidate Vaccine Strain against Helicobacter pylori, Expressing HpaA Antigen Present on Non-Toxigenic V. cholerae
J. Tobias
Department of Microbiology and Immunology, The Sahlgrenska Academy of Göteborg university, Institute of Biomedicine, Göteborg, Sweden

P16  Phase 1 Study of Pandemic H1 DNA Vaccine in Healthy Adults
NIH/NIAID/VRC, Bethesda, MD
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<tr>
<td>P17</td>
<td>Full Adjuvant Activity of the Whole Cell Pertussis Vaccine in Combination with the Pneumococcal Surface Protein A Requires Pertussis Toxin</td>
<td>C. Salcedo Rivillas¹, E. N. Miyaji¹, P. L. Ho¹, C. Locht², N. Mielcarek², M. S. Oliveira¹</td>
<td>Centro de Biotecnologia, Instituto Butantan, São Paulo, Brazil, Center for Infection and Immunity of Lille, Institut Pasteur de Lille, Lille, France</td>
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<td>P18</td>
<td>Improved Adjuvanting of Seasonal Influenza Vaccines: Pre-Clinical Studies of MVA-NP+M1 Co-Administration with Inactivated Influenza Vaccine</td>
<td>C. E. Mullarkey¹, A. Boyd¹, A. van Laarhoven¹, E. A. Lefevre¹, N. Temperton³, B. Carr², C. Butter², B. Charleston², T. Lambe¹, S. C. Gilbert¹</td>
<td>Clinical Medicine, University of Oxford, Oxford, UK, Institute for Animal Health, Compton near Newbury, UK, Medway School of Pharmacy, University of Kent, Medway, UK</td>
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<td>P19</td>
<td>Chitosan-Encapsulated Plasmid Coding for LipL32 and Loa22: A Promising Formulation of Leptospirosis DNA Vaccine</td>
<td>S. Umthong¹, K. Patarakul¹, S. Wanichwecharungruang³, T. Palaga³</td>
<td>Interdisciplinary Program in Medical Microbiology, Graduate School, Chulalongkorn University, Bangkok, Thailand, Department of Microbiology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand, Department of Chemistry, Faculty of Science, Chulalongkorn University, Bangkok, Thailand</td>
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<td>P20</td>
<td>Characterization of a Yersinia pestis Double Isogenic Mutant Δlpp/Δpla Mutant in a Mouse Model of Pneumonic and Bubonic Plague: A Potential New Live-Attenuated Vaccine</td>
<td>C. J. van Lier, J. Sha, M. L. Kirtley, T. E. Erova, E. V. Kozlova, B. L. Tiner, A. K. Chopra</td>
<td>Microbiology &amp; Immunology, UTMB, Galveston, TX</td>
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<td>P21</td>
<td>Genetic Stability of Rift Valley Fever Virus MP-12 Lacking NSs in Type-I Interferon-Incompetent Vero Cells</td>
<td>N. Lokugamage</td>
<td>Pathology Research, UTMB, Galveston, TX</td>
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<td>P22</td>
<td>WITHDRAWN</td>
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<td>P23</td>
<td>Immune Suppression Induced by Vi Capsular Polysaccharide is Overcome by Vi-DT Conjugate Vaccine</td>
<td>S. An, Y. Yoon, R. Carbis</td>
<td>Vaccine Development (Conjugate vaccine section), International Vaccine Institute, Seoul, Republic of Korea</td>
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<td>P24</td>
<td>Novel Function of Sandfly Fever Sicilian Virus NSs Modifying Host and Viral Gene Expressions</td>
<td>O. Lihoradova, S. V. Indran, T. Ikegami</td>
<td>Pathology, University of Texas Medical Branch, Galveston, TX</td>
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P25 Development of a Novel Method for Deriving Thresholds of Toxicological Concerns for Vaccine Constituents
J. White, C. Wrzesinski, M. Green
Department of Vaccines and Related Products Applications, FDA, Rockville, MD

P26 Fatigue and Fear with Shifting Polio Eradication Strategies in India: A Study of Social Resistance to Vaccination
1Warren Alpert Medical School, Brown University, Providence, RI, 2Department of Epidemiology, International Health Institute, Brown University, Providence, RI, 3Department of Paediatrics, Jawaharlal Nehru Medical College, Aligarh, India, 4Department of Anthropology, Brown University, Providence, RI

P27 Perception of Childhood Immunization: A Qualitative Study of Fathers in Kano, Northern Nigeria
A. L. Adamu1, N. S. Nass2, U. M. Lawan1
1Community Medicine, Bayero University/Aminu Kano Teaching Hospital, Kano, Nigeria, 2Community Medicine, Aminu Kano Teaching Hospital, Kano, Nigeria

P28 Treatment with Aqueous Phyllanthus niruri Extract Promotes the Phenotypic Maturation of Bone Marrow-Derived Dendritic Cells and their Antigen Presentation Functions, In Vitro
C. S. Nworu1, C. O. Esimone2
1Pharmaceutical Pharmacology & Toxicology, University of Nigeria, Nsukka, Nigeria, 2Pharmaceutical Microbiology & Biotechnology, Nnamdi Azikiwe University, Awka, Nigeria

TRAVEL GRANT RECIPIENTS (TG1-TG11)

TG1 Immunomodulatory Potential of QS-21 on Protective Efficacy of DPT Vaccine
C. Goyal, S. K. Mishra, S. Gairola, B. Patwardhan
1Panacea Biotec Limited, Lalru, India, 2Symbiosis International University, Pune, India

TG2 Pichia pastoris-Expressed Dengue 2 Envelope Forms Virus-Like Particles and Induces High Titer Neutralizing Antibodies
N. Khanna, S. Swaminathan, S. Mani, L. Tripathi
International Centre for Engineering & Biotechnology, New Delhi, India

TG3 Allelic Diversity of Merozoite Surface Protein 2 Gene of Plasmodium falciparum among Children in Osogbo, Nigeria
D. O. Ojurongbe, A. F. Fagbenro-Beyioku, O. A. Adeyeba, J. F. Kun
1Ladoke Akintola University of Technology, Osogbo, Nigeria, 2University of Lagos, Lagos, Nigeria, 3Institute for Tropical Medicine, Tuebingen, Germany
The Sixteenth Annual Conference

POSTER SESSIONS

TG4 Concern and Resistance to Immunization and their Causes among Key Stakeholders in the Context of Introduction of Rotavirus Vaccine in Georgia
M. Topuridze, M. Shishniashvili
National Center for Disease Control and Public Health, Tbilisi, Georgia

TG5 Ensuring Comprehension of Study Information among Vaccine Trial Participants in The Gambia
Y. Saidu
MRC, Bajul, The Gambia

TG6 Predictors of Delay in Immunization of Children in Rural Communities of Kano, Northern Nigeria
A. L. Adamu, U. M. Lawan
BAYERO UNIVERSITY/AMINU KANO TEACHING HOSPITAL, KANO, NIGERIA

TG7 Immunization Knowledge, Attitude, and Practice among Parents: Malaysian Experience
A. I. Awadh, M. A. Hassali, O. Q. B. Al-lela, S. H. Bux, R. M. Elkalmi
1Pharmacy Practice Department, Kulliyyah of Pharmacy, International Islamic University Malaysia, Malaysia, 2Discipline of Social and Administrative Pharmacy, School of Pharmaceutical Sciences, Universiti Sains Malaysia, Malaysia

TG8 Knowledge and Practice of Injection Safety amongst Primary Healthcare Professionals in Kano, North Nigeria
S. Abubakar, M. U. Bashir
BAYERO UNIVERSITY KANO/AMINU KANO TEACHING HOSPITAL, KANO, NIGERIA

TG9 Induction of Protective Immune Response in Mice by a DNA Vaccine Encoding ε-Toxin Gene of Clostridium perfringens, a Causative Agent of Enterotoxemia in Sheep
S. K. Deshmukh
National Institute of Immunology, New Delhi, India

TG10 Translational Fusion of Heat Labile Enterotoxin BSubunit and Immunodominant Epitopes of Epsilon Toxin of Clostridium perfringens and its Evaluation as a Potential Subunit Vaccine
H. Kaushik
National Institute of Immunology, New Delhi, India

TG11 Risk of Tuberculosis Disease among BCG Vaccinated, HIV Uninfected South African Infants with Tuberculosis Exposure and/or Infection
University of Cape Town, Worcester, South Africa
INVITED SPEAKER BIOGRAPHIES
INVITED SPEAKER BIOGRAPHIES

Jon S. Abramson, MD
Dr. Abramson received his undergraduate degree at Boston University and medical degree from Wake Forest University School of Medicine (WFUSM). He completed his pediatric residency at Wake Forest University Baptist Medical Center and a pediatric infectious diseases fellowship at the University of Minnesota. He joined the faculty at WFUSM in 1981 and has served as chair of the Department of Pediatrics at WFUSM and physician-in-chief of Brenner Children’s Hospital since 1996. He also served as the elected chair of the Wake Forest University Physicians clinical practice group from 2001-07.

Dr. Abramson served as a council member of the Society for Pediatric Research (SPR) and was elected President of the SPR in 1995. From 1995-2003 he was a member and Chair (1999-2003) of the American Academy of Pediatrics (AAP) Committee on Infectious Diseases and as part of this activity was involved in the publication of the 2000 and 2003 Red Book. From 2003-07 he was a member and chair (2005-07) of the Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices.

Since 2009 he has served as a member of the World Health Organization (WHO) Strategic Advisory Group of Experts on Immunizations (SAGE) and SAGE Liaison to Pan American Health Organization. In his role with SAGE he served as chair of the Cholera Vaccine and Meningococcal Vaccine working groups and as a member of the Ad Hoc Policy Advisory Group on Influenza A (H1N1) Pandemic. Dr. Abramson’s current roles on SAGE include serving as chair of the Varicella Vaccine working group and a member of the Influenza Seasonal and Pandemic Vaccine working group. He also serves as a consultant to the Gates Foundation on maternal-infant influenza immunization. Dr. Abramson also serves as a Food and Drug Administration (FDA) consultant as a member of the Antiviral Drugs Advisory Committee and on the CDC Peer Review Panel.

Pedro L. Alonso, PhD
Dr. Pedro Alonso is the director of the Barcelona Institute for Global Health (ISGlobal), professor of International Health of the University of Barcelona, and Chief of the Department of Tropical Medicine at Hospital Clinic de Barcelona. He started his career in International Health 25 years ago as a young physician working in West Africa. Since then his work has been focused in the key determinants of morbidity and mortality in the two most vulnerable population groups in Africa: young children and pregnant women. Building and strengthening human and institutional capacity in developing countries as well as in Europe, together with increasing support for other global health initiatives, has become a growing area of activity.

Some of his most relevant work has been carried out in the field of malaria, leading to the development and testing of new control tools for the prevention or treatment of *P. falciparum*. He has published more than 310 papers in international peer reviewed journals.

In 1996 he led the creation of the Manhia Health Research Centre (CISM) in Southern Mozambique. Despite its relative short life, the Centre has become one of the leading research infrastructures in Africa.

He has served in several national and international committees. Currently, he is a board member of the Medicines for Malaria Venture, co-chair of the Steering Committee of the Decade of Vaccines Collaboration (initiative promoted by the World Health Organization, UNICEF, the National Institute of Allergy and Infectious Diseases, and the Bill and Melinda Gates Foundation), and chair of the Steering Committee of the Malaria Eradication Scientific Alliance. He is also a member of the WHO Malaria Policy Advisory Committee.

Peter L. Andersen, DVM, DMS
Dr. Andersen is vice president of vaccine research and development at Statens Serum Institut (SSI). Dr. Andersen’s research has been focused on the identification and characterization of antigens, immune mechanisms, and vaccine delivery systems that mediate protection against important pathogens such as *Mycobacterium tuberculosis, Chlamydia trachomatis* and Influenza. He has pioneered work both on novel diagnostic assays (the IGRA assays), novel TB vaccines (H1/H4/H56), and the CAF series of liposomal adjuvants. In his current position, Dr. Andersen is responsible for the overall coordination of vaccine research and development at the SSI, covering activities from early
research and to clinical development with more than 80 employees. This program currently has three different TB vaccines, a novel liposomal adjuvant formulation, and a new TB skin test under clinical testing and a number of experimental vaccines in the late preclinical stage. In collaboration with industrial partners, the SSI antigen discovery programs has furthermore resulted in three commercially available tests for TB diagnosis.

Dr. Andersen has served on a number of committees to advise and coordinate strategies for vaccine and diagnostic development. He has been organizing and chairing several international meetings and has given numerous keynote presentations at scientific meetings over the last eight years. Dr. Andersen is the inventor of more than 20 patent families and the author of more than 260 papers (current H-index 66), within the fields of infection, immunity, and vaccine research in peer-reviewed journals. Dr. Andersen is the most cited Danish immunologist in the period 1990-2005 (analysis by Thomson Scientific) and a recent analysis by Essential Science Indicators (ESI) has established him as the third most cited scientist worldwide in the Tuberculosis field.

Carol J. Baker, MD
Dr. Baker is professor of pediatrics and of molecular virology and microbiology at Baylor College of Medicine in Houston, TX. She was head of the section of infectious diseases in the Department of Pediatrics at Baylor College of Medicine for 25 years.

Dr. Baker is immediate past chair of the Centers for Disease Control and Prevention’s Advisory Committee on Immunization Practices. Previously, she has been president of the Infectious Diseases Society of America (IDSA), president of the National Foundation for Infectious Diseases, secretary of the Pediatric Infectious Diseases Society, and a member of the American Academy of Pediatrics Committee on Infectious Diseases from 1997-2012.

Dr. Baker’s work has focused on all aspects of pediatric infectious diseases, particularly all aspects of group B streptococcal infections including research to develop a vaccine. Her policy work in the early 1990s led to the US recommendations for intrapartum chemoprophylaxis to prevent early-onset group B streptococcal disease in neonates. In 1997, Dr. Baker was the recipient of the Distinguished Service Award and in 2007 of the Distinguished Physician Award, each from the Pediatric Infectious Diseases Society. In 2008 she received the Distinguished Alumna Award from Baylor College of Medicine, in 2010 the Mentor Award, and 2011 a Society Citation for outstanding achievements in the field of Infectious Disease, both from the IDSA.

A widely published researcher in pediatrics and infectious diseases, Dr. Baker has authored or co-authored more than 400 published studies, reviews, and book chapters. She also was an associate editor of the 2000, 2003, 2006, 2009, and 2012 Red Book published by the American Academy of Pediatrics.

Morven S. Edwards, MD
Dr. Edwards is professor of pediatrics at Baylor College of Medicine and she is an attending physician at Texas Children’s Hospital in Houston, TX. She is board certified in general pediatrics and pediatric infectious diseases. Dr. Edwards received her medical degree from Baylor College of Medicine and completed a pediatric residency and fellowship in Pediatric Infectious Diseases at Baylor and a research fellowship at the Channing Laboratory of Harvard Medical School.

Dr. Edwards has a longstanding interest in group B streptococcal infections. Her research efforts have as their goal the prevention of invasive group B streptococcal infections through immunization. Currently, she is involved in a clinical trial to evaluate immune responses to invasive group B streptococcal infections in adults. Dr. Edwards has authored or co-authored more than 200 articles and book chapters.

In 2009-10 she served as the president of the medical staff at Texas Children’s Hospital. She is a member of the American Academy of Pediatrics, the Infectious Diseases Society of America, and the Pediatric Infectious Diseases Society. She is a supporting member of the National Foundation for Infectious Diseases.
**Cyril G. Gay, DVM, PhD**

Dr. Gay obtained a BS in Chemistry and a DVM from Auburn University, and a PhD in microbiology from The George Washington University. Dr. Gay has worked in the animal health research field for the last 25 years holding several positions of increasing responsibility in the federal government and the pharmaceutical industry. As chief, biotechnology section, Center for Veterinary Biologics (CVB), United States Department of Agriculture (USDA), Dr. Gay developed the procedures for licensing molecular vaccines that led to the first license for a live recombinant vectored vaccine. In the pharmaceutical industry (SmithKline Beecham Animal Health and Pfizer Animal Health) Dr. Gay led several cross-functional teams that successfully developed and licensed veterinary vaccines for companion animals and livestock. As director, global product development, Pfizer Inc., Dr. Gay developed strategic and tactical plans that interfaced R&D, clinical development, manufacturing, marketing, and product life-cycle management. Dr. Gay joined Agricultural Research Service (ARS), USDA, in 2002. Dr. Gay currently holds the position of senior national program leader and provides program direction and national coordination for the department’s intramural animal health research program, with focus on eight research laboratories located in Ames, IA, East Lansing, MI, Clay Center, NE, Athens, GA, Orient Point, NY, Beltsville, MD, Pullman, WA, and Manhattan, KS. Dr. Gay was the 2010 recipient of the USDA Secretary’s Honors Award for interagency response to the pandemic H1N1 influenza outbreak and the ARS Special Administrator’s Award for outstanding and rapid research support for pandemic H1N1.

**John I. Glass, PhD**

Dr. Glass is a professor in the J. Craig Venter Institute (JCVI) Synthetic Biology Group. This is the team that created a synthetic bacterial cell based on *Mycoplasma mycoides* in 2010. Dr. Glass directs the mycoplasma biology and genome transplantation components of this project. From the lessons learned through building a synthetic cell with a minimal gene set, the JCVI synthetic biologists hope to design and create cells with extraordinary properties that address human needs in medicine, bioenergy, and the environment. Dr. Glass also leads a Venter Institute team that is working with Novartis Vaccines to produce influenza virus vaccines faster and better.

Dr. Glass’s expertise is in molecular biology, microbial pathogenesis, and microbial genomics. He is an adjunct faculty member of the University of Maryland Department of Cell Biology and Molecular Genetics. Prior to joining the JCVI, Dr. Glass spent five years in the Infectious Diseases Research Division of Eli Lilly where he directed a hepatitis C virology group and a microbial genomics group (1998-2003).

Dr. Glass earned his undergraduate and graduate degrees from the University of North Carolina at Chapel Hill. His PhD work was on RNA virus genetics in the laboratory of Gail Wertz. He was on the faculty and did postdoctoral fellowships in the Microbiology Department of the University of Alabama at Birmingham in polio virology with Casey Morrow and mycoplasma pathogenesis with Gail Cassell (1990-98). On sabbatical leave in Elison Chen’s lab at Applied Biosystems Inc. (1995-97), he sequenced the genome of *Ureaplasma parvum* and began his study of mycoplasma genomics.

**Willem Hanekom, MBChB, DCH**

Dr. Hanekom trained in pediatrics in Cape Town, and in pediatric infectious diseases at Northwestern University in Chicago. He then completed a postdoc in immunology at Rockefeller University in New York City.

Dr. Hanekom is currently director of the South African Tuberculosis Vaccine Initiative (SATVI) at the University of Cape Town (UCT), where he is also co-director of the Wellcome Trust-Funded Clinical Infectious Disease Research Initiative. He is professor in the Institute of Infectious Diseases and Molecular Medicine and in the School of Child and Adolescent Health, of UCT.

SATVI tests new TB vaccine strategies in humans and addresses many clinical and immunological questions that hamper TB vaccine development. Among these, large cutting edge studies aim to identify biomarkers of risk of TB disease, or protection against TB disease.

Dr. Hanekom has authored more than 100 publications, and has been successful in generating competitive research funding from the NIH, EDCTP, and Bill and
Melinda Gates Foundation, among others. He is actively involved in training postgraduate students and has won various research and teaching awards.

Dr. Hanekom is past-president of the South African Immunological Society and of the Federation of African Immunological Societies. He is a regular reviewer for international funding agencies, and an editor/reviewer for many scientific journals. He serves on multiple World Health Organization-affiliated and other international advisory committees in TB vaccine development and translational immunology.

**D.A. Henderson, MD, MPH**

Dr. Henderson is presently a resident scholar at the Center for Biosecurity (Baltimore) and professor of medicine and public health, University of Pittsburgh. Former positions include: director of the WHO Smallpox Eradication Program 1966-77; dean and professor of epidemiology, Johns Hopkins Bloomberg School of Public Health 1977-90; associate director, Office of Science and Technology Policy, Executive Office of the President 1990-93. He has received a number of awards including: the Presidential Medal of Freedom, the National Medal of Science, the Japan Prize, and the Edward Jenner Medal of the Royal Society of Medicine.

**Ret. COL Charles H. Hoke, Jr., MD**

Dr. Hoke completed his bachelors degree at Stanford University and his medical degree at the University of Rochester School of Medicine and Dentistry. He served in the US Public Health Service and the US Army and, at retirement from the Army, was the director of the Military Infectious Diseases Research Program. He worked under contract with the Army from 2003 until 2012, during which time he completed training equivalent of Department of Defense Level III certification in Program Management. He has made substantial contributions to the study of Japanese encephalitis, hepatitis A, chikungunya, dengue, and adenovirus vaccines. He is licensed to practice medicine in Maryland.

**Ruth A. Karron, MD**

Dr. Karron is a professor in the department of international health and director of the Center for Immunization Research and of the Johns Hopkins Vaccine Initiative at the Johns Hopkins Bloomberg School of Public Health. Dr. Karron is a pediatrician, trained in infectious diseases, who has extensive experience in the evaluation of respiratory virus vaccines, including vaccines for respiratory syncytial virus (RSV), in adult and pediatric populations. Dr. Karron’s research interests also include the development of immune responses to respiratory viral infections in early life, the epidemiology of RSV and other respiratory viral diseases in resource-poor settings, and public policy issues related to vaccine development and distribution. She has served on a number of national and international vaccine advisory committees and panels, and chaired the FDA Vaccine and Related Biological Products Advisory Committee from 2006-08. She is currently a member of the CDC Advisory Committee on Immunization Practices.

**David C. Kaslow, MD**

Dr. Kaslow is a physician-scientist with over 25 years of vaccine research and development experience, encompassing the academic, governmental, private and, non-profit sectors. David joined the PATH Malaria Vaccine Initiative (MVI) as director in 2012. Prior to joining MVI, he was vice president and head of vaccines project leadership and management at Merck Research Laboratories, where his responsibilities included oversight of clinical biomarkers and project leadership and management of Merck Vaccine’s pipeline. David’s professional career also includes more than a decade with the National Institutes of Health (NIH) as a tenured scientist. While at NIH, he founded the Malaria Vaccine Development Unit. He received an MD from the School of Medicine at the University of California, San Francisco, and a BS in Biochemistry from the University of California, Davis.

**Stefan H.E. Kaufmann, PhD**

Dr. Kaufmann is the founding director and director of the Department of Immunology of the Max Planck Institute for Infection Biology in Berlin. He is also professor for microbiology and immunology, Charité, Humboldt University, Berlin, and honorary professor, Free University, Berlin.
Dr. Kaufmann also serves as a guest professor, Tongji University, School of Medicine, Shanghai, China and honorary professor, Universidad Peruana Cayetano Heredia, Lima, Peru. He has a Doctor Honoris Causa from Université de la Méditerranée, Aix-Marseille II.

He is a past-president and honorary member of the German Society for Immunology, past-president of the European Federation of Immunological Societies. He is currently the president of the International Union of Immunological Societies.

Dr. Kaufmann studied biology at the Johannes Gutenberg University of Mainz, and received his PhD in 1977. From 1987-91, he was a professor for medical microbiology and immunology, and from 1991-98 a full professor for immunology at the University of Ulm. His scientific interests include: immunity to bacterial pathogens with emphasis on tuberculosis and rational vaccine design. He is a co-developer of a recombinant BCG-vaccine candidate which is in a phase II-clinical trial. He is also a representative of research and technological health institutes as Alternate Board Member of the Global Alliance for Vaccines and Immunisation. Dr. Kaufmann initiated the Day of Immunology to raise public awareness in immunology.

Dr. Kaufmann is the recipient of numerous scientific awards. He is the coordinator of several international and interdisciplinary projects and the author of more than 600 publications, mostly in high-ranking journals. He is also a highly cited immunologist (ISI Thomson). H-Index (according to J. E. Hirsch): 84. He is the editor or member of editorial boards of more than 20 international scientific journals and is a member of numerous professional societies and academies: including American Academy of Microbiology, Berlin-Brandenburg Academy of Sciences, German Academy of Natural Sciences ‘Leopoldina’, World Innovation Foundation, and European Molecular Biology Organization.

Sabra L. Klein, PhD
Dr. Klein received her BA in psychology from Randolph-Macon College, her MS from the University of Georgia in biological psychology, and her PhD in behavioral neuroscience from Johns Hopkins University. She did postdoctoral training at the Johns Hopkins Bloomberg School of Public Health in molecular microbiology and immunology where she is now an assistant professor. Dr. Klein is a leading expert on sex differences in infectious diseases and currently has over 80 peer-reviewed publications in journals including Lancet Infectious Diseases, Nature Medicine, Proceedings of the National Academy of Sciences, Vaccine, and PLoS Pathogens. She has authored several book chapters and edited a book entitled Sex Hormones and Immunity to Infection. Her research has been highlighted in Commentaries appearing in PNAS and U.S. News and World Reports. She has provided commentary on issues regarding sex differences in response to infection and vaccination for the New York Times, Wall Street Journal, and Fox 45 News in Baltimore, among many other media outlets. Dr. Klein’s research examines the impact of hormones on immune responses to viruses. Working with influenza viruses, her research indicates that females typically mount more robust immune responses than males, which can be beneficial for clearance of viruses, but also can be detrimental by causing immune-mediated pathology. She has further demonstrated that females mount higher adaptive immune responses following vaccination against influenza, which leads to greater cross-protection in females than males. Her research has been supported by grants from the National Institute of Allergy and Infectious Diseases, the National Science Foundation, and the National Foundation for Infectious Diseases. In 2010, she won the Society for Women’s Health Research Medtronic Award for Science Contributions.

Kirsten E. Lyke, MD
Dr. Lyke is an associate professor of medicine in the Division of Geographic Medicine and joined the Center for Vaccine Development (CVD) at the University of Maryland School of Medicine, Baltimore (UMB) in 2002. Dr. Lyke earned her MD at Georgetown University in 1992 and completed a residency in internal medicine at Duke University in 1995. She completed her infectious diseases fellowship training at The Johns Hopkins University of Medicine and is board certified in infectious diseases.
Dr. Lyke is a clinical translational investigator with recognized expertise in malaria, tropical diseases, and parasite immunology. In collaboration with colleagues at the University of Bamako in Mali, Dr. Lyke has aided in the development of a field research site in the Dogon country of Mali, West Africa. In addition, she conducted the training and transfer of technology for humoral and cellular immunology assays and operated the day-to-day trial activities for the project. This field station has been the site of studies of drug resistance and pathogenesis of severe malaria and malaria vaccine trials. Of special interest is the helminth-malaria interaction model for the immunomodulatory effects of *Schistosoma haematobium* and *Plasmodium falciparum*, which Dr. Lyke has studied for many years.

In addition to field work in Mali, West Africa, she has rebuilt the malaria challenge capabilities at UMB CVD. This capacity has led to novel vaccine work including leading the first-in-humans challenge trial of a whole-organism malaria vaccine and the first-in-humans aseptic malaria challenge. She has planned and led innovative studies aimed at developing parenterally-administered malaria challenges and simultaneously leads a busy immunology laboratory as the head of the UMB Immunoparasitology Unit. She continues clinical duties for the University of Maryland Medical Center and attends on the wards and in an HIV clinic.

**Philip D. Minor, PhD**

Dr. Minor is the deputy director of the National Institute for Biological Standards and Control. He earned his BA in biochemistry from Oxford University in 1970 and his PhD in 1973. After completing his postdoctoral work in 1979 at the University of Warwick, he joined NIBSC as a tenured scientist until 1985. While a tenured scientist, he worked on poiovirus virulence, attenuation, epidemiology, antigenic structure and receptor sites. He became the head of the Division of Virology in 1985 (and still remains the head). He is the author or co-author of over 250 publications.

**Walter A. Orenstein, MD**

Dr. Orenstein is associate director of the Emory Vaccine Center and director of the Influenza Pathogenesis and Immunology Research Center at Emory University, since October 2011.

From 2008 through 2011, Dr. Orenstein was deputy director for immunization programs in the Vaccine Delivery Department of the Global Health Program at the Bill & Melinda Gates Foundation. His primary focus at the foundation had been on polio eradication, measles control, and improving routine immunization programs.

Between 2004 and 2008, he was a professor of medicine and pediatrics at Emory University, associate director of the Emory Vaccine Center and director of the Emory Program on Vaccine Policy and Development among other responsibilities. Prior to 2004, he served as Assistant Surgeon General of the United States Public Health Service and Director of the National Immunization Program at the Centers for Disease Control and Prevention, where Dr. Orenstein successfully developed, promoted, facilitated, and expanded new vaccination strategies to enhance disease prevention.

Dr. Orenstein has authored and co-authored numerous books, journals, and reviews. Along with Stanley Plotkin, MD and Paul Offit, MD, Dr. Orenstein co-edited *Vaccines*, 5th edition in 2008—the leading textbook in the field. He is a fellow of the American Academy of Pediatrics, the Infectious Diseases Society of America, and the Pediatric Infectious Diseases Society. In 2006, he was elected to the Institute of Medicine. He is a past-Chair of the WHO’s Poliomyelitis Technical Consultative Group, Chair of the National Vaccine Advisory Committee, and currently serves as NFID Vice President. Dr. Orenstein received his BS at The City College of New York and his medical degree from the Albert Einstein College of Medicine in 1972. In 2006, he received an honorary Doctor of Science degree from Wake Forest University.

**Peter Palese, PhD**

Dr. Palese is a professor of microbiology and the chair of the department of microbiology at the Icahn School of Medicine at Mount Sinai. His research is in the area of RNA-containing viruses with a special emphasis on influenza viruses. Specifically, he established the first genetic maps for influenza A, B, and C viruses, identified the function of several viral genes, and defined the mechanism of neuraminidase inhibitors (which are now FDA-approved antivirals). He was also a pioneer in the field of reverse genetics for negative strand RNA viruses,
which allows the introduction of site-specific mutations into the genomes of these viruses. This technique is crucial for the study of the structure/function relationships of viral genes, for investigation of viral pathogenicity, and for development and manufacture of novel vaccines. An improvement of this technique has been effectively used by him and his colleagues to reconstruct and study the pathogenicity of the highly virulent, but extinct, 1918 pandemic influenza virus. His recent work in collaboration with Garcia-Sastre has revealed that most negative strand RNA viruses possess proteins with interferon antagonist activity. Dr. Palese has been a member of the National Academy of Sciences since 2000. At present he serves on the editorial board for the Proceedings of the National Academy of Sciences. Dr. Palese was president of the Harvey Society in 2004, president of the American Society for Virology in 2005, a recipient of the Robert Koch Prize in 2006, and the recipient of the European Virology Award (EVA) in 2010. In 2012 he was awarded the 2012 Sanofi-Institut Pasteur Award and he was elected to the Institute of Medicine.

Mark H. Sawyer, MD
Dr. Sawyer is a professor of clinical pediatrics and a pediatric infectious disease specialist at the University of California, San Diego School of Medicine and Rady Children’s Hospital San Diego. Dr. Sawyer is active in several groups involved in developing vaccine policy and is the current chair of the California Immunization Committee, an advisory committee to the California State Immunization Branch, and a member of the CDC’s Advisory Committee on Immunization Practices. Dr. Sawyer is also a fellow of the American Academy of Pediatrics and Vice President of AAP Chapter 3, District IX. He belongs to numerous professional societies including the Society of Pediatric Research, the Infectious Diseases Society of America, and the Pediatric Infectious Diseases Society.

He is the medical director of the UCSD San Diego Immunization Partnership, a contract with the San Diego County Agency for Health and Human Services to improve immunization delivery in San Diego. The San Diego Immunization Partnership involves work in all areas of immunization delivery including support of the San Diego Immunization Registry, quality improvement activities in both public and private clinics in San Diego, education of primary care residents about immunization delivery, adult immunization initiatives, and community outreach.

John T. Schiller, PhD
Dr. Schiller received his BS in molecular biology from the University of Wisconsin, Madison in 1975, and his MS and PhD degrees in microbiology from the University of Washington, Seattle, in 1978, and 1982, respectively. He is currently the chief of the neoplastic disease section of the Laboratory of Cellular Oncology, Center for Cancer Research, National Cancer Institute (NCI), Bethesda, MD. Prior to becoming a senior investigator in the NCI intramural program, he was a postdoctoral fellow, under the direction of Dr. Douglas Lowy, and then a senior staff fellow in the same laboratory.

In his 30 years at the NCI, Dr. Schiller has studied various aspects of papillomavirus molecular biology, immunology, and epidemiology. The laboratory headed by Dr. Schiller and Dr. Lowy led in the initial discovery, development, and clinical testing of virus-like particle (VLP) vaccines to prevent the HPV infections that cause cervical cancer. His current interests include basic studies of papillomavirus virion assembly and infection, the development of 2nd generation HPV vaccines, and the generation of virus-like display and HPV pseudovirus-based vaccines for other antigens.

Mark C. Steinhoff, MD
Dr. Steinhoff is a pediatrician with infectious disease sub-specialty training. He received his BA and MD from the University of Chicago. He was a pediatric resident, chief resident, and pediatric infectious diseases fellow at University of Rochester, New York. He served on the faculty of the Department of Child Health, CMC Hospital, Vellore, India from 1980-85. He has held faculty positions in the Departments of Public Health and Pediatrics at the University of Michigan, and since 1986 has been at the School of Medicine, and the Bloomberg School of Public Health at Johns Hopkins University in Baltimore. He is currently Professor of Pediatrics and Director of the Children’s Global Health Center at Cincinnati Children’s Hospital in Ohio.
He has carried out research projects in a variety of regions including South and East Asia, Africa, South America, and Europe. He has authored over 170 peer-reviewed research papers and over 20 textbook chapters in pediatric and tropical medicine textbooks. His major research interest is in assessing the burden of preventable infectious diseases, and the effectiveness of vaccines in low resource settings. He has served as a consultant to CDC, NIH, FDA, WHO, the Rockefeller Foundation, the Ford Foundation, and as an advisor to the Bill and Melinda Gates Foundation. With colleagues he is currently conducting a large antenatal influenza vaccine trial in Nepal, with Gates Foundation support, and a post-partum influenza vaccine trial in the United States with NIH funding.

Amy L. Vincent, DVM, PhD
Dr. Vincent obtained a BS in recombinant genetics from Western Kentucky University in Bowling Green and an MS in genetics, a DVM, and a PhD in immunobiology from Iowa State University in Ames. Dr. Vincent has 20 years of experience in swine production and animal health research and is currently a research veterinary medical officer at the USDA-ARS National Animal Disease Center (NADC). The primary focus of her work is influenza A virus (IAV), but the project’s objectives include IAV, porcine respiratory and reproductive syndrome virus, porcine circovirus type 2, and other emerging or reemerging viral pathogens of swine. IAV represents a unique agent that is a pathogen to both pigs and humans and the NADC studies focus on the virus in the natural swine host. Three areas of swine influenza research involve investigating virulence properties, characterization of currently circulating and emerging IAV in swine, and developing novel vaccine approaches. Recent efforts focused on the 2009 pandemic H1N1 and H3N2v-like viruses in swine. Dr. Vincent was the recipient of the Pfizer Animal Health Ten Under 40 Swine Veterinarians Award in 2011; the American Association of Swine Veterinarians Howard Dunne Memorial Award in 2011; a USDA ARS Midwest Area Early Career Scientist Award in 2010; a USDA Secretary’s Award in 2010; and a USDA ARS Special Administrator’s Award in 2010.

W. Ray Waters, DVM, PhD
Dr. Waters received a BS in Biological Sciences and DVM from Auburn University, Auburn, AL in 1985 and 1988, respectively, and a PhD in immunobiology from Iowa State University, Ames, IA in 1996. Currently, he is a veterinary medical officer with the Tuberculosis Research Project at the National Animal Disease Center (NADC), Agricultural Research Service, Ames, IA and collaborator/assistant professor with the veterinary microbiology and preventive medicine department at Iowa State University. Past work experience includes five years of small animal veterinary practice; research associate at the NADC; microbiologist at Plum Island Animal Disease Center, Greenport, NY; and associate scientist at Iowa State University. The current focus of Dr. Waters’ research is: (1) evaluation of the immune response of cattle and various wildlife hosts to Mycobacterium bovis infection, (2) discovery and development of vaccines for the control of tuberculosis in cattle and white-tailed deer, and (3) development of improved ante-mortem diagnostic assays for the detection of tuberculosis infected animals. Dr. Waters has authored or co-authored more than 150 research papers and book chapters on veterinary immunology and tuberculosis research topics, is an editor for Clinical and Vaccine Immunology, and a member of several professional societies.

David E. Wentworth, PhD
Dr. Wentworth is the director of viral programs at the J. Craig Venter Institute. The goals of his team’s research are to understand viral evolution (particularly adaptation of viruses to a new host), to identify molecular determinants that affect the transmission or pathogenesis of the virus, and to use this information to create/develop vaccines and/or antivirals. His previous studies have focused on the transmission of swine viruses to humans, highly pathogenic H5 influenza viruses, coronavirus-host interactions, and emergence of new human pathogens (e.g., H1N1 pandemic, and SARS-CoV). His team continues to study mechanisms of pathogenesis and evolution of influenza A viruses, and coronaviruses such as SARS-CoV, and they are creating and analyzing novel vaccines against influenza A viruses. Dr. Wentworth received his doctorate in virology studying influenza at the University of Wisconsin-
Madison. He studied coronaviruses as a postdoctoral fellow, and later as an instructor at the University of Colorado Health Sciences Center in Denver. He was the director of the Influenza Virus and Coronavirus Pathogenesis laboratory at the Wadsworth Center, NYSDOH, and an assistant professor at the State University of New York-Albany prior to joining JCVI. Dr. Wentworth has also taught virology and microbiology to undergraduate, graduate, veterinary, and medical students.
ABSTRACTS OF INVITED PRESENTATIONS
Eradication of Disease through Vaccination: The 35th Anniversary of the Last Case of Smallpox
D.A. Henderson, MD, MPH
Johns Hopkins Bloomberg School of Public Health
Center for Biosecurity of University of Pittsburgh Medical Center
Baltimore, MD

Objective: Understand the factors that were responsible for the eradication of smallpox and the relevance of the most salient, current, and contemplated initiatives for the eradication of other infectious diseases.

Abstract: In January 1967, the World Health Organization (WHO) with its member countries commenced a 10 year program of global smallpox eradication intended to interrupt transmission of the virus by December 31, 1976. It missed that target, but only by 10 months and 26 days. However, a year later, two additional cases occurred, in September 1978, in Birmingham, England, as a result of a laboratory mishap. No other cases have subsequently been identified. Thus, this year, the world celebrates the 35th year without a smallpox case. The program of smallpox eradication was launched under less than auspicious conditions. WHO’s only eradication program-for malaria-was in its 13th year but it was foundering. A proposal to undertake smallpox eradication was opposed by many delegates and by the Director General on the grounds that the concept of disease eradication was not tenable and the costs were too great. Some five years later, malaria eradication was dropped as a goal.

Meanwhile, as smallpox eradication was being certified, many former smallpox staff, both national and international, began or joined national “Expanded Programs of Immunization” which had been launched during the course of the smallpox eradication program. The vaccines initially included measles and polio, along with DTP (diphtheria, tetanus, pertussis). Gradually, other vaccines were selectively added; in some countries numbering ten or more. Meanwhile, a belief in eradication as a feasible public health program objective lay dormant for nearly a decade until, in 1986, WHO embarked upon a Guinea worm disease eradication program and, in 1988, a polio eradication program. They were targeted to accomplish their objectives by 2000. Both have made extraordinary progress but both are struggling with endemic foci in areas locked in civil conflict. Efforts to launch a global measles eradication effort have been endorsed and successful in two WHO regions but have yet to be accepted elsewhere, including Europe. Meanwhile, eradication enthusiasts with a special interest in a particular disease have been emerging with increasing frequency. Individual programs are now identified that are intended to eradicate trachoma, leprosy, lymphatic filariasis, and sleeping sickness (African trypanosomiasis). Several of these, in theory, could perhaps be eradicated, as could measles, but there is a substantial gap between theories of the possible and the practical realities of execution, as those engaged in the polio and Guinea worm eradication programs will testify. The virtues of launching a special eradication campaign, with the attendant publicity and pleas for funds, need to be weighed against possible repercussions of credibility and disillusionment associated with failure – as malarialogists will agree.

References:
Measles and Rubella—Will They Ever be Eradicated?

Walter A. Orenstein, MD
Emory Vaccine Center
Emory University
Atlanta, GA

Objective: Evaluate the biologic feasibility of measles and rubella eradication by reviewing current elimination and control of these diseases and identify the major barriers to achieving eradication.

Abstract: Measles and rubella cause substantial morbidity and mortality in the world. Measles was estimated to kill 158,000 people (more than 400 per day) in 2011, a 71% decrease from 2000 estimates but still a substantial killer, and in 2010, more than 100,000 children were born with congenital rubella syndrome (CRS).

Both measles and rubella meet biologic criteria for eradication feasibility. Both measles and rubella require human-to-human transmission to be sustained. There is no non-human or environmental reservoir. There are effective tools for diagnosis and highly effective interventions. Proof of principle for eradication has been provided by the successful elimination of indigenous measles and rubella in the Region of the Americas. At the moment there is no global goal for eradication of either disease although the Global Vaccine Action Plan (GVAP) endorsed by the World Health Assembly, calls for elimination of measles and rubella in five of the six World Health Organization (WHO) regions by 2020. If successful, these efforts would provide the foundation for eradication. The Strategic Advisory Group of Experts (SAGE) of the WHO has urged the single region without a measles elimination goal, Southeast Asia, to establish one, and for the four regions without a rubella elimination goal, to also develop such goals.

Nevertheless, substantial obstacles remain to eradication. Chief among them is the need for political will and champions. It will be difficult to embark on a new eradication effort as long as polio eradication is not accomplished. In contrast to other diseases targeted for eradication, vaccine hesitancy in industrialized countries is a barrier to overcome. As measles and rubella are endemic in Europe, political will and support will likely be more forthcoming with greater emphasis on how eradication efforts will strengthen routine health systems. Although current tools are adequate, a robust research program can help develop better tools for vaccine delivery and diagnostics. Measles and rubella can and should be eradicated. With time it is likely many of the barriers can be eliminated. But eradication is not likely to take place anytime soon.

References:
Polio Eradication
Philip D. Minor, PhD
National Institute for Biological Standards and Control
Hertfordshire, UK

Objective: Review the polio eradication program short- and long-term challenges and possible solutions. 
Abstract: Poliovirus is an enteric virus most commonly transmitted by the fecal oral route. Only a small percentage of infections lead to disease following spread of the virus from the gut to the central nervous system via the blood stream; this is the accepted explanation for the emergence of poliomyelitis in annual epidemics in the early twentieth century as hygiene improved and infants were exposed to the virus after maternal antibodies had declined. As most infections are silent, quarantine or ring vaccination are ineffective; moreover there are many examples of reintroduction of the virus from endemic countries to polio free countries and if one country still has circulating virus the world is at risk. In 1988 the governing body of the World Health Organization adopted a resolution to eradicate polio and the main strategy involved use of the live Oral Polio vaccines developed by Sabin in the late 1950s delivered through mass campaigns in order to interrupt virus transmission. The challenges of this program are logistics, sociological, political, and virological. The oral vaccine infects the recipient and the virus changes rapidly and freely. This can lead to a generation of viruses able to spread from person-to-person and the occurrence of epidemics caused by vaccine derived viruses. Thus, the inactivated vaccines developed by Salk are becoming more important as eradication approaches although they pose their own hazards. Currently there are only three countries that have never interrupted poliovirus transmission and the number of cases is at an all-time low. Eradication seems possible although assurance will be difficult.

References:

Development of Vaccines toward the Global Control and Eradication of Foot-and-Mouth Disease
Cyril G. Gay, DVM, PhD
Agricultural Research Service
US Department of Agriculture
Beltsville, MD

Objective: Explain the molecular, biological, and clinical characteristics and ideal vaccine profile for controlling and eradicating foot-and-mouth disease.

Abstract: Foot-and-mouth disease (FMD) is one of the most economically and socially devastating diseases affecting animal agriculture throughout the world. Although mortality is usually low in adult animals, millions of animals have been killed in efforts to rapidly control and eradicate it. The causing virus, FMD virus (FMDV), is a highly variable RNA virus occurring in seven serotypes (A, O, C, Asia 1, Sat 1, Sat 2, and Sat 3) and a large number of subtypes. FMDV is one of the most infectious agents known, affecting cloven-hoofed animals with significant variations in infectivity and virus transmission. Although inactivated FMD vaccines have been available for decades, there is little or no cross-protection across serotypes and subtypes, requiring vaccines that are matched
to circulating field strains. Current inactivated vaccines require growth of virulent virus, posing a threat of escape from manufacturing sites; have limited shelf life; and require re-vaccination every 4-12 months. These vaccines have aided in the eradication of FMD from Europe and the control of clinical disease in many parts of the world, albeit at a very high cost. However, FMDV persists in endemic regions impacting millions of people dependent on livestock for food and their livelihood. Usually associated with developing countries that lack the resources to control it, FMD is a global problem and the World Organization for Animal Health (OIE) and the United Nations’ Food Agriculture Organization (FAO) have called for its global control and eradication.

One of the main limitations to FMDV eradication is the lack of vaccines designed for this purpose; vaccines that not only protect against clinical signs but that can actually prevent infection and effectively interrupt the natural transmission cycle. These vaccines should be safely and inexpensively produced, easy to deliver, and be capable of inducing lifelong immunity against multiple serotypes and subtypes. Furthermore, there is a need for better integrated strategies that fit the specific needs of endemic regions. Availability of these critical components will greatly enhance the chances for the global control and eradication of FMDV.

References:

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RTS,S
Pedro L. Alonso, PhD
Barcelona Centre for International Health Research
Barcelona, Spain

Objectives: Understand the particularities and challenges of malaria vaccine clinical development. Understand the rationale for the principal antigen targets chosen for malaria vaccine development and the potential effects on malaria infection/disease/transmission that such vaccines may confer. Obtain an adequate knowledge of current development of the most advanced malaria candidate vaccine RTS,S.

Abstract: With no vaccine against any parasitic disease developed to date, a vaccine against malaria is among the most urgent needs of public health. In 2010 alone, an estimated 219 million malaria cases resulted in some 660,000 deaths from a disease which is particularly deadly in children and pregnant women. Even if it had only a partial efficacy, a malaria vaccine deployed in the highest endemic areas would therefore mean thousands of lives saved each year.

Why has such a crucial tool taken so long to be properly developed? Malaria vaccines represent an extraordinary scientific challenge. The Plasmodia parasites have a myriad of antigens that vary across its different life cycle stages, and in addition to this, parasites present a high protein polymorphism. Our knowledge of malaria immunological particularities is still incomplete: there is no correlate between clinical immunity and immune response, there is uncertainty about the relative importance of key antigens, the relevant factors (both natural and induced), that trigger and maintain immunity over time are incompletely understood, and there is no animal model suitable for malaria vaccine experimental purposes.
Despite all these difficulties, there is enough argument to sustain that an effective malaria vaccine is attainable.

1. Individuals living in endemic areas progressively develop a partial immunity against malaria, consisting in a protection against the most severe forms of the disease and the eventual suppression of parasitaemia, although they can still be infected, even if they do not develop any clinical symptoms.

2. There is evidence of a potential passive immunity derived both from the protective effect observed after the administration of immunoglobulin from immune patients and in the fact that newborn from endemic areas seem to be protected against clinical forms of malaria.

3. Studies during the seventies showed protection following the inoculation of sporozoites attenuated by radiation, showing the feasibility of induced immunity, although also posing important practical challenges for administration. The most advanced vaccine candidate is the RTS,S, currently undergoing a Phase III clinical study in Africa. This pre-erythrocytic vaccine is based in the fusion of the circumsporozoite antigen with a Hepatitis B antigen added to the adjuvant AS02A. Final results are expected in 2014, and an official recommendation by WHO will be issued in 2015. Critical for such a recommendation will be not only the effectiveness of the vaccine in different groups of age, but also the duration of protection.

References:

The Whole Organism, *P. falciparum* Sporozoite, Vaccine Approach

Kirsten E. Lyke, MD
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Baltimore, MD

**Objective:** Understand the worldwide impact of malaria in 2013 and review the role of whole organism *P. falciparum* Sporozoite (PfSPZ) vaccines.

**Abstract:** After 30 years in the pursuit of a sub-unit *P. falciparum* malaria vaccine, a licensed product has yet to reach the market. Radiation-attenuated, whole Pf sporozoites (PfSPZ) administered by mosquito bites, historically, were the only immunogens shown to induce protection in humans\(^1,2\). Attenuation of the PfSPZ is necessary to abrogate blood stage infection. Inoculated sporozoites elicit an asymptomatic infection of hepatocytes with protective immunity dependent upon CD8\(^+\) T-cell-mediated production of IFN-γ, in mice,\(^3,4\) non-human primates,\(^5\) and humans.\(^6\) Practical limitations have prevented the development of vaccines composed of whole PfSPZ. However, recent technology has allowed for the first vaccine testing in humans of radiation-attenuated PfSPZ.\(^6\) Efforts to create genetically-attenuated PfSPZ are ongoing. New strategies that rely upon ultra-low-dose blood stage exposure to PfSPZ, by the bite of mosquito, while under anti-malarial prophylaxis therapy, have induced long-term protection against controlled human malaria infections (CHMI).\(^7,8\) Testing to refine dosing strategies, inoculation methodology, and vaccine efficacy is underway. The whole organism PfSPZ approach may offer a promising alternative to the sub-unit vaccine approach in the creation of an effective *P. falciparum* malaria vaccine.

References:
ABSTRACTS OF INVITED PRESENTATIONS

References:

Decade of Vaccines
Jon S. Abramson, MD
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Winston-Salem, NC

Objective: Discuss the goals of the Decade of Vaccines (DOV) and how the Global Vaccine Action Plan (GVAP) will be used to achieve these goals.

Abstract: In 2010, the Gates Foundation declared the next ten years to be the DOV (2011-20). Over the next two years, the GVAP was conceptualized using a consultative process involving various stakeholder groups including, national governments, multilateral organizations, civil society, the private sector, and philanthropic organizations. This process identified critical policies, resources, and other gaps that needed to be addressed to realize the life-saving potential of vaccines.

The major goals of the (DOV) are to:
1. Achieve a world free of poliomyelitis.
2. Meet global and regional elimination targets.
3. Meet vaccination coverage targets in every region, country and community.
4. Develop and introduce new and improved vaccines and technologies.
5. Exceed the Millennium Development Goal 4 target for reducing child mortality.

The GVAP six strategic objectives to enable the achievement of the goals of the DOV:
1. All countries commit to immunization as a priority.
2. Individuals and communities understand the value of vaccines and demand immunization as both their right and responsibility.
3. The benefits of immunization are equitably extended to all people.
4. Strong immunization systems are an integral part of a well-functioning health system.
5. Immunization programs have sustainable access to predictable funding, quality supply and innovative technologies.
6. Country, regional, and global research and development innovations maximize the benefits of immunization.

If these immunization-specific goals are achieved, hundreds of millions of cases and millions of deaths will be averted by the end of the decade and immunization will contribute to exceeding the Millennium Development Goal 4 target of reducing by two-thirds mortality in children less than 5 years of age.

References:

Maternal Immunizations: An Overview
Carol J. Baker, MD
Baylor College of Medicine
Houston, TX

Objectives: Understand the disease burden of influenza and pertussis and the safety and efficacy of these vaccines to prevent these infections in pregnant women and young infants. Implement the current guidelines for use of influenza and tetanus and diphtheria toxoid, acellular pertussis (Tdap) vaccines during pregnancy.

Abstract: It is well documented that pregnant women have excessive mortality and morbidity from seasonal and pandemic influenza. During the 2009-10 H1N1 pandemic, pregnant women accounted for 5% of all US deaths while only representing 1% of the population. Infants less than 6 months of age, for whom no vaccine is licensed or recommended, have the highest influenza hospitalization rate and account for the majority of deaths under 1 year of age.

Infants are dependent on maternal vaccination to acquire influenza-specific IgG passively or to surround them with fully immunized children and adults (cocoon strategy) for protection. Despite a 1996 recommendation for vaccination during pregnancy, uptake in pregnant women during the 2011-12 influenza season was only 47%. During the past decade overwhelming evidence indicates not only of the safety and effectiveness of maternal influenza vaccination in preventing influenza complications in women and their young infants, but also of the harm of withholding immunization. Maternal immunization reduces the risk for fetal death and growth restriction, preterm delivery, and laboratory-confirmed influenza hospitalization in infants <6 month. Pertussis is the most poorly controlled vaccine-preventable disease in the US. Epidemics in California in 2010, Washington in 2011, and nationwide in 2012, led to reported case numbers approaching pre-vaccine levels in the 1950’s.
Infant protection is not achieved until completion of the 3-dose series at age 6 months. Ninety percent of pertussis-related mortality occurs in infants <3 months of age. Maternal immunization, to prevent young infants from pertussis, was recommended by the ACIP, AAFP, and ACOG in 2011. This recommendation, plus immunization of all infant contacts with tetanus and diphtheria toxoid/acellular pertussis (Tdap) vaccine, was based on ongoing burden of young infant mortality and morbidity, poor implementation of cocooning of young infants with Tdap immunized contacts, low uptake of Tdap vaccine by adults (<10% in 2010), and cost-effectiveness of maternal immunization versus cocooning. In 2012, the recommendation for maternal immunization with Tdap vaccine was modified to include every pregnancy in response to data that Tdap-induced antibody levels rapidly decayed.

By contrast to influenza, further studies are needed to document the safety of the recommendation in women, to improve the effectiveness of the aP component in the Tdap vaccine or provide a highly immunogenic aP vaccine for this indication, and ongoing surveillance to determine effectiveness of this prevention strategy for young infants as well as their pregnant mothers. The current ACIP/AAFP/ACOG recommendations are that healthcare professionals provide inactivated influenza vaccine to women who will be pregnant during influenza season (any trimester) and that pregnant women receive Tdap vaccine early in the third trimester of each pregnancy disregarding the interval between the last tetanus-containing vaccine. As these recommendations represent the “standard of care” for pregnant women, high vaccine uptake is imperative.

References:
Overall, the incidence of pertussis has increased in the last decade in all age groups and infant deaths from pertussis in the United States more than doubled in 2000-09 compared to the previous decade. This has prompted changes in pertussis immunization recommendations that include modification of the interval between a previous tetanus-diphtheria (Td) vaccine and subsequent Tdap vaccine, expansion of the use of Tdap vaccine to pregnant women, including a new recommendation for immunization during each pregnancy, and a recommendation that all adults, including adults 65 years of age and older, should be immunized with Tdap vaccine. Unfortunately, evidence is accumulating that immunity from pertussis vaccine wanes within a few years following vaccination. Immunity following five doses of DTaP in young children wanes steadily and by 5 years after vaccination may be as low as 69%.

References:
Group B Streptococcal Vaccine Developments
Morven S. Edwards, MD
Baylor College of Medicine
Houston, TX

Objectives: Describe the need for a group B streptococcal (GBS) vaccine based upon the current GBS disease burden in the US and globally. Understand the rationale for potential GBS glycoconjugate vaccine constructs. Discuss the evidence base supporting the potential efficacy of a GBS conjugate vaccine.

Abstract: Group B Streptococcus is a leading cause of bacteremia and meningitis in young infants and an increasingly recognized cause of invasive infection in adults, especially those with predisposing medical conditions. The range in reported incidence of group B streptococcal infection varies globally and additional high-quality information is needed to attain a more accurate estimate the burden of disease, especially in low-income countries. Based upon the distribution of capsular polysaccharide types causing invasive disease, a glycoprotein conjugate vaccine containing the five major group B streptococcal types, Ia, Ib, II, III, and V, could prevent most global disease in infants and adults.

Other important vaccine design issues include a consideration of the capacity for capsule switching among group B streptococci and the potential to incorporate surface proteins, such as the group B streptococcal pilus-like structures, as vaccine components. Considerable experience in phase I and II testing of group B streptococcal polysaccharide-protein conjugates has demonstrated that these vaccines are well-tolerated and immunogenic. Immunization during the third trimester of pregnancy induces group B streptococcal-specific IgG in concentrations sufficient, in concept, to protect infants against invasive early-onset or late-onset invasive infection. The commitment by industry to develop and test multivalent glycoconjugate group B streptococcal vaccines holds great promise for disease prevention in young infants and their mothers and in adults.

References:
LAIV Provides Protection from Heterologous Influenza A Virus without Inducing Vaccine-Associated Enhanced Respiratory Disease
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Agricultural Research Service
US Department of Agriculture
Ames, IA

Objectives: Review the phenomenon of vaccine-associated enhanced respiratory disease (VAERD) described in swine to identify consistent predisposing factors associated with the disease. Describe the consistent pathologic features and immune response associated with VAERD in pigs following IAV challenge to identify possible similarities to other IAV hosts. Compare WIV to LAIV in naïve and pigs with passively acquired immunity for efficacy against heterologous IAV challenge to understand the impact of prior immune status on vaccination.

Abstract: Control of swine influenza A virus (IAV) in the US is hindered since inactivated vaccines do not provide robust cross-protection against the multiple antigenic variants co-circulating in the field. Vaccine efficacy can be further limited when administered to young pigs that possess maternally derived immunity. We previously demonstrated that a recombinant A/sw/Texas/4199-2/1998 (TX98) (H3N2) expressing a truncated NS1 protein is attenuated in swine and has potential for use as an intranasal live attenuated influenza virus (LAIV) vaccine. In the present study, we compared one dose of intranasal LAIV with two intramuscular doses of TX98 whole inactivated virus (WIV) with adjuvant in weanling pigs with and without TX98-specific maternally-derived antibodies (MDA). Pigs were subsequently challenged with wild type homologous TX98 H3N2 virus or with an antigenic variant A/sw/Colorado/23619/1999 (CO99) (H3N2). In the absence of MDA, both vaccines protected against homologous TX98 and heterologous CO99 shedding, although the LAIV elicited lower hemagglutination inhibiting (HI) antibody titers in serum. The efficacy of both vaccines was reduced by the presence of MDA; however, WIV vaccination of MDA-positive pigs led to dramatically enhanced pneumonia following heterologous challenge, a phenomenon known as vaccine-associated enhanced respiratory disease (VAERD). A single-dose of LAIV to MDA-positive pigs still provided partial protection from CO99 and may be a safer vaccine for young pigs in field conditions where dams are routinely vaccinated and diverse IAV strains are in circulation. These results have implications not only to pigs but to other influenza virus host species.

References:
Vaccines for Respiratory Syncytial Virus
Ruth A. Karron, MD
Johns Hopkins Bloomberg School of Public Health
Baltimore, MD

Objective: Describe the types of RSV vaccines currently in development, their utility in various target populations, and obstacles to vaccine development.

Abstract: Respiratory syncytial virus (RSV) is the most important cause of viral acute lower respiratory tract illness (ALRI) in infants and children worldwide, and it is also a significant respiratory pathogen in immunocompromised patients and the elderly.

Although the significance of RSV as a respiratory pathogen has been recognized for over 50 years, several obstacles have hindered vaccine development, including the need to immunize in early infancy, the need to develop vaccines to protect diverse populations, and the need to avoid vaccine-mediated enhanced disease, which occurred when RSV-naïve children were naturally infected with RSV after having received a formalin-inactivated RSV vaccine.

In recent years, appreciation of the global importance of RSV has led to the development of new RSV vaccine candidates and new immunization strategies to protect vulnerable populations. This presentation will consider several different types of RSV vaccines in development, including: 1) RSV fusion (F) glycoprotein subunit vaccine candidates to be used for induction of passive and active immunity; 2) live recombinant RSV vaccine candidates containing combinations of known attenuating mutations; and 3) live recombinant RSV vaccine candidates that express RSV surface glycoprotein(s) in replication-competent paramyxovirus vectors or replication-defective vectors. The relevant populations and strengths and limitations of each approach will be discussed.

References:
Objective: Review the Department of Defense's (DoD) development, use, and loss of adenovirus vaccine, followed by reemergence of adenovirus disease and successful development and deployment of a new adenovirus vaccine.

Abstract: Homogenous in age, housed in close quarters, and undergoing stressful training, military basic trainees are at uniquely high risk of morbidity and mortality due to respiratory pathogens. Careful studies of etiology and methodical development of influenza, meningococcal, and adenovirus vaccines reduced illness rates to low levels.

Adenovirus vaccine had been manufactured by a sole manufacturer for 20 years, and facilities required updating. Despite requests from the manufacturer for support in modernizing these facilities, Department of Defense (DoD), perhaps complacent due to low rates of febrile respiratory illness, did not act. In 1994, the sole vaccine manufacturer stopped production, and the DoD’s consumed remaining stocks by 1999. Adenovirus serotype 4-associated febrile respiratory illness returned to basic training populations.

To address the situation, DoD commissioned the Institute of Medicine to convene a committee on Military Vaccines. This committee, along with the Armed Forces Epidemiological Board, urged the DoD to restore the adenovirus vaccine. The Deputy Chief of Staff of the Army defined the required performance of a new vaccine and assigned responsibility to the Army Medical Research and Materiel Command. The Surgeon General of the Army, and the Assistant Secretary of Defense for Health Affairs provided funding.

Simultaneously, the DoD’s system for acquiring goods was revised and updated, mandating, among other things, the use of Integrated Product Teams and executive oversight of complex acquisition programs. The Medical Research and Materiel Command adapted the new requirements to the acquisition of the adenovirus vaccine. The processes of contracting, building, equipping, manufacturing, testing and securing approvals from the US Food and Drug Administration required about ten years, involved over 100 DoD Army, Air Force, and Coast Guard personnel and over 100 contractor personnel, and cost approximately $100 million.

Careful logistical planning allowed near-simultaneous distribution of the vaccine to all military basic training installations in October 2011. Intensive surveillance of respiratory illness in basic trainees had been established by the Naval Health Research Center to document the need for the vaccine, and this surveillance was also useful in documenting the impact of the restored vaccine. Rates of febrile respiratory illness have fallen about 85%, and isolations of adenovirus type 4 no longer occur. Careful management will be required for sustainment of the supply of the vaccine (called Total Life Cycle Systems Management in the DoD).

References:

Novel Influenza Vaccines
Peter Palese, PhD
Mount Sinai School of Medicine
New York, NY

Objective: Understand the complex epidemiology and mechanism of influenza viruses and review developments in universal influenza vaccines.

Abstract: Available influenza virus vaccines are effective in healthy individuals but are usually re-formulated annually due to antigenic drift of the circulating viruses. Thus, influenza vaccination programs requiring yearly reimmunization are both expensive and difficult to implement. Recent reports on broadly neutralizing anti-influenza hemagglutinin antibodies suggest that eliciting broad-spectrum humoral immunity against influenza viruses should be possible, given the right immunogen. Most broadly neutralizing anti-influenza hemagglutinin antibodies bind to the conserved but immuno-subdominant stalk region of the hemagglutinin molecule. In order to induce such antibodies via vaccination, we have designed different hemagglutinin-based immunogens. These novel constructs (for example, headless hemagglutinins, chimeric hemagglutinins) direct the immune response against the stalk domain, efficiently boosting a cross-reactive immune response. Preliminary data from heterologous virus challenge experiments in mice suggest that these novel vaccine constructs are able to induce high levels of broadly neutralizing antibodies that protect against morbidity and mortality. The development of a universal influenza virus vaccine that—similar to the existing polio and measles virus vaccine—requires a single or only a few immunizations, represents a major advance towards the control of influenza worldwide.

References:
Progress towards Live Vaccines for Tuberculosis
Stefan H.E. Kaufmann, PhD
Max Planck Institute for Infection Biology
Berlin, Germany

Objective: Review information on the current status of live mycobacterial vaccines for tuberculosis undergoing clinical assessment.

Abstract: The current vaccine, Bacille Calmette Guérin (BCG), provides insufficient protection against tuberculosis requesting for novel vaccination strategies 1-3. BCG is an attenuated derivative strain of Mycobacterium bovis, the etiologic agent of cattle tuberculosis (TB) which can cause human TB. Several new vaccine candidates have entered clinical trials 1-3. The first group comprises subunit vaccines which booster BCG 4. The second group encompasses viable attenuated mycobacterial vaccines aimed at replacing BCG.

Viable vaccine candidates against tuberculosis fall into two groups:
1) Recombinant (r) BCG expressing improved immunogenicity, antigenicity or both. The r-BCG30 overexpresses Antigen 85B shared by both Mycobacterium tuberculosis and BCG 5, 6. It shows superior protection and has proven its safety in a phase I clinical trial. Its development is currently on hold. VPM1002 expresses listeriolysin to improve its immunogenicity 7, 8. It has shown superior protection and safety over BCG in preclinical trials, has passed phase I clinical trials successfully and is currently undergoing phase IIa clinical assessment (NCT 01479972). Aeras 422 expresses mycobacterial antigens and perfringolysin. Hence, it was aimed to combine concepts underlying VPM1002 and r-BCG30. A phase I clinical trial with this candidate had to be terminated because of severe adverse events (NCT 01340820).

2) Mycobacterium tuberculosis has been attenuated by genetic modification. MTBVAC has been created by deleting the PhoP and fadD26 gene loci to achieve its attenuation10. It has recently entered a phase I clinical trial (Swissmedic 2012GT1002). This presentation will summarize the status of the different live vaccine candidates aimed at replacing BCG, discuss their likely modes of action and speculate on future vaccination strategies.

References:
Prospects for Subunit Vaccines Targeting Tuberculosis Latency

Peter L. Andersen, DVM, DMS
Statens Serum Institut
Copenhagen, Denmark

Objective: Understand the scientific rationale for the design of tuberculosis subunit vaccine development and review recent progress in the development of novel post-exposure vaccines for latently infected individuals.

Abstract: Tuberculosis (TB) is an infection that you live with in a long-term relationship, and a successful outcome of a protective immune response is the prevention of reactivation and disease. A TB vaccine for either pre- or post-exposure administration, able to prevent or delay TB reactivation and the contagious lung disease, would have a huge impact on transmission and global health.

The current vaccine, BCG (Bacillus Calmette-Guérin) reduces TB incidence in children, but the vaccine does not prevent the establishment of latent TB or reactivation of pulmonary disease in adult life\(^1\). Recent data suggest that one of BCG’s major shortcomings seems to be a lack of a sufficient memory T-cell reservoir that continuously replenishes the T-cells at the site of infection and prevent attrition and functional exhaustion. Another problem may relate to the antigens missing in BCG.

While significant progress is made in the development of preventive TB vaccines, a key remaining problem is which antigens should be targeted for efficient post-exposure vaccination. The ESX systems from Mycobacterium tuberculosis are responsible for the secretion of antigens of key importance in bacterial physiology and host-pathogen interactions. The two prototypic molecules, ESAT-6 and TB10.4, share a lot of characteristics and antigenic properties, but have different roles in bacterial physiology. We found that although these two molecules had similar activity in preventive vaccination models, only ESAT-6 containing vaccines protected against relapse of bacterial growth in animal models of TB. Our studies provide new insight into the different requirements for effective pre- and post-exposure vaccines, and suggest that ESAT-6 has the unique potential for post-exposure vaccination that may relate to its important biological function and role as a virulence factor.
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An ESAT-6 containing vaccine may have two potential clinical applications; a post-exposure vaccine for populations where latent TB is widespread, and as an adjunct immuno-therapy to shortened chemotherapy treatment regimens for active TB. The ongoing clinical development of two ESAT-6 bearing subunit vaccines (H1 and H56), which includes testing in latently infected individuals, will in the near future provide a clinical proof-of-concept testing, the outcome of which will be of critical importance for the feasibility of both applications.

References:

Biomarkers for Assessing Immunity to Tuberculosis
Willem Hanekom, MBChB, DCH
University of Cape Town
Cape Town, South Africa

Objective: Review status of tuberculosis studies to delineate correlates of risk and analyze assays used in clinical tuberculosis vaccine trials.

Abstract: Lack of correlates of protection against tuberculosis (TB) disease hampers TB vaccine development. The South African Tuberculosis Vaccine Initiative aims to delineate prospective determinants of risk of TB disease, as a first step toward ultimately identifying correlates of protection. In three large-scale projects, we are studying correlates after vaccination with BCG, after exposure to M. tuberculosis, and after infection with the pathogen. In each of the three studies we have identified participants who ultimately progressed to TB disease (cases) and those who did not (matched controls). Blood products collected prior to developing disease (cases) were used to describe correlates of risk, by comparing gene expression profiles with those of controls.

Preliminary results from two of the projects, one focusing on BCG-vaccinated infants and one on M. tuberculosis-infected adolescents, appear remarkably similar. A striking and consistent finding is that expression of genes associated with inflammation and myeloid cell activity were up regulated in cases, compared with controls. We concluded that gene expression signatures identify persons at risk of TB, long before disease manifests.

References:
**Objective:** Understand the current status of veterinary tuberculosis (TB) vaccine research for cattle and wildlife and their potential applications for development of human TB vaccines.

**Abstract:** Vaccines are lacking for many chronic intracellular pathogens requiring cell-mediated immunity for protection. A serious impediment to vaccine discovery is a lack of animal models predictive of efficacy in humans. For TB, vaccine efficacy studies using *Mycobacterium tuberculosis* (*M. tb*) in non-human primates (NHPs) offer a logical model for prediction of efficacy in humans. Availability (especially of neonates) and costs associated with BL-3 care, however, hinder widespread use of NHP’s for vaccine testing. Thus, many candidate TB vaccines are tested using mice and guinea pigs; yet, only a few of the vaccines deemed effective with rodent models have emerged for evaluation in Phase 1 human trials.

*Mycobacterium bovis* (*M. bovis*) infection of cattle and relevant wildlife reservoirs results in disease that is similar to *M. tb* infection in humans. Prior to pasteurization, ~25% of TB cases in humans were attributable to *M. bovis*. Infection with *M. bovis* in humans is clinically indistinguishable from *M. tb* infection and these two organisms have ~99.95% sequence identity. While the mainstay of bovine TB control has been abattoir inspection and targeted antemortem testing, vaccines are being considered as an additional control tool, both for cattle and wildlife reservoirs of bovine TB. Field efficacy trials performed in the early 20th century demonstrated the partial effectiveness of *M. bovis* Bacillus Calmette Guerin (BCG) for the control of bovine TB. Recent experimental trials with cattle have demonstrated that: (1) select attenuated *M. bovis* mutants provide similar to improved efficacy as BCG, (2) subunit vaccines may boost immunity elicited by BCG in cattle, (3) BCG is particularly protective when administered to neonates, (4) T-cell central memory immune responses evoked by protective vaccines correlate with protection upon subsequent *M. bovis* challenge, and (5) differentiation of infected from vaccinated animals (DIVA) is feasible in cattle using both *in vitro* (interferon-release assays) and *in vivo* (skin test) methods. In regards to wildlife reservoirs, the efficacy of BCG delivered orally has been demonstrated for brushtail possums (in field trials) as well as Eurasian badgers, wild boar, and white-tailed deer (each in experimental challenge studies). In addition to typical efficacy parameters, efforts are ongoing to develop experimental biology approaches to evaluate vaccine efficacy based upon reduced transmission, both for cattle and white-tailed deer. Vaccine efficacy trials, particularly field studies and trials evaluating ability of vaccines to limit transmission, with cattle and wildlife reservoirs of bovine TB represent a primary example of the one health approach, with outcomes relevant to both veterinary and medical applications.

**Reference:**
Induction of Vaginal Intraepithelial CD8+ T-Cells by HPV Vector Vaccination

John T. Schiller, PhD
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National Institutes of Health
Bethesda, MD

Objectives: Understand the characteristics of HPV pseudovirions as gene transfer agents and the immune responses they induce so they can be appropriately applied to mucosal vaccine applications. Recognize the differences in the ability of systemic versus local mucosal immunization strategies to induce long-lived tissue resident CD8+ T-cells in a mucosal epithelium.

Abstract: The induction of robust and persistent intraepithelial CD8+ T lymphocytes (IELs) may be key to the development of vaccines against mucosally-transmitted pathogens, particularly for sexually-transmitted diseases. We investigated CD8+ T-cell responses in the mouse female cervicovaginal mucosa after intravaginal immunization with human papillomavirus vectors (HPV pseudoviruses) that transiently expressed a model antigen, respiratory syncytial virus (RSV) M/M2, in cervicovaginal keratinocytes. An HPV intravaginal prime/boost with different HPV serotypes induced 10-fold more cervicovaginal antigen-specific CD8+ T-cells than priming alone, with local proliferation and retention of antigen-specific CD8+ T-cells after boosting. The number of specific T-cells decreased only two-fold after 6 months. Most genital antigen-specific CD8+ T-cells were intra- or sub-epithelial and expressed $\alpha_v\beta_3$-integrin CD103, produced IFN-\(\gamma\) and TNF-\(\alpha\), and displayed in vivo cytotoxicity. Intravaginal HPV prime/boost reduced cervicovaginal viral titers 1,000-fold after intravaginal challenge with vaccinia virus expressing the CD8 epitope M2\(^{[82-90]}\). In contrast, intramuscular (IM) prime/boost with an adenovirus type-5 vector induced higher systemic CD8+ T-cells but failed to induce CD103+CD8+ IELs or protect against recombinant vaccinia vaginal challenge. Ad5 IM prime/HPV genital boost generated 10-fold higher genital responses than HPV/HPV genital prime/boost and many induced T-cells were IELs, whereas HPV genital prime/Ad5 IM boost was not as effective at generating IELs. Thus, HPV vectors are attractive gene-delivery platforms for inducing durable tissue resident CD8+ T-cell responses in cervicovaginal epithelium by promoting local proliferation and retention of antigen-specific CD8+ T-cells.

Co-authors on this paper are:
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\(^1\)National Cancer Institute and \(^2\)Vaccine Research Center, National Institutes of Health, Bethesda, MD

Reference:
Gender-Based Differences in Vaccine Response

Sabra L. Klein, PhD
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Baltimore, MD

Objective: Review data from diverse vaccines showing that higher immune responses in females compared with males are well conserved across diverse antigens and examine whether genes and/or sex hormones, including estrogens and androgens, influence immune responses to vaccines.

Abstract: Mounting evidence from clinical trials shows that females consistently develop higher adaptive immune responses to viral vaccines than males. After vaccination against rubella, measles, mumps, smallpox, yellow fever, hepatitis, herpes simplex 2, dengue virus, or influenza viruses, protective antibody responses are at least twice as high in females than in males. Measures of cell-mediated immunity following vaccination also are higher in females than males. However, females develop more frequent and severe adverse reactions, including fever, pain, and inflammation, to viral vaccines.

Despite significant immunological differences between the sexes, a majority of studies in vaccinology do not disaggregate and analyze outcome data by sex. Unique to females, pregnancy also significantly alters immune responses to vaccines. Greater consideration should be given to the biological mechanisms, including genetic and hormonal factors, which underlie differential responses to vaccines in males and females. Identification of the mechanisms by which adaptive immune responses differ between males and females might assist with developing vaccines that better protect both sexes equally.

References:

Synthetic Genomics Vaccines for Human Health

John I. Glass, PhD
The J. Craig Venter Institute
Rockville, MD

Objective: Discuss how the new field of Synthetic Genomics will catalyze the expansion of vaccine science by enabling researchers to rapidly and inexpensively create new vaccines using synthetic DNA.

Abstract: The common feature of all vaccines is that they contain molecules or viruses or even whole cells whose production was programmed by information encoded in RNA or DNA genomes. The active ingredients in vaccines are made by or of cells. Cells are comprised of, to continue the computer metaphor, both software or an operating system, which is the DNA, and hardware, which is the cytoplasm, organelles, and envelope, essentially
everything but the DNA. Even real viruses, like computer viruses, are packaged bits of information, i.e. RNA and DNA that reprogram cells to make more viruses.

Synthetic Genomics is a set of methods and experimental approaches that enable genome scale engineering of cells and viruses. This science will allow us to design and build cells whose genomes have been engineered on a grand scale.

Over the past 13 years biologists have used synthetic DNA to produce infectious viruses and even living bacterial cells from what amounts to digital information. These approaches are now being used to speed and improve the production of influenza vaccines in anticipation of future pandemics, and to produce bacteria that will serve as a live attenuated vaccine against contagious bovine pleuropneumonia. One of the great advantages of synthetic vaccines is they can be designed to not include specific cellular components that are unwanted in a vaccine. For instance a vaccine comprised of whole bacteria could be made that lacked pathogenicity factors. In the case of viral vaccines, such as vaccines for influenza virus, vaccine made from a virus produced from synthetic DNA is equivalent to a virus produced by conventional approaches if the sequences of the viral genomes are the same.

References:

Using Synthetic Genomics to Create Influenza Vaccine
David E. Wentworth, PhD
The J. Craig Venter Institute
Rockville, MD

Objective: Understand and describe the two major mechanisms of influenza evolution (antigenic drift and antigenic shift) that are critical to vaccine development and how genetically engineering vaccines differs.

Abstract: Annual influenza A epidemics infect 250-500 million people, resulting in 3-5 million cases of severe illness and 250,000-500,000 deaths worldwide. Vaccination is the most important strategy to prevent influenza infections and alleviate the severity of epidemics and pandemics. The majority of influenza vaccines currently administered in the United States are inactivated vaccines, which have proven to be safe and fairly effective over decades of use in humans.
One of the major problems with our current approaches is the long lead time required to create vaccines. To speed vaccine production synthetic genomics approaches are being developed to rapidly create inactivated vaccines directly from electronic information. A problem with inactivated vaccines is their inability to induce cross protective immune responses. Live attenuated influenza vaccines (LAIVs) can elicit IgA mucosal immunity and cellular immunity and are therefore believed by some to be a superior approach.

The licensed LAIV in the United States is created by making a reassortant containing six internal genes from a cold-adapted master donor strain (ca A/AA/6/60) and two surface glycoprotein genes from a circulating/emerging strain (e.g., A/CA/7/09 for the 2009/2010 H1N1 pandemic). Technologies to rapidly create recombinant viruses directly from patient specimens were used to engineer alternative LAIV candidates that have genomes composed entirely of vRNAs from pandemic or seasonal strains. Multiple mutations involved in the temperature-sensitive (ts) phenotype of the ca A/AA/6/60 master donor strain were introduced into a 2009 H1N1 pandemic strain to create unique temperature sensitive experimental vaccines. Another approach tested was to rationally engineer attenuating mutations into the NS gene segment, which is in interferon antagonist, of the 2009 pandemic virus. Clinical symptoms and virus replication in the lungs of mice and ferrets showed that engineering key mutations directly into the genomes of influenza A viruses attenuates divergent lineages and provides an alternative strategy for the generation of LAIVs.

References:

ABSTRACTS OF SUBMITTED ORAL PRESENTATIONS
Vaccine-Associated Enhanced Respiratory Disease following Heterologous Influenza Vaccination is Associated with Cross-Reactive Anti-HA2 Antibodies with Virus Fusion Enhancing Activity

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1FDA, Bethesda, MD, 2USDA, Ames, IA

Objectives: Understand the mechanism of enhanced clinical disease due to Influenza infection following heterologous inactivated influenza vaccines. Outline the role of anti-HA2 antibodies in enhancement of influenza virus fusion and entry.

Background: Vaccine-associated enhanced respiratory disease (VAERD) was reported after vaccination with certain RSV and measles vaccines. During the 2009 influenza pandemic several reports suggested prior vaccination with the 2008-09 seasonal inactivated influenza vaccine increased severity of clinical disease following infection with pH1N1 influenza virus in humans. The mechanism of VAERD has not been fully understood.

Methods: To understand the mechanism of VAERD, a previously described swine model was used1-2. Pigs vaccinated with whole virus inactivated hu-like (δ-cluster) H1N2 vaccine (A/Sw/MN/02011/08) (WIV-H1N2) followed by a challenge with pH1N1 A/CA/04/09 (pH1N1) (V/C) demonstrated enhanced pneumonia and respiratory disease compared with non-vaccinated challenged animals (NV/C). We elucidated the quality and specificity of antibody response elicited by the heterologous WIV-H1N2 vaccine in different functional assays.

Results: (A) WIV-H1N2 (δ-cluster) induced HI antibodies against H1N2 strain, but not pH1N1, (B) the WIV-H1N2 immune sera enhanced infection of MDCK with pH1N1 and competed with anti-pH1N1 neutralizing antibodies in a dose-dependent manner in the microneutralization assay; (C) the WIV-H1N2 immune sera contained high titers of cross-reactive anti-pH1N1 hemagglutinin antibodies that bound exclusively to the HA2 domain and not to the HA1 globular head; binding was mapped to HA2 epitope adjacent to the fusion peptide using gene fragment phage display libraries; (D) these HA2 targeting antibodies mediated the enhanced infection of MDCK via increased virus-membrane fusion.

Conclusions: VAERD following heterologous vaccination with inactivated influenza vaccines may be correlated with fusion-enhancing cross-reactive anti-HA2 antibodies in the absence of HA1 targeting neutralizing antibodies. These findings could have an impact on future universal vaccines designed to elicit exclusively HA2 stem antibodies in the absence of anti-HA1 specific antibody response.

References:
IL18R1 and IL18 Gene Polymorphisms are Associated with Immune Responses to Smallpox Vaccine
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Objective: Discuss the effect of IL18R1 and IL18 gene polymorphisms on variations in vaccinia virus-induced immune responses observed in healthy subjects who received a single dose of smallpox vaccine.

Background: Host genetic factors play an important role in inter-individual variations in immune response to vaccination.

Methods: We examined the association of genetic polymorphisms (across 32 cytokine and cytokine receptor genes) with humoral (neutralizing antibodies) and cellular (IFN-γ Elispot) immune responses to smallpox vaccine in a racially diverse cohort of 1,056 healthy immunized individuals (18 to 40 years old) after one dose of vaccine (Dryvax®).

Results: Our study cohort consisted of 569 (54%) Caucasians and 214 (20%) African-Americans, primarily men (n=778, 74%). The median neutralizing antibody ID₅₀ values and vaccinia virus-specific IFN-γ Elispot counts was 132 (inter-quartile range/IQR, 79-206) and 52 spot-forming cells (SFC)/200,000 cells (IQR, 24-88), respectively. In the study cohort (n=1,056), we found 17 single-nucleotide polymorphisms (SNPs) significantly associated with variations in antibody titers (p<0.01). Of these, 11 SNPs (65%) were located in the IL18R1 and IL18 genes. Similarly, we found 20 SNPs associated with IFN-γ-Elispot responses (p<0.01). Of these, 16 SNPs (80%) were located in the gene encoding IL18R1. A functional coding IL18R1 polymorphism (rs1035130/Phe251Phe, in strong LD with intronic rs4851570, p=0.01) was significantly associated with an allele dose-related increase in vaccinia-specific IFN-γ production and was also associated with neutralizing antibody titers (p<0.02). Several significant associations were also found between IL18R1 haplotypes and variations in vaccinia-specific antibody titers (global p<0.001) and IFN-γ Elispot responses (global p<0.0001).

Conclusions: Our data suggest the importance of polymorphisms in the IL18R1 and IL18 genetic loci in smallpox vaccine-induced adaptive immune responses. Understanding molecular mechanisms behind these associations may help to improve smallpox vaccines and will add to our knowledge of vaccine-induced immune responses.

References:
Influence of Maternal Murine Immunization with *Neisseria meningitidis* Outer Membrane Vesicle Antigens on the Immune Response in Offspring

E. N. De Gaspari

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**Objective:** Summarize the influence of maternal murine immunization with *Neisseria meningitidis* outer membrane antigens on the immune response in offspring.

**Background:** The primary objective of meningococcal vaccination strategies should be to protect infants against severe disease and death, particularly in the very young. Maternal exposure to *N. meningitidis* outer membrane vesicle (OMV) antigens could exert an influence on the newborn’s immune repertoire and the later development.

**Methods:** Balb/c adult mice received 50μg in four doses at three day intervals intranasally. On the 35th day, the animals were immunized intramuscularly with 20μg of OMV of *N. meningitidis* and *Bordetella pertussis* as adjuvant before mating with normal Balb/c males. Serum samples were collected from newborn mice delivered by cesarean section, and maternal milk samples were extracted from the stomachs of newborn mice. Groups of offspring 45 days old were *N. meningitidis* OMV immunized and boosted on the 10th day after sensitization. The animals were bled 7 days after the booster. IFNγ level was measures by ELISPOT assay.

**Results:** High levels of anti-*N. meningitidis* IgG isotypes mainly IgG1, but also IgG2a and IgG2b were transmitted by immunized mice via the placenta to the offspring. In the sera and milk from immunized mothers, significant levels of anti-OMV IgG subclasses and anti-OMV IgM and IgA antibodies were detected. Mice immunized as neonates induced OMV-specific mucosal and systemic immunoglobulin A (IgA) and IgG. IFN-γ is an abundant cytokine produced by Th1 cells. IFN-γ production in response to OMV A mixed Th1- and Th2-type response to OMVs was established after the boost and was maintained thereafter. OMVs induce specific antibodies and cell-mediated immunity in the presence of high levels of maternal antibodies.

**Conclusions:** Our study showed that maternal immunization with OMVs promotes the transference of specific antibodies and suggests that maternal pre-exposure to OMVs before mating can protect mice during the early phase.

**Reference:**

Background: Human hookworm infection, a neglected tropical disease, infects more than 600 million people. One of the new vaccines which will target the human hookworm infection is *Necator americanus* aspartic protease-1 M74 (Na-APR-1 M74). Hookworms ingest erythrocytes containing hemoglobin and *Necator americanus* aspartic protease-1 wild type (Na-APR-1wt), a hemoglobinase, cleaves hemoglobin to heme and globin. Globin is digested by other gut enzymes and the nutritional end-products are absorbed by the hookworm’s gut wall. Neutralizing Na-APR-1wt by potent antibodies will block this digestion cascade. Deprivation of essential nutrition will lead to reduction in fecundity and/or death of hookworms.

Methods: Serum for IgG was generated by vaccinating BALB/c mice twice subcutaneously with Na-APR-1 M74, an enzymatically inactive mutant form of Na-APR-1wt formulated with Alhydrogel®. Assessment of neutralizing capacity of IgG was performed using cathepsin-D protease assay. Dose response (% inhibition vs. dose) was assessed using linear regression. Potency testing of the Na-APR-1M74 clinical drug product was performed by standard bioassay. Median effective dose 50 (ED$_{50}$) with the 95% fiducial limits (95% FL) was estimated using probit analysis (SAS® 9.3). Also, relative potency (RP) was estimated by the methods described in European Pharmacopeia’s Chapter 5.3.

Results: Five micrograms of IgG neutralized 51.06% of the enzymatic activity of 250ng of Na-APR-1wt. An excellent dose response was also observed. ED$_{50}$ of 14.15μg (95%FL = 10.47μg-18.93μg) and 11.46μg (95%FL = 4.86μg-27.42μg) was estimated for time 1 and 7 months post manufacture respectively. RP at 7 months was found to be 1.23 (95%FL = 0.792-1.917).

Conclusions: These preclinical results of the Na-APR-1 M74 vaccine lay the foundation for a phase 1 Clinical Trial in the US and Brazil.

References:

Design of Vaccine Adjuvants through Regulated Induction of Programmed Necrosis

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Objective: Demonstrate that necrotic cell death promotes and is necessary for the effects of certain adjuvants and review new adjuvants identified using a programmed necrotic cell death paradigm of design.

Background: Immunologic adjuvants are critical components of antigen-based vaccines. Despite the importance of adjuvants to vaccine design, little is known about how most adjuvants regulate the adaptive immune response. As a result, rational adjuvant design is extremely limited. Here we evaluate a novel paradigm for adjuvant function and demonstrate its utility for adjuvant design.

Methods & Results: Using alum (the most widely used adjuvant worldwide) as a model, we show that adjuvant-mediated cytotoxicity is critical to adjuvant function and can be used as a basis to design new adjuvants. We show that alum triggers a novel form of programmed necrotic cell death. We found that a soluble peptide-based compound that mimics alum-mediated necrosis also promotes an adaptive immune response strikingly similar to
the particulate adjuvant. Furthermore, we found that inhibiting the cell death prevents this response. We then examined if we could expand this model to LPS, a well-known TLR-activating adjuvant. LPS is known to induce a distinct form of programmed necrosis-pyroptosis. Though a weak inducer by itself, when exogenous ATP or potassium ionophores (e.g., nigericin) are added to LPS, it becomes a potent inducer. Similarly, we found that when ATP or nigericin were added to an LPS-adjuvanted immunization, it substantially enhanced the potency of immune response over any of the individual components.

Conclusions: These data suggest that programmed necrosis also plays a role in TLR-stimulating adjuvants. Taken together, these results indicate a central role for programmed necrotic cell death in the function of two classes of immunologic adjuvant. More broadly, these data suggest that instead of attempting to formulate adjuvants that minimize toxicity, adjuvant formulations should instead be formulated to trigger a small degree of self-limited cell death.

Reference:

Comparison of the Live Attenuated Yellow Fever Vaccine 17D-204 to its Virulent Parental Strain Asibi by Deep Sequencing

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Objective: Discuss a framework for comparison of variant populations for live yellow fever vaccine strain 17D with the virulent parental strain to increase understanding of massively parallel sequencing in assessment of RNA vaccine quality control.

Background: The yellow fever virus (YFV) vaccine strain 17D was empirically derived in 1937. Despite production of over 550 million doses, our understanding of how the vaccine works is very limited. Quasispecies identity of viral vaccines may be a determinant of attenuation, therefore the well-described YFV vaccine 17D is an ideal model to directly compare population structures of virulent and attenuated viruses. A live viral vaccine was compared to its wild-type parental strain through deep sequencing.

Methods: Wild-type parental strain Asibi and commercial 17D (YF-Vax) strain viruses were sequenced using Illumina chemistry, and quasispecies structures were assessed by several methods. First, variants were directly compared by intersection of population identity with consensus sequences of both viruses. Paired-samples comparison was performed using binomial models, assessing the significance of change in variant population between the viruses.

Results: The virulent strain Asibi contains a significantly higher percentage of vaccine-identity bases at key sites in the viral population. However, the recovery of virulent-identity variants in the 17D vaccine population was largely not observed. For many sites that were overtly variable in the virulent genome, we observed fixation to a homogenous identity in 17D vaccine. Binomial models recovered clusters of highly variable regions of the YFV genome.
Conclusions: Our observation of low variability for the 17D vaccine genome may contribute to the excellent safety record of the vaccine. Selection pressures giving rise to the fixation of variable sites in the wild-type genome, and the intra-host significance of this homogeneity to the success of the vaccine has not been studied. The data will inform further studies of YFV vaccine attenuation and safety, which is not understood on a discrete genomic level.

References:

Outcome-Based Vaccine Safety Surveillance
R. Baxter, E. Lewis, B. Fireman, J. McDonald, N. Klein
Kaiser Permanente Vaccine Study Center, Oakland, CA

Objective: Describe a method for improved control of confounding in vaccine safety studies and how it can be utilized as a method for screening large numbers of possible adverse events.

Background: Ongoing surveillance of adverse events following immunization (AEFI) is necessary to ensure vaccine safety and provide reassurance to maintain high rates of vaccine coverage.

Methods: We developed a case-centered method, which compares the odds of vaccination of individuals who have had an AE, during a risk interval prior to the AE, with the odds of vaccination with the same vaccine, in the same calendar time interval, of the entire available population, matched for age and sex. We constructed summary data tables containing the pertinent information for the entire membership of the Kaiser Permanente health plan of Northern California (KPNC). Using these tables, we were able to rapidly calculate the relative risk (RR) of prior vaccination for any AEFI identifiable in the electronic medical records. We tested this method on multiple outcomes and vaccines in KPNC, looking retrospectively from 2009 through 1999, using different risk intervals, with vaccines currently in use.

Results: For Kawasaki’s disease there were no elevated RRs that were statistically significant for any vaccine exposure. The application was found to be sensitive: an increased risk of febrile seizure was noted for Pneumococcal conjugate vaccine in the three days prior (RR 1.43, 95% CI 1.11-1.81), while for MMR it was only noted in the two-week window (RR 1.61, 95% CI 1.41-1.85).

Conclusions: Outcome-based surveillance is a potentially powerful tool for ongoing monitoring of vaccine safety. We hope to expand this surveillance to the Vaccine Safety Datalink project of the CDC.

References:
Guillain-Barré Syndrome and Pneumonia and Influenza Hospitalizations: An Ecologic Overview

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**Objective:** Recognize that Guillain-Barré Syndrome (GBS) hospitalization has a seasonal peak similar to pneumonia & influenza (P&I) and that P&I hospitalization positively correlates with GBS hospitalizations.

**Background:** Studies have determined a small risk of GBS following influenza vaccination. It has recently been suggested that this observed risk may be confounded by P&I, which are seasonal; however, seasonality of GBS has not been clearly demonstrated. We conducted an ecologic analysis to better understand GBS seasonality and its relationship with P&I.

**Methods:** We used data from the Healthcare Cost and Utilization Project’s 2000-09 nationwide inpatient samples that included nearly eight million nationally representative hospitalization data annually. Monthly hospital admissions with principal diagnosis of GBS (ICD-9-CM 357.0) and P&I (ICD-9-CM 480-488) were included. Rates were calculated using census population estimates. Poisson models were used to determine the seasonality of GBS hospitalizations, temporal clusters of GBS and P&I hospitalizations, and association between GBS and P&I hospitalizations.

**Results:** GBS hospitalization rates ranged from 20.1 per million population in 2002 to 21.8 in 2005. P&I hospitalization rates was also highest in 2005 (470 per 100,000 population). Significant clusters of P&I (p=0.001) and GBS (p=0.001) hospitalizations were observed from December 2004-March 2005 and January 2005-February 2005, respectively. Winter months (December, January, and February) had higher (p<0.05) GBS hospitalizations compared to other seasons. P&I hospitalizations were positively associated with GBS hospitalizations that occurred during the same month (b=0.0062, p<0.0001) and the following month (b=0.0060, p<0.0001).

**Conclusion:** Highest rates of GBS and P&I hospitalizations occurred during the 2004-05 influenza season when there was a large scale influenza vaccine shortage. Seasonal peak of GBS hospitalizations followed the peak of P&I. The risk of GBS following influenza vaccines may be confounded by P&I and the benefit from effective influenza vaccination campaigns might outweigh any apparent risk.

**References:**

Adverse Events after Fluzone Intradermal® Vaccine Reported to the Vaccine Adverse Event Reporting System, 2011-13

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Objective: Explain the post-licensure safety and reported adverse events for intradermal trivalent inactivated influenza vaccine in VAERS between 2011 and 2013.

Background: In May 2011, the first trivalent inactivated influenza vaccine exclusively for intradermal administration (TIV-ID) was licensed in the US for adults age 18-64 years. The objective of this study was to characterize adverse events (AEs) after TIV-ID reported to the US Vaccine Adverse Event Reporting System (VAERS), a spontaneous reporting surveillance system.

Methods: We searched VAERS for US reports after TIV-ID from July 2011-November 2012. Medical records were requested for reports coded as serious (death, hospitalization, prolonged hospitalization, disability, life-threatening-illness), and those suggesting anaphylaxis, or Guillain-Barré Syndrome (GBS). Clinicians reviewed available information and assigned a primary clinical category to each report. Empirical Bayesian data mining was used to identify disproportional AE reporting following TIV-ID.

Results: VAERS received 318 reports after TIV-ID; 11 (3.5%) were serious. Median age was 44 years (range 6-89 years). The most common AE categories were: 153 (48.1%) injection site reactions [2 serious reports]; 55 (17.3%) other non-infectious; and 51 (16.0%) allergy. Eight reports (2.5%) of anaphylaxis were reported and verified by the Brighton criteria or a documented physician diagnosis. These eight vaccinees received only TIV-ID and seven of the eight recovered by the time the AE was reported. Neurological AEs of interest included one report each of GBS (Brighton level 2), chronic inflammatory demyelinating polyneuropathy, and Bell’s palsy, all occurring within 42 days of vaccination. Disproportionality analysis revealed an elevated value for two AEs, injection site nodule, and injection site pruritus, which were not unexpected.

Conclusions: Review of VAERS reports did not identify any concerning pattern of AEs after TIV-ID. Injection site reactions were the most commonly reported AEs, as they were during the pre-licensure clinical trials. We will continue routine surveillance of VAERS to monitor the safety of TIV-ID.

References:
Use of Live-Attenuated Influenza Vaccine in Children and Adolescents with Cystic Fibrosis
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Objective: Understand the safety profile of influenza vaccination in children with cystic fibrosis.

Background: In Canada, live-attenuated influenza vaccine (LAIV) is recommended for preferential use in healthy children (2-17 years). Data on LAIV safety for children with chronic conditions is lacking. Our objective was to determine rates of serious adverse events following immunization (AEFI) in a cohort of participants with cystic fibrosis (CF) vaccinated against influenza in the fall of 2012.

Methods: A prospective cohort of CF children (2-17 years), vaccinated against influenza as part of their recommended immunization schedule, was recruited at the time of vaccination. Participants were actively followed-up for AEFIs, using a daily diary and weekly phone calls. The main outcome was a respiratory deterioration leading to a medical visit or hospitalization. Using the self-controlled risk interval design, we compared rates of respiratory deterioration between the at-risk (D0-28) and non-at-risk intervals (D29-56). As follow-up is ongoing, patient-days (pd) are presented.

Results: 318 children were approached, 232 were eligible and 175 (75%) were enrolled: 156 (LAIV) and 19 (TIV). Four participants were hospitalized: 1 of 19 (5.3%) post-TIV (respiratory deterioration on D16), and 3 of 156 (1.9%) post-LAIV (2 respiratory deteriorations - D36 and 53 and one acute intestinal obstruction - D0). All were considered unrelated to vaccination. Rates of respiratory deterioration requiring admission during the at-risk and non-at-risk periods were 1/308 and 0/84 pd (3.2 vs. 0/1000 pd), respectively post-TIV (p=1.0); and 0/2576 and 2/392 pd (0 vs. 5.1/1000 pd), respectively post-LAIV (p=0.02).

Conclusion: Despite our limited number of patients, LAIV administration in children 2-17 years with CF does not seem to increase the risk of respiratory deterioration requiring admission in the 4 weeks following vaccination. These results need to be confirmed in a larger study.

References:
ABSTRACTS OF SUBMITTED ORAL PRESENTATIONS

S11 Birth Outcomes Following H1N1 Immunization
A. Eaton, N. Lewis, B. Fireman, J. Hansen, R. Baxter, N. Klein
Vaccine Study Center, Kaiser Permanente Vaccine Study Center, Oakland, CA

Objective: Evaluate the probability of adverse birth outcomes due to H1N1 vaccine.

Background: During the 2009-10 influenza season pregnant women were recommended to receive H1N1 and trivalent inactivated influenza vaccines (TIV). This study assessed birth outcomes following H1N1 immunization.

Methods: We telephone surveyed pregnant Kaiser Permanente Northern California members to assess nonmedically-attended reactions following H1N1, TIV, or both vaccines during 2009-10 (n=5,365). We assessed birth outcomes (preterm birth, very preterm births, low birth weight [LBW], very LBW, congenital anomalies, spontaneous abortion, still births) among this cohort by comparing rates and 95% confidence intervals (CI) between those exposed to H1N1 with those who received only TIV.

Results: Rates did not vary significantly between groups. Comparing H1N1 rates and associated 95% CI with those for TIV, rates were similar for: preterm births 6.37 (95% CI, 5.65-7.16) vs. 6.28 (95%CI, 4.10-9.20) per 100 births, LBW 4.19 (95%CI, 3.60-4.84) vs. 2.90 (95%, 1.50-5.06) per 100 births, congenital anomalies 26.64 (95%CI, 25.18-28.15) vs. 24.27 (95%CI, 19.91-29.30) per 1000 births, spontaneous abortion 7.10 (95%CI, 4.95-9.88) vs. 6.83 (95%CI, 1.41-19.97) per 1000 pregnancies, still births 7.10 (95%CI, 4.95-9.88) vs. 4.57 (95%CI, 0.55-16.49) per 1000 pregnancies, very preterm births 5.30 (95%CI, 3.28-8.10) vs. 8.29 (95%CI, 1.71-24.22) per 1000 births, very LBW 4.54 (95%CI, 2.69-7.18) vs. 5.52 (95%CI, 0.67-19.96) per 1000 births and small for gestational age 9.99 (95%CI, 7.29-13.37) vs. 9.24 (95%CI, 2.52-23.65) per 1000 births.

Conclusion: Compared with TIV, this study found no association between adverse birth outcomes and H1N1 immunization.

Reference:

S12 Chance Associations are Lopsided in Unbalanced Studies of Infrequent Events in Vaccine Safety
R. Baxter, B. Fireman, N. Klein
Kaiser Permanente Vaccine Study Center, Oakland, CA

Objective: Explain how chance findings in vaccine safety studies can differ when events are rare and comparison intervals differ.

Background: In a study of vaccine safety we noticed that chance events were more frequently found in a smaller comparison window.

Methods: We describe and explain the phenomenon of “lopsided windows,” and how it can affect studies of vaccine safety.

Results: In vaccine safety surveillance, where the treatment and comparison groups differ in size or the duration of follow-up, and adverse events (AEs) are infrequent, type 1 errors can be expected to be lopsided. Even if the vaccine is entirely safe, chance associations tend to be unfavorable in the smaller study group. Type 1 errors become increasingly infrequent and lopsided as the frequency of adverse events decreases and as the size of the study groups becomes more unequal.

Conclusion: We believe that the lopsided phenomenon described here should be considered in the interpretation of safety “signals” in unbalanced studies of infrequent events.
Logistical Implications of Implementing a Universal Rotavirus Program in Canada
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Objective: Understand the advantages and disadvantages of public health versus physician delivery of immunization.

Background: In Canada, the National Advisory Committee on Immunization recommends rotavirus vaccine (RVV) for all infants, but not all provinces/territories provide RVV in universal publicly funded programs. In a demonstration project we compared vaccine coverage (VC) rates and public knowledge, attitudes, and beliefs (KAB) in a province with a public health nurse-delivered universally funded rotavirus vaccination program (PHN-URVP) to a province with a physician-delivered URVP (P-URVP). A third province with no RV program acted as a control.

Methods: Information about KAB of parents whose children were eligible for the URVP was collected through two validated surveys. Vaccine utilization was measured as number of doses officially recorded by the study in both sites. A parent and provider post-survey as well as key informant interviews with program managers are currently underway.

Results: After year one, VC in PHN-URVP for the first dose was 94.0% and 92.0% for dose 2; during the same period in P-URVP, VC was 30.0% and 27.0% respectively (n=722). Vaccine knowledge was higher in PHN-URVP than P-URVP; both were higher than in the control where there was no program. Awareness about RV and RVV tended to be higher in PHN-URVP. Attitudes were similar in both the PHN-URVP and P-URVP, but there was less concern with vaccine safety in PHN-URVP. Results from post-surveys and key informant interviews will highlight changes in KAB over time.

Conclusion: In general, attitudes and knowledge were similar in URVP jurisdictions however, more PHN-URVP respondents felt that their province was doing a good job providing information about the URVP and were comfortable making a decision about receiving the vaccine.

Reference:
Trends in RSV-Associated Hospitalizations among Children and Adults in the United States, 2005-10

C. Archer, P. Kilgore, E. Martin, T. Taylor
Wayne State University, Detroit, MI


Background: Respiratory syncytial virus (RSV) is associated with significant morbidity and is the main cause of lower respiratory infection in young children, and is recognized as a cause of illness in older adults in the US.1,2

Methods: In this study, we describe age-group and seasonal patterns for RSV-associated hospitalizations using MarketScan, the largest compilation of employer-based patient records in the US. ICD-9-CM diagnostic codes (079.6, 466.11, 480.1) were used to identify hospitalizations in the Commercial Claims and Encounters and Medicare Supplemental Databases (2005-10). Hospitalizations were estimated in 7 age groups (<12 and 12-23 months; 2 to 4, 5 to 17, 18 to 49, 50 to 64, and ≥65 years). Seasonal patterns of RSV were examined by plotting weekly and monthly numbers of RSV-associated hospitalizations.

Results: From 2005-10, a total of 36,489 RSV-associated hospitalizations were identified among all ages. Of this total, 64% (n=23,421) RSV-associated hospitalizations occurred among infants aged <12 months and 17% (n=6094), 11% (n=3943) were found among children 12-23 months and 2-4 years. RSV-associated hospitalizations were identified among adolescents (n=839), adults 18-49 years (n=711) and 50 to 64 years (n=709) as well as Americans age 65 years and older (n=772). The mean and median number of monthly RSV-associated hospitalizations was 496 and 181. In the US, distinct seasonal peaks of RSV-associated were identified from November through April each year.

Background: The RSV-associated burden of hospitalizations remained large during the period 2005-10 and these patterns of hospitalizations appear consistent with national and regional RSV laboratory reports. The high burden of RSV across several age groups suggests that the impact of targeted prevention will have substantial direct and indirect effects in the US population.

References:

Epidemiology of Herpes Zoster in Ontario, Canada, 1992-2011

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Objective: Discuss the epidemiology of HZ with respect to Ontario’s current varicella vaccine (VV) and HZ vaccine funding contexts.

Background: Publicly-funded childhood varicella vaccine (VV) was introduced in Ontario, Canada in 2004. Herpes zoster (HZ) vaccine has been available for older adults since 2008 but is not publicly-funded.
ABSTRACTS OF SUBMITTED ORAL PRESENTATIONS

Methods: We sought to examine HZ trends in Ontario, focusing on ≥50 year-olds using healthcare administrative data, from Ontario, Canada’s universal health insurance program. We extracted population-based administrative data, from Ontario’s universal health insurance program, on emergency room (ER) and office visits using physician billing claims and on hospitalizations from the Canadian Institute for Health Information’s Discharge Abstract Database, between April 1992 and March 2012 (Fiscal years [FYs] 1992-2011). ER data were only available to FY2010. Statistics Canada population denominators were used for rate calculations. We examined trends in incidence rates using Poisson regression.

Results: During the study period, incidence rates ranged from 29.9 (1993) to 52.1 (2010) per 100,000/year for ER visits; 287.6 (1996) to 327.4 (2011) per 100,000/year for office visits; and 6.8 (2009) to 10.7 (1992) per 100,000/year for HZ hospitalizations. ER and office visit rates increased over time (both p<0.05), whereas hospitalization rates decreased (p<0.01). Among persons ≥50 years, HZ rates were substantially higher (e.g., 2011: ER visits 106.5/100,000; office visits 595.1/100,000; and hospitalizations 18.8/100,000), but trends by setting paralleled overall observations, with the exception of office visits (only increased among 60-69 year olds [p<0.05]). Comparing FY2011 to FY2008 for those ≥50 years, rates of ER (FY2010 vs. FY2008) and office visits increased 3.5% and 7.0%, respectively, while hospitalizations decreased 1.4%.

Conclusions: Medically-attended HZ rates vary by time, age, and clinical setting in Ontario. Increasing ER and office visits suggest a growing HZ burden, in the current VV and HZ vaccine funding contexts, which could be attenuated through a publicly-funded HZ vaccine program.

References:

Invasive Pneumococcal Disease in Adults During the age of Prevnar®

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Objective: Explain how trends in invasive pneumococcal disease are different in adults than in children and differ by race.

Background: Prevnar 7® was introduced in 2000 and replaced by Prevnar 13® in 2010 to prevent S. pneumoniae, a major cause of invasive infection in children. This study examined annual Invasive Pneumococcal Disease (IPD) rates by age and race for the Kaiser Permanente Northern California healthcare population (KPNC), from May 2000 until April 2012.

Methods: KPNC is an integrated healthcare plan serving approximately 3.3 million members. IPD cases were identified from the KPNC Lab Information System, and defined as S. pneumoniae from a normally sterile body site. Age and race were derived from KPNC demographic tables. Rates were calculated as annual incidence of IPD = (IPD cases/(Membership/105). We divided time into three 4-year periods.

Results: For children under six years, for all serotypes, IPD rates decreased over the 12 year period. In adults,
18 years and older, IPD rates fell from 9.47 to 8.74 per 100K PY between the first and second 4-year periods, then rebounded in the last 4 years to 10.55 per 100K PY. In adults, overall rates of IPD were higher in African Americans (18.54 per 100K PY [95% CI 17.89-19.78]) and lower in Asians (5.19 95% CI 4.55-5.83) and Hispanics (6.15, 95% CI 5.26-7.05) than Caucasians (11.77, 95% CI 10.99-12.54).

**Conclusions:** Following introduction of Prevnar® vaccines, children under six years in KPNC experienced a sustained decrease in IPD. Over the same period, adults experienced the same reductions when comparing the first four-year period to the second four years. However, during the third four-year period, annual IPD rates tended to increase for adult populations. IPD rates were higher in African-Americans, and lower in Asians and Hispanics than in Caucasians.

**References:**

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**A Universal Influenza Virus Vaccine Based on the Stalk Domain of the Hemagglutinin**

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**Objective:** Explain why influenza vaccines have to be reformulated annually and which vaccines lead to longer lasting protection.

**Background:** Influenza virus infections remain a significant cause of morbidity and mortality worldwide. Current vaccines show good efficacy against antigenically matched viruses, but fail to protect against drifted and pandemic strains since they do not induce broadly neutralizing antibodies. Due to the rapid antigenic drift of influenza viruses, these vaccines have to be re-formulated and administered through a cumbersome and expensive process every year. The membrane-proximal stalk domain of the viral hemagglutinin exhibits a high degree of both sequence and structural conservation across influenza virus subtypes. Furthermore, antibodies directed against this region typically show broad neutralizing activity. We therefore hypothesize that a vaccine strategy that stimulates a robust immune response towards this region of the hemagglutinin could provide “universal” influenza virus protection. Such a vaccine would thus abolish the need for annual vaccine reformulation and further enhance our pandemic preparedness.

**Methods:** We developed a universal influenza virus vaccine based on the conserved stalk domain of group 1 and group 2 hemagglutinins. By sequential vaccination of mice with these chimeric hemagglutinin constructs we were able to boost broadly neutralizing antibody titers against conserved epitopes in the hemagglutinin stalk domain. Mice vaccinated with our constructs were protected from morbidity and mortality induced by infection with a panel of heterologous and heterosubtypic influenza A viruses. Further, we used passive transfer and CD8+ T-cell depletion experiments to show that the observed protection is solely antibody mediated.

**Conclusions:** The present data suggest that this vaccine strategy could be successfully developed in humans to provide broad influenza virus protection. A universal influenza virus vaccine that requires a single or only a few immunizations would represent a major advance towards the control of influenza worldwide.
CD4⁺ T-Cell Responses to Cross-Reactive Influenza H1N1 T-Cell Epitopes Identified by Immunoinformatic Methods

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Objective: Illustrate the benefit of targeting T-cells for universal influenza vaccine design.

Background: Immune responses to cross-conserved T-cell epitopes in novel H1N1 influenza might explain reports of diminished influenza-like illnesses and confirmed infection among older adults, in the absence of cross-reactive humoral immunity, during the 2009 pandemic. We set out to identify and characterize cross-conserved H1N1 T-cell epitopes to develop a universal H1N1 influenza vaccine.

Methods: An immunoinformatic analysis was conducted using all available pandemic and pre-pandemic HA-H1 and NA-N1 sequences dating back to 1980. Conserved 9-mer sequences were screened for potential T-cell epitopes, which were used to construct immunogenic consensus sequences (ICS) that broadly cover both host HLA and H1N1 influenza diversity. ICS peptide-HLA interactions were confirmed in binding assays. Cytokine production induced by ICS peptides was measured by cultured IFNyELISpot assay and intracellular cytokine staining of CD4⁺ T-cells (IL-2, IFNy, TNFa) using peripheral blood mononuclear cells provided by 2011 seasonal trivalent influenza vaccinees before and 3 weeks post-vaccination.

Results: From 5,738 HA-H1 and 5,396 NA-N1 sequences, 13 HA and 4 NA ICS were selected that each cover >84% of pre-pandemic and pandemic H1N1 influenza strains, bear EpiMatrix scores ≥95th percentile and cover ≥4 HLA Class II archetypal alleles. HLA binding assays for 6 Class II archetypal alleles showed that immunoinformatic predictions were 78% accurate. Individual ICS peptides were immunoreactive in IFNyELISpot assays after antigen-specific in vitro expansion. The magnitude of cytokine⁺ CD4⁺ T-cells was boosted by immunization for vaccine-matched and ICS HA peptide pools.

Conclusions: Immunoinformatic methods identify cross-reactive influenza H1N1-specific CD4⁺ T-cell epitopes. This approach can be readily applied to other influenza subtypes to develop a universal influenza vaccine that will protect against antigenically novel influenza viruses.

References:
Phylogenetic Considerations in Designing a Broadly Protective Multimeric L2 Vaccine


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Objective: Examine the immunologic competition between the subunits with respect to the generation of protective immunity.

Background: While the oncogenic human papillomavirus (HPV) types with the greatest medical impact are clustered within the α9 and α7 species, a significant fraction of cervical cancers are caused by α5, α6, and α11 viruses. Benign genital warts are principally caused by α10 viruses HPV6 and HPV11.

Methods: In an effort to achieve broad protection against both cervical cancer and genital wart-associated types, we produced at high levels in bacteria a multimeric protein (α11-88x8) fusing eight polypeptides corresponding to a protective domain comprising L2 residues ~11-88 derived from HPV6 (α10), HPV16(α9), HPV18(α7), HPV31(α9), HPV39(α7), HPV51(α5), HPV56(α6), and HPV73(α11) respectively, and a truncated derivative, deleted of the last three units (α11-88x5). Mice were immunized three times with α11-88x8 or α11-88x5 adjuvanted with alum, or the licensed HPV vaccines and challenged intravaginally with HPV6, HPV16, HPV26, HPV31, HPV33, HPV35, HPV45, HPV51, HPV56, HPV58, or HPV59 pseudovirions.

Results: The α11-88x5 and α11-88x8 vaccines induced similar HPV16 neutralizing antibody titers and robust protection against each HPV type tested, although α11-88x8 was marginally more effective against α5 viruses. Passive transfer of α11-88x8 antisera was protective. Further, rabbit antisera to α11-88x8 and α11-88x5 similarly neutralized native HPV18 virions.

Conclusions: These findings suggest that immunologic competition between units is not a significant issue and that it is not necessary to include a unit of L2 derived from each species to achieve broader protection against diverse medically-significant HPV types than is achieved with the licensed HPV vaccines.

References:
Norovirus Consensus GII.4 Virus-Like Particles in Monovalent and Bivalent Vaccine Formulations Provide Broad Immunogenicity and Cross-Reactivity

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Objective: Analyze approaches to increase the broad reactivity of virus-like particle (VLP) norovirus vaccine candidates by investigating serum antibody responses to monovalent Consensus VLPs as well as a bivalent vaccine formulation containing VLPs.

Background: Noroviruses are the most common cause of epidemic gastroenteritis, and their antigenic diversity must be considered for the development of an effective vaccine. Multiple antigenic sites in the norovirus capsid P domain can be targeted to block the interaction of the norovirus with human ABH histo-blood group antigens (HBGA)1. These HBGA are believed to be important binding ligands for infection and illness. A number of these antigenic sites represent epitopes that appear to be conserved across genotypes and strains evolving through time, and thus these epitopes may provide antigenic targets that are important to achieve broad protection through vaccination.

Methods: The immunogenicity of a norovirus type GII.4 “consensus” VLP that was engineered from the P domain sequences of three distinct naturally-occurring time-based GII.4 strains was examined for its ability to induce cross-reactive immune responses against different noroviruses using monovalent and bivalent formulations2.

Results: Rabbits immunized with different GII.4 Consensus VLP formulations developed high serum antibody titers against VLPs derived from several distinct wild-type GII.4 viruses, including some that had been circulating over 30 years ago, with the highest homologous and heterologous antibody titers elicited following immunization of animals with the bivalent vaccine via the intramuscular route2.

Conclusions: Our data suggest that both the use of genetically engineered norovirus VLPs that incorporate relevant epitopes from multiple strains and the use of vaccine formulations representing both the GI and GII norovirusgenogroups increase the breadth of the immune response to a broad set of variants within a genotype. We therefore consider these approaches as valuable methods for the rational design of VLP-based human norovirus vaccines.

References:
Immunogenicity and Protective Efficacy of a Multi-Epitope Vaccine Composed of Ebola Virus and Venezuelan Equine Encephalitis Virus HLA Class II T-Cell Epitopes in HLA Transgenic Mice

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Objective: Illustrate how to produce multi-pathogen biodefense vaccines by reverse vaccinology.

Background: Ebola virus (EBOV) and Venezuelan equine encephalitis virus (VEEV) are NIAID high priority biothreat pathogens. Currently, there are no licensed vaccines or therapeutics to prevent or treat EBOV and VEEV infection in humans. We employed advanced immunoinformatics to develop a human T-cell epitope-driven vaccine for EBOV and VEEV.

Methods and Results: The EpiMatrix algorithm was used to predict putative HLA Class II T-cell epitopes present in the envelope glycoproteins and nucleoproteins of EBOV strains Zaire and Sudan and the structural proteins of VEEV subtype IAB. Five putative Class II T-cell epitopes that provide coverage across eight archetypal Class II alleles were chosen for each of the five analyzed antigens. Class II HLA binding assays confirmed the sequences to be promiscuous binders. A multi-epitope vaccine was constructed and evaluated for immunogenicity and protective efficacy using a DNA-prime/peptide-boost vaccination strategy in HLA DR3 transgenic mice. Vaccine immunogenicity was observed for many individual epitopes in IFN-γ ELISpot assays. Interestingly, EBOV- and VEEV-specific antibody responses were elicited, likely due to overlap between T-cell epitope and linear B-cell epitope sequences. Partial protection against a lethal aerosol VEEV challenge was observed in mice receiving the multi-epitope DNA vaccine, similar to that observed for a whole-antigen VEEV vaccine. In contrast, mice receiving the multi-epitope DNA vaccine did not protect against lethal EBOV challenge.

Conclusions: The results of our studies provide important early proof-of-concept for a T-cell epitope-driven approach to vaccine design for bioterror agents. We are currently completing studies to evaluate the immunogenicity and efficacy of a multi-epitope DNA vaccine that also contains putative HLA Class I EBOV and VEEV T-cell epitopes.

Supported by JSTO-CBD/DTRA Projects R.R.0001_07_RD_B and CBM.VAXPLAT.04.10.RD.003.

References:


Evaluation of Canadian Workplace Policies Used to Promote Influenza Vaccination among Healthcare Personnel

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Objective: Understand the role of policies and the use of evidence-based policies in improving healthcare personnel influenza immunization (HPII) programs in an effort to understand the key elements of effective HPII policies.

Background: Poor healthcare policies hinder the implementation of effective interventions. Given the sub-optimal rates of healthcare personnel influenza immunization (HPII) in Canada, this study is examining the role of policies and the use of evidence-based policies in improving HPII programs in an effort to understand the key elements of effective HPII policies.

Methods: From the results of two national surveys, we identified a mix of organizations with high HPII rates. We conducted a detailed analysis of 19 organizational policies. The analysis was done using the Bardach framework and informed by the evidence conducted through the program of research of the Canadian Healthcare Influenza Immunization Network (www.chiin.ca).

Results: Nineteen organizational policies were analyzed with a mix of acute care hospitals, continuing care, and mixed (i.e., regional health authorities) organizations. Overall policy strengths included identification of personnel groups covered by the policy (14/19); identification of personnel responsible for the policy (11/19) and outbreak management provisions (15/19). Weaknesses included missing linkages to organizations’ mission (1/19) and poor communication planning (3/19). All policies were missing provisions for rate calculation, reporting requirements, team membership, role models, monitoring, or evaluation.

Conclusions: We will explore these strengths and weaknesses further by interviewing key stakeholders in healthcare organizations and policy management and will report on this at NFID Vaccine Conference in April 2013. There is a significant gap between existing best-practice evidence recommendations and existing HPII policies.

Reference:
Objective: Discuss how immunization polices requiring documentation of immunization for school attendance, may influence immunization data collection.

Background: Ontario legislation requires that Health Units (HUs) maintain immunization records for school pupils. For six antigens (diphtheria, tetanus, polio, measles, mumps, and rubella), students with incomplete immunizations must be vaccinated or provide an exemption statement (religious/conscientious or medical) or risk school suspension. We present coverage and exemption data for Ontario (population 13.3 million) for the 2011/12 school year.

Methods: In June 2012, immunization coverage data were requested of all 36 HUs for select publicly-funded vaccine antigens. A child was considered “covered” if all doses required for that age and antigen had been received (e.g., two doses of measles or mumps and one dose of rubella). Data reflected immunizations delivered as of June 30, 2012. HU-specific data were compiled to derive provincial estimates following validation.

Results: All 36 HUs participated. Among 7 year olds, vaccine coverage for tetanus, diphtheria, pertussis, and polio was 79.7%, 79.7%, 76.0%, and 79.2%, respectively. Measles, mumps, and rubella coverage was 89.1%, 88.6%, and 95.1%. Coverage for tetanus, diphtheria, pertussis, and polio among 17 year-olds was 82.6%, 82.6%, 67.7%, and 93.5% respectively. Measles, mumps, and rubella coverage was 94.8%, 92.9% and 96.7%. Among antigens required for school attendance, the proportion of 7 year olds reporting a religious/conscientious exemption ranged from a high of 1.8% (polio) to a low of 1.1% (both mumps and rubella). Among 17 year olds it ranged from 1.4% (polio) to 0.5% (rubella). There was great variability in exemptions by HU.

Conclusions: Lower coverage for pertussis, in contrast with other antigens contained within multi-component vaccines, may suggest antigens required for school attendance are the focus of information collection. Ontario has a small proportion of students declaring religious/conscientious objections to vaccines.

References:

Objective: Engage healthcare professionals and website bloggers in order to enhance awareness and increase the vaccination rate for all girls and women eligible for HPV vaccine.
Background: HPV vaccines can deter the viral infection which causes 70% of cervical cancer. However, barriers to acceptance range from lack of awareness of availability and benefits, to moral concerns about implications for sexual behavior. Communication to address these barriers requires creativity. This study analyzed a case in which HPV vaccine communication occurred organically on a social media site.

Methods: Observations were collected from the Chinese microblog SinaWeibo to discern whether health topics were posted. Descriptive statistics on the number of followers, gender ratio, and qualitative methods were applied to analyze microblog conversation patterns and possible influences on replies.

Results: The comparison of followers’ blog entries shows that attention paid to healthcare is relatively less than other topics, such as technology, shopping, and fashion. However, unexpectedly, a popular account called DealMoon on SinaWeibo was found to serve as a forum for exchanges on HPV vaccine. DealMoon provides the latest shopping news and over 60% of followers are females. Analysis showed that many replies and detailed discussion occurred across multiple blogs by multiple followers. This activity pattern prompted DealMoon webmasters to post a convenient link for an ideal HPV vaccine schedule.

Conclusions: Websites offering the latest fashion, fitness, or beauty news can inadvertently facilitate informative blogs and build online communities that attract female users with health issues. Health professionals as website bloggers could introduce vaccine news or respond to blogger conversations as expert sources. By transforming the medical vocabulary into ordinary chat, microblogs have unexpected potential to efficiently reach a motivated audience for vaccine education and attitude change. The SinaWeibo’s DealMoon case suggests deliberate reciprocal engagement of health professionals and website bloggers as a potential approach.

Reference:

The Use of a Massively Open Online Course (MOOC) for Global Vaccine Trial Education

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Objective: Discuss the benefits and limitations of MOOC courses as an educational option for clinical vaccine trials training.

Background: In October 2012, we launched a free MOOC entitled Vaccine Trials: Methods and Best Practices. This Johns Hopkins School of Public Health (JHSPH)/Coursera collaboration was an adaptation of our current online academic course offered through the JHSPH Center for Teaching and Learning.

Methods: The course targeted healthcare professionals interested in clinical trials and vaccine research. The 7-week course covered 12 topics and delivered 9 hours of lectures including in-video self-assessments. A Statement of Accomplishment was awarded to students scoring an average of 80% on 12 graded quizzes. Weekly announcements and discussion forums provided ongoing student-student and student-instructor interactions.
communication. Pre- and post-course surveys were conducted to investigate student characteristics and to evaluate the learning experience.

**Results:** The pre-course survey was sent to 9,835. Of the 19% who responded, 81% intended to earn a Statement of Accomplishment, 16% intended to watch all lectures and 3% planned to watch selected lectures. Twenty-one percent had a degree or other educational experience, 37% had some coursework in vaccines/research, 21% had no formal coursework, and 20% were new to the subject. The course averaged 2,500-3,000 active participants with 101,389 video views, 5,435 unique viewers and 3,220 unique quiz submissions. The 170 discussion threads had 840 posts and 17,531 views. Of the 11,546 enrolled students, preliminary calculations indicate that at least 1,238 (11%) will earn a Statement of Accomplishment.

**Conclusions:** MOOCs can reach a large global audience to educate the public and health professionals about vaccines. Success of a course in this learning environment changes from an academic or assessment-driven model to one including access and student engagement. Faculty resources, team-based teaching, and institutional technical support are required to create and deliver a dynamic course of this magnitude.

**References:**

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Jet Injection for Influenza: A Randomized Controlled Clinical Trial to Demonstrate Non-Inferiority of Jet Injection vs. Needle and Syringe for Administration of TIV Influenza Vaccine (Afluria® Season 2012-13)

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**Objective:** Discuss the non-inferiority demonstration design and the clinical experience of a jet injector device with split inactivated influenza vaccine.

**Background:** Currently, influenza vaccines in the US are not labeled for delivery by needle-free jet injection (JI), although JI has been used for decades for many vaccines, including conventional and live attenuated vaccines. Newly developed devices overcome the risk of cross-contamination, and can be adapted for subcutaneous, intramuscular, or intradermal administrations. There is a general acceptance, based on numerous small studies with a variety of vaccines¹³, that the immunological response generated by JI is comparable, with an acceptable safety profile, to needle and syringe (NS) administrations. However, this has not been formally demonstrated.

**Method:** Randomized (1:1 ratio), controlled, observer-blinded design. Safety: reporting 30 minutes post-administration, at seven, and through 28 days for immediate complaints, reactogenicity, systemic complaints, and spontaneously reported adverse events. Immunogenicity: analysis of serum HAI antibody specific for the three current vaccine strains, with six co-primary endpoints: Day 28 seroconversion rates and geometric mean titers (GMTs) for each of the three strains.
ABSTRACTS OF SUBMITTED ORAL PRESENTATIONS

Results: Greater than 1,200 subjects (aged 18-65) completed the study in Fall 2012. No SAE related to the administration mode have been reported on the first 1,200 subjects. Validation of the HAI assay was performed by Focus Diagnostics for the 2012-13 vaccine. The non-inferiority demonstration of JI to NS administration requires the upper 95% confidence bound for the true difference of proportions in seroconversion rates to not exceed 10% and the upper 95% confidence bound for the true ratio of the Day 28 GMTs to not exceed 1.5.

Conclusions: Results support a supplemental Biological License Application to include the use of JI with the same indication as NS for delivery of split inactivated influenza.

References:

A Novel Vaccine Presentation to Address the Challenges of Vaccine Delivery in Low-Resource Settings

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Objective: Review the technical research on the latest vaccine applications and public health impact of fast-dissolving tablets (FDTs) to (1) live attenuated oral vaccines containing multiple bacterial strains and (2) a veterinary vaccine against Newcastle disease.

Background: Innovative delivery systems could improve the distribution and administration of vaccines, especially in low-resource settings. A fast-dissolving tablet (FDT) packaged in a stackable blister sheet is an attractive option for formulating oral vaccines since it can be dissolved and swallowed or administered sublingually. Its reduced product volume could also result in a smaller cold chain footprint. In addition to live attenuated oral vaccines containing multiple bacterial strains, the FDT approach can be applied to veterinary vaccines for the low-cost oral immunization of “backyard” poultry by rural poor farmers in developing countries.

Methods: The applicability of the FDT approach was initially evaluated using a vaccine candidate for the prevention of enterotoxigenic Escherichia coli (ETEC)-induced diarrhea. The vaccine formulations were freeze dried in blister packs to produce FDTs. Bacterial viability was tested by assaying for colony-forming units. Evaluation of physical properties included structural integrity, dissolution time, moisture content, and glass transition temperatures. The tablet technology was also applied to a veterinary vaccine against Newcastle disease. Virus infectivity of the formulated vaccine was tested using a plaque assay and an EID50 assay. The immunogenicity and protection against a lethal challenge were evaluated in chickens.

Results: The ETEC and Newcastle disease vaccine tablets were successfully produced when freeze dried in blister packs. The viability of the bacteria and virus was respectively maintained with less than 0.5 log process loss and preserved for more than six months when stored at 2°C to 8°C. The final tablets were robust yet disintegrated in water in less than 10 seconds.
Conclusions: FDTs are a viable option for formulating vaccines for oral immunization and for veterinary vaccines delivered via the oral/ocular route.

References:

A Novel Intramuscular W805EC Nanoemulsion Adjuvanted Respiratory Syncytial Virus Vaccine Protects Cotton Rats against RSV Challenge

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Objective: Understand the role of adjuvants in eliciting protection against respiratory syncytial virus (RSV) infection and describe the importance of neutralizing antibody and Th1 in RSV vaccine development.

Background: W805EC nanoemulsion (NE) inactivated and adjuvanted RSV vaccine was administered intranasally (IN) in mice and cotton rats. The adjuvanted vaccine elicited high neutralizing antibodies and protected against RSV challenge. Here we report immunogenicity and efficacy in the cotton rat following intramuscular (IM) administration.

Methods: RSV L19 virus preparation containing 3.3µg F protein was formulated in 5% W805EC NE adjuvant, then 50µl were administered IM to six male Cotton rats at 0 weeks and boosted at 4 and 12 weeks. Sera were analyzed for anti-F antibodies and neutralization against RSV A2 strain. Animals were challenged IN with 5x10^5 PFU of RSV A2 and then sacrificed at day 4 or day 8 post challenge (PC) to assess viral clearance. Splenocytes were assessed for IFN-γ and IL-4 production.

Results: Intramuscular immunization with L19/W805EC vaccine was well tolerated and resulted in a significant production of anti-F antibody with a geometric mean (GM) of 168 µg IgG/mL at week 14. Neutralizing antibodies showed GM titers of 560 against RSV A2, with all vaccinated animals reaching a titer ≥100. All vaccinated animals were protected from challenge with no detectable virus in the lungs on day 4 while lungs from all naïve animals were positive for virus titers. IFN-γ levels trended higher in vaccinated animals whereas IL-4 levels did not approach statistical significance.

Conclusions: Intramuscular vaccination with L19 RSV vaccine inactivated and adjuvanted with W805EC generates a robust Th1/Th2 immune response which was protective against a heterologous A2 challenge in cotton rats. Neutralizing antibody and Th1 immune response may be important in eliciting protection from RSV.

References:
Development of a Multi-Valent Chimeric OspA Vaccine to Prevent Lyme Disease

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Objective: Explain how Lyme disease is transmitted, recognize the burden of Lyme Disease globally, and recognize the symptoms of disease.

Background: Lyme disease (LD) is the most frequent tick-transmitted disease in the northern hemisphere and is associated with multiple clinical manifestations. LD is caused by *Borrelia burgdorferi* in the US and by multiple *Borrelia* species in Europe and Asia. No human vaccine is available. A vaccine based on *Borrelia* Outer Surface Protein (OspA) serotype-1 was previously licensed in the US. However, multiple OspA serotypes are associated with disease in Europe.

Methods: A novel multivalent vaccine comprising protective epitopes from OspA serotypes 1-6 has been developed to prevent LD in the US and Europe. A putative hLFA-1-reactive epitope on OspA-1 was removed to eliminate the theoretical potential for T-cell cross-reactivity. The safety and immunogenicity of 30µg, 60µg or 90µg antigen doses, formulated with or without aluminum hydroxide, was investigated in 300 healthy adults. Subjects received three primary immunizations and a booster immunization. Antibody responses were determined by ELISA as well as *Borrelia* surface binding and killing assays. ANCOVA was used to determine the optimum dose and formulation.

Results: Adverse reactions were predominantly mild, with no vaccine-related serious adverse events. Substantial mean IgG antibody titers against all OspA serotypes were induced after the primary immunizations. The frequency and severity of systemic reactions was significantly lower in adjuvanted formulations, which also induced significantly higher post-booster antibody titers, compared to non-adjuvanted formulations. Vaccine-induced antibodies bound to and killed *Borrelia* strains representing all major human pathogenic species. The 30µg adjuvanted dose was determined to be the optimum formulation with respect to immunogenicity and tolerability.

Conclusions: The multivalent OspA vaccine is a promising candidate vaccine to prevent LD in the US and Europe, and possibly globally.

References:
Reduced Effectiveness of Pertussis Vaccine without an 18 Month Booster

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Objective: Understand the role of waning immunity in the pertussis epidemiology of children.

Background: A three-component acellular pertussis vaccine has been used in Australia for all doses since 1999. In 2003, the 4th dose at 18 months of age was removed and replaced with an adolescent booster, in response to increased case notifications in adolescents. Pertussis case notification rates age <10 years then increased markedly in 2008-11. This study aims to establish the effectiveness of pertussis vaccine in children aged 2 months to 4 years who had not received a 4th dose of pertussis vaccine.

Methods: A case control study was conducted. All cases notified between 2005 and 2009 in seven of eight Australian states and territories were included. Controls were obtained from the Australian Childhood Immunisation Register, matched on date of birth +/- one day, and state of residence, four controls randomly selected for each case. Vaccine effectiveness was estimated from odds ratios, produced by conditional logistic regression. Cases recorded as hospitalized were analyzed separately.

Results: There were 142 hospitalized pertussis cases with 698 controls, and 1,339 non-hospitalized pertussis cases and 5,797 controls. The effectiveness of three doses of vaccine in preventing hospitalization for pertussis was 86% (95% CI 77-92) age <1 year, 84% (65-93) at 1 year, and 49% (16-78) at 2-3 years of age. The effectiveness of three doses against non-hospitalized pertussis was 61% (45-73), 76% (66-82), and 64% (56-71) for ages <1, 1, and 2-3 years respectively.

Conclusions: Waning vaccine effectiveness, especially against more severe pertussis, may have been at least partly responsible for the increases in cases in children age 1-4 years.

References:
Immunogenicity of Heterologous H5N1 Influenza Booster Vaccination 6 or 18 Months after Primary Vaccination in Adults

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**Objective:** Understand immune responses to a prime-boost influenza vaccine as a strategy to protect against highly pathogenic influenza.

**Background:** Highly pathogenic avian influenza A/H5N1 viruses continue to circulate in birds and cause serious illness and death in infected humans.

**Methods:** In a randomized, observer-blinded study, adults ≥18 years of age (n=841) received 3.75 or 7.5 µg hemagglutinin antigen (HA) of an AS03-adjuvanted (adj) (AS03A or AS03B) A/Indonesia/5/2005 H5N1 (subclade 2.1) vaccine (priming), followed by the same HA dose of AS03-adj A/turkey/Turkey/1/05 H5N1 (clade 2.2) influenza vaccine (booster) 6 or 18 months (mo) after priming; an un-primed group received placebo at Day 0, and 3.75 µg HA of booster vaccine at 6 and 18 months. We report here vaccine response rates (VRR) for microneutralization titers (MN) and cellular immune responses (CMI). NCT00719043

**Results:** Corresponding with higher hemagglutination inhibition (HI) titers, VRRs were higher in primed versus un-primed subjects against the booster strain at 10 days post-booster at month 6 and month 18. CD4+ responses were also consistently observed 10 days post AS03-adj H5N1 vaccines and increased further after the 6 or 18 month booster. No induction of CD8+ T-cell responses was observed.

**Conclusions:** Heterologous vaccination with AS03-adjuvanted H5N1 vaccines demonstrated rapid and durable immunogenicity when given as a prime-boost schedule either 6 or 18 months apart.

**References:**


Objective: Application of a scale-down model of a legacy viral vaccine production process to implement improvements and optimizations for scale-up and future large-scale production purposes and technology transfer.

Background: A production process for inactivated polio vaccine (IPV) using attenuated Sabin poliovirus strains was developed based on the current large-scale Salk-IPV production technology. This activity for WHO plays an important role in the polio eradication strategy since the use of attenuated Sabin poliovirus strains, instead of wild-type Salk strains, provides additional safety during vaccine manufacturing. Development of a new Sabin-IPV opens opportunities to implement improvements in the process, and for antigen sparing by using adjuvants. In this way, a more affordable IPV for the post-eradication era can be achieved.

Methods: To achieve these objectives, a scale-down/scale-up strategy was followed using historical manufacturing data. Based on this, a 2.3-L scale-down model of the current 750-L bioreactors has been set up. This lab-scale process, both USP (cell and virus culture) and DSP (clarification, concentration, purification, and inactivation) unit-operations approximate the large-scale. Subsequently, using this scale-down model, a modified process using attenuated Sabin poliovirus strains, was developed. This process was used to produce Sabin-IPV (both plain and alum adjuvanted) batches under cGMP for the currently ongoing phase I/IIa safety and dose-finding clinical trial in naïve infants.

Results: The preceding safety and immunogenicity study in adults showed that Sabin-IPV induces an immunological booster response against three wild-type, and three Sabin, poliovirus strains without safety concerns. Concurrently, technology transfer to vaccine manufacturers in low and middle-income countries has started. In parallel, using the scale-down model, a research program was initiated to further reduce the cost per dose.

References:
Randomized Trial of Human Papillomavirus Vaccination Schedules among College Age Males

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**Objective:** Higher vaccination rates among college male students may be achievable with a more convenient dosing schedule.

**Background:** Quadrivalent human papillomavirus (HPV) vaccine, for protection against sexually transmitted HPV infection, is licensed for males age 9-26 years on a three-dose schedule (0, 2, and 6 months; standard). This schedule may be difficult to implement in a college calendar year, limiting vaccination rates in this age group. This study tested the non-inferiority of the immunogenicity of an alternate dosing schedule (0, 2, 12 months) to the standard schedule.

**Methods:** 220 males age 18-25 year old were randomly assigned to standard or alternate dosing schedules. Blood samples for both groups were drawn immediately prior to the first dose and 2-6 weeks after the third dose and analyzed for antibody titers using a Luminex immunoassay. Baseline seropositive values for any genotype were excluded. Geometric mean titers (GMTs) and two-sided 95% confidence intervals (CI) were calculated. A 1.5-fold or greater difference in the lower bound for the 95% CI for the third dose GMT ratio (LIGMTr) of the two schedules defined non-inferiority.

**Results:** Participants averaged 21.3 years old; 19.1% were non-white and 9.6% were smokers. Completion rate was 93%. Compared with the standard group, the titers for anti-HPV were non-inferior for HPV-11, -16, and -18 genotypes in the alternate schedule group with LIGMTr of 2.15, 1.53, and 2.15, respectively. HPV-6 was not non-inferior in the alternate group with an LIGMTr of 1.4.

**Conclusions:** A delayed third dose at 12 months is immunologically non-inferior for three HPV genotypes. Using alternate dosing schedules may result in higher vaccination rates among college male students.

**References:**
ABSTRACTS OF SUBMITTED POSTER PRESENTATIONS
Identification of EHEC-Specific Protective Antigens Using Whole Genome Approach
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Objective: Evaluate antigens specific to EHEC serotype that are putatively secreted or surface localized for their protective activity against EHEC infection in the murine model.

Background: Enterohemorrhagic E. coli (EHEC) O157:H7 are major human food-borne pathogens, responsible for bloody diarrhea and hemolytic uremic syndrome worldwide¹. Although substantial progress has been made to understand virulence mechanisms associated with the disease - there is still no effective vaccine available for humans against EHEC infections. Our goal was to identify EHEC-specific antigens by screening whole genome E. coli sequences that can be used as potential vaccine candidates.

Methods: EHEC O157:H7 strains EDL933 and Sakai, the non-pathogenic E. coli K-12 strain MG1655, and the commensal E. coli HS strain were used to perform a comparative bioinformatics analysis to acquire coding sequences (predicted to encode secreted or surface-expressed proteins), exclusive to the EHEC serotype. These sequences were analyzed for various physico-chemical characteristics of antigenicity, such as transmembrane regions, signal-peptides, sub-cellular localization, and adhesiveness. A sequence was assigned a given characteristic by generating a consensus from multiple programs for each. Further, they were subjected to B- and T-cell epitope predictions. Finally, sequences were ranked based on combined immunogenicity score from all predictions. The best “vaccine-prone” candidates were selected and cloned into pVAX1 vector. The protective ability of these potential DNA-vaccine candidates will be determined in our EHEC murine model of infection.

Results: Bioinformatics analysis rendered 25 high-scoring EHEC-specific protein sequences and 12 were selected for further evaluation based on their higher combined ranking as vaccine candidates.

Conclusions: We identified 25 DNA sequences as potential vaccine targets against EHEC infection using bioinformatics analysis and the vaccine properties of the top 12 are currently being evaluated in a murine model of EHEC O157:H7 infection.

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Process Development for a Live-Attenuated Respiratory Syncytial Virus Vaccine
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Objective: Use a statistical design of experiments approach for process development purposes to quickly define a process design space.

Background: Respiratory syncytial virus (RSV) is the leading cause of lower respiratory tract disease in infants and young children. A vaccine to prevent the high burden of disease caused by RSV is urgently needed, but not available. At the Institute for Translational Vaccinology (InTraVacc) a new vaccine against RSV is being developed. This vaccine is a live-attenuated vaccine that is administered intranasally. RSV presents two major glycoproteins
on its surface: the fusion (F) protein and the attachment (G) protein. While the F protein is indispensable for virus replication and growth, the G protein is non-essential for virus replication in vitro\(^1\).

**Methods & Results:** Using reverse genetics, recombinant (r)RSV and a RSV lacking the G gene (ΔG) were constructed based on a clinical RSV isolate (strain 98-25147-X)\(^2\). Next, a Vero cell line expressing the G-protein was constructed. When replicating ΔG-RSV on this Vero-G cell line a G-complemented GΔG-RSV virus is produced. This virus particle contains the G-protein on its surface but not in its RNA genome. It is anticipated that a good immune response will result from vaccination with the GΔG-RSV while the virus remains highly attenuated. Presently, a vaccine production process is being setup to prepare for pre-clinical and phase I clinical studies. Culture conditions for the Vero-G cell line and efficient virus production, both using animal-component-free culture media under well-controlled conditions in stirred-tank type bioreactor vessels, are being developed using a design of experiments approach.

**Conclusions:** The unique approach of using the statistical design of experiments for process development allowed fast screening of factors influencing the virus culture yields and harvest quality with respect to subsequent virus purification opportunities.

**References:**

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**Helicobacter pylori** Vaccine Development by Reverse Vaccinology

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**Objective:** Demonstrate integration of genomics, informatics, and immunology for vaccine candidate selection.

**Background:** *H. pylori* infection promotes development of gastric carcinoma, lymphoma, and peptic ulcer disease in a subset of the *H. pylori*-colonized population. Animal studies suggest that *H. pylori* may reprogram mucosal and systemic immunity resulting in increased regulatory T-cell function, underscoring the need to carefully select immunogens for *H. pylori* vaccination. We set out to comprehensively characterize the *H. pylori*-specific peripheral T-cell response to HLA class II epitopes to aid the design of a vaccine without adverse sequelae.

**Methods & Results:** Seven genomes of genetically diverse *H. pylori* strains were computationally screened to identify immunogenic consensus sequences derived from the core genome. Of the 90 highest-scoring HLA class II epitopes, 76% bound strongly to a panel of 6 HLA class II alleles, representing >90% of the global human population. The ability of individual peptides to induce interferon-gamma (IFNγ) from peripheral blood mononuclear cells (PBMCs) was then measured in ex vivo ELISpot assays using cells from 14 *H. pylori*-infected and nine *H. pylori*-negative subjects. The average number of spot-forming cells/million PBMCs was 44.1 ± 5.7 in *H. pylori*-positive subjects versus 7.8 ± 1.0 in uninfected subjects (p<0.0001). On average each peptide was
recognized by a mean (±SE) of 19.7% (± 1.2%) of \textit{H. pylori}-infected versus 13.9% (± 1.3%) of uninfected subjects (p<0.001).

\textbf{Conclusion:} A panel of immunogenic consensus sequences has been chosen through immunoinformatic screening of multiple \textit{H. pylori} genomes, validated by HLA binding assays and shown to be functional in IFN\textgamma ELISpot assays. Our goal is to use this panel of peptides to formulate a multi-epitope T-cell based vaccine for therapeutic vaccination and to probe the immunoregulatory effect of \textit{H. pylori} infection.

\textbf{References:}

\textbf{Evaluation of Immune Response against \textit{Neisseria meningitidis} B Using DDA-BF as Adjuvant}

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\textbf{Objective:} Explain how adjuvants modulate the immune response against \textit{N. meningitidis} B antigens dioctadecyldimethylammonium bromide (DDA-BF) and aluminum compounds (H.A.).

\textbf{Background:} Vaccination against meningococcal disease is recognized as the best prophylactic means against mortality and cannot be applied to the serogroup B due to its polysaccharidic capsule. Outer membrane vesicles (OMVs) of \textit{N. meningitidis} have emerged as an alternative.

\textbf{Methods:} Bilayer fragments of the cationic lipid dioctadecyldimethylammonium bromide (DDA-BF) obtained by the dispersion in the aqueous solution, low ionic strength, after sonication were used as adjuvant, with the advantage of requiring a lower lipid concentration than traditionally used. Alum remains the only currently licensed adjuvant. Complex of 2 µg of OMVs of \textit{N. meningitidis} in 0.1 mM of DDA-BF were stable, showing an average diameter and optimum load for the antigenic presentation. Immunogenicity tests were carried out in mice, being the OMVs of \textit{N. meningitidis} associated with DDA-BF and compared to alum. The evaluation of animal serum cross-reactivity was held 60 days after the first immunization. Different meningococcal strains of Brazil were tested by Dot-ELISA: 120 strains from 2011 and 2012.

\textbf{Results:} Using immunoblot, we reviewed the cross-reactivity against OMVs of \textit{N. meningitidis}, also evaluated by ELISA. Additionally, we evaluated the individual response of IgG antibodies produced. Of 120 strains analyzed using Dot-ELISA, 98% of \textit{N. meningitidis} showed reactivity with polyclonal serum from immunized mice with \textit{N. meningitidis} (OMVs DDA-BF) compared to 10% reactivity with alum. The serum proteins of cross reactivity presented in the range of 160-20 kDa. Moreover, the antibodies induced from a single immunization with OMV/DDA-BF had an intermediate avidity, but antibodies with a similar avidity were only induced by OMV/alum after two doses.

\textbf{Conclusions:} The compound obtained with the new adjuvant was immunogenic in mice, opening prospects for the use of a new adjuvant meningococcal vaccine.
Delayed-Type Hypersensitivity Response is a Predictor of Cell Immunity after Immunization with Neisseria meningitidis Outer Membrane Antigens

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Objective: Use delayed-type hypersensitivity (DTH) to evaluate the immune response to a new adjuvant and analyze the types of cells in inflammatory infiltrate.

Background: In our studies, immunizing with outer membrane vesicles (OMVs) of N. meningitidis (alum) or cationic lipid dioctadecyldimethylammonium bromide (DDA-BF) as adjuvants allows study of the specific immune response.

Methods: DDA-BF can be obtained by dispersion of the white powder in an aqueous solution at low ionic strength after sonication at a temperature below 60°C. Delayed-type hypersensitivity (DTH) responses are the most common, most widely available measurements, and one of the few measurements used to determine effective immunization. However, little is known about the ability of DTH to actually reflect the development of specific immunity after vaccination. OMV antigen is introduced intradermally, and swelling in the footpads of the animals vaccinated with outer membrane vesicles of N. meningitidis at 24 hours post-injection indicates a positive reaction. A footpad assay was used to measure the DTH of mice to N. meningitidis (OMVs) day 5, 15, and 60 after immunization in outbred mice. On day 60, the spleen and footpad of mice were extracted and fixed in formalin and stained with hematoxylin and eosin.

Results: DTH to OMVs was observed on day 5 and 15 and reached its maximum on day 60 post-vaccination. A single dose of OMV/DDA-BF was sufficient to induce a (DTH) response. An intense inflammatory infiltrate was noted, constituted predominantly by neutrophils, lymphocytes, and macrophages at day 60. There was no significant difference when comparing the two adjuvants. Histopathologic examination of the spleen revealed a predominance of lymphocytes and neutrophils.

Conclusions: The DTH response is a technically simple test and reflects the development of systemic antigen-specific immunity. The results suggest that further investigation of cell-mediated immune reactions, to a better understanding of events underlying the development and expression of immunity.
Serum Levels of Th1 and Th2 Cytokines Produced in Nigerian Children with Measles Vaccine Failure in Measles Outbreak in Ogun State Nigeria

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Objective: Describe the pathogenesis of measles infection during an outbreak in a situation of vaccine failure in vaccinated children to evaluate the degree of inflammatory reaction developed despite their immunization against measles.

Background: Measles cases in vaccinated children frequently occur in older children due to waning immunity with age. When this occurs, infection is reported to be of reduced severity and mild clinical symptoms, but occurrence of measles vaccine failure in younger children can portend danger. This informed our study of the pathogenesis of measles infection in children with measles vaccine failure in a measles outbreak in Ogun State, Nigeria. We studied the pattern of infection, level of protection in the vaccinated children, the serum cytokines, and associated clinical symptoms across the ages of infected children.

Methods: Sixty-five infected children were tested for IgM and IgG antibodies to establish measles infection and protection. Associated clinical presentations were evaluated and serum cytokines were assessed using ELISA technique.

Results: The 65 children had IgM antibody confirming measles infection, while the 37 matched control group had none. Out of 65 infected children, 31 were vaccinated with 10 (32.3%) having IgG, while 34 were not vaccinated and of these, 19 (55.9%) had IgG probably developed from subclinical infection. Of the 31 vaccinated children, 17 developed severe infection with 15 (88.2%) less than 5 years of age and they developed high inflammatory cytokines (IL-1β, IL-12, and TNF-α), while 14 developed mild infection. But only two children above 5 years of age developed severe infection with high inflammatory cytokines. All the vaccinated children that developed severe infection had high TGF-β cytokine. This pattern of Th1/Th2 cytokines observed in the vaccinated group was not different from unvaccinated children.

Conclusions: There was no effectiveness of measles immunization in the vaccinated children. This can be dangerous especially in younger children as observed in this study.

References:
Oral DNA Vaccination Encoding Turkey Coronaviral Spike Protein Containing Neutralizing Epitope Delivered by Attenuated Salmonella Elicits Protective Immune Responses in Turkeys

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Objective: Examine the efficacy of DNA vaccine carrying by attenuated Salmonella against turkey coronavirus for practical application in the turkey industry.

Background: Turkey coronavirus (TCoV) causes atrophic enteritis and uneven growth in turkey flocks.

Methods: Oral DNA vaccination encoding TCoV spike (S) protein containing neutralizing epitopes delivered by attenuated Salmonella typhimurium SL1344 aroA mutant was evaluated. In vitro stability of plasmid in transformed Salmonella after serial passages without ampicillin was accessed by the inserted gene-specific PCR and the expression of encoded S fragments in chicken macrophages infected with transformed Salmonella. Oral immunization of 7-day-old turkey poults with 10¹⁰ colony forming unit of transformed Salmonella with the plasmid encoding for TCoV S₄₇₆₋₅₂₀, S₄₈₂₋₆₇₈, or S₁₋₅₇₃ was followed by second dose of transformed Salmonella (group 1 to 3) or intramuscular injection of 100µg purified S₄₇₆₋₅₂₀ (group 4) or S₄₈₂₋₆₇₈ (group 5) in 14-day-old turkey poults.

Results: After viral challenge, the protection efficacy was examined by enteritis-related alterations, TCoV infection detected by immunofluorescent antibody assay (IFA) in ileum, S protein-specific antibody level measured by enzyme-linked immunosorbent assay (ELISA), and virus neutralization (VN) titers. The data were analyzed by independent samples t-test or one-way ANOVA (SPSS). All plasmids remained stable in attenuated Salmonella after nine passages without the selection of ampicillin and the plasmid-encoding S fragments were expressed in chicken macrophages infected with transformed Salmonella. In vaccinated turkeys, the VN titers ranged from 1:4 to 1:64, the S-specific antibody level increased before viral challenge and no enteritis-related alterations were observed after challenge. According to the results of IFA, group 5 showed the highest protection, 40%, followed by groups 2 and 3.

Conclusions: Conclusively, oral immunization with DNA vaccine encoding TCoV S fragment containing neutralizing epitopes delivered by attenuated Salmonella can stimulate partially protective immune responses against the infection of TCoV.

References:

Aerosol Vaccination against Ebola Virus

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Objective: Determine the feasibility and efficacy of aerosol delivery of a respiratory vaccine.

Background: The increased incidences of Ebola virus (EBOV) outbreaks in Africa and the threat of global outbreaks heighten the need for safe, needle-free vaccines enabling prompt broad-scale immunization against this virus. Previously, we demonstrated that a mucosal paramyxovirus-vectored vaccine based on the human parainfluenza virus type 3 expressing the glycoprotein (GP) of EBOV (HPIV3/EboGP) generated a robust neutralizing antibody response and provided 100% protection against lethal EBOV challenge in Rhesus macaques when delivered as a liquid via the combined intranasal/intratracheal (IN/IT) route.

Methods: In the present study, Rhesus macaques were administered with an aerosolized form of the vaccine, which represents an ideal and feasible means of delivery that has never been trialed for hemorrhagic fever viruses. Groups of macaques received the 1) HPIV3/EboGP vaccine, delivered to the respiratory tract as a small particle (2.5-4.0 μM) aerosol using an Aeroneb® Lab Nebulizer, 2) as a liquid, 3) the intramuscular Venezuelan equine encephalitis virus replicon vaccine expressing EBOV GP, previously shown to protect macaques against EBOV, and 4) the control empty HPIV3 vector via the IN/IT route.

Results and Conclusions: The EBOV-specific IgG and IgA and EBOV-neutralizing serum antibody responses to aerosolized HPIV3/EboGP were equal to or exceeded that observed in the group which received the liquid form. Current studies focus on the cell-mediated immune response exhibited in blood and tissues of the vaccinated animals, thus providing insight into the correlates of protection. The ability of a single aerosolized HPIV3/EboGP dose to confer protection against EBOV is under evaluation in a lethal challenge experiment given that robust neutralizing antibody titers were generated after the first dose. These results warrant further studies on aerosol delivery of the respiratory vaccine against EBOV.

References:
Immunogenicity Assessment of In Silico-Selected T-Cell Epitopes for a Burkholderia Biodefense Vaccine

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Objective: Describe the development of an epitope-driven biodefense vaccine for Burkholderia by using informatics tools, in vitro binding assay, and mouse model.

Background: Burkholderia pseudomallei (BPM) and Burkholderia mallei (BM), the causative agents of melioidosis and glanders, are Category B pathogens due to their potential use in bioterrorism. Burkholderia cepacia (BC) causes severe disease in cystic fibrosis patients. No licensed vaccines are available for these pathogens. We are developing a single Burkholderia “Multipathogen” vaccine that is effective against all three.

Methods: We used our in-house immunoinformatics tools to screen 31 Burkholderia genomes for immunogenic consensus sequences (ICS) that are enriched for promiscuous CD4+ T-cell epitopes and conserved in at least two Burkholderia species. The ICS peptides were evaluated for HLA binding in vitro and for immunogenicity in Balb/C mice (peptide immunizations) and in HLA transgenic mice (DNA-prime/peptide-boost immunizations).

Results: 2,880 highly conserved ICS were identified. Of these, 70 ICS were evaluated for HLA binding. All of the ICS bound to at least one HLA class II allele in vitro, 92.7% bound to at least two alleles, 82.9% to three. 75.6% of the overall binding results were concordant with the immunoinformatics predictions. 28.6% ICS elicited significant IFN-γ responses (p<0.01) in Balb/C mice (by ELISpot). Of these, 80% ICS bound to all five HLA alleles, 15% bound to four alleles, and 5% bound to three alleles. In HLA DR3 transgenic mice, significant IFN-γ responses (p<0.01) were elicited by 11% ICS. Of these, 60% bound to five HLA alleles and 40% bound to four alleles.

Conclusions: This study illustrates the power of immunoinformatics tools for efficiently isolating high quality vaccine candidates from an enormous genome sequence space. The next step will be to evaluate the string-of-beads multi-epitope vaccine for protective efficacy in HLA transgenic mouse challenge studies.

References:
be vaccinated. Data are needed on whether these rates differ by region, especially in areas with high minority concentrations.

**Methods:** Women 18-26 years of age seeking prenatal care in a publicly funded clinic were interviewed between January and April 2012 regarding their HPV vaccination status.

**Results:** Overall, 11.9% (56/469) stated they had initiated and 7.6% (32/469) completed the vaccine series. Ethnic differences were noted with 20% of non-Hispanic whites, 14.6% of blacks, and 7.6% of Hispanics ($P=.002$) initiating the vaccine and 13.2%, 7.3%, and 4.0% ($P=.006$) completing all three doses, respectively. Among Hispanics, those who had moved to the US within the past 5 years ($n=70$) had the lowest initiation (4.3%) and completion (1.4%) rates. Older women were less likely to be vaccinated; each one year increase in age resulted in a 17% decrease in odds of initiation (OR 0.83, 95% CI 0.73-0.93) and 20% decrease in completion (OR 0.80, 95% CI 0.68-0.93).

**Conclusions:** HPV vaccine uptake and completion was lower than the national average among women in south Texas. Hispanics who moved to the US during past 5 years had the lowest vaccination rates. Intervention programs are needed to increase HPV vaccine uptake among this vulnerable population.

**Reference:**

**P11** WITHDRAWN
Efficacy of Live-Attenuated Influenza Vaccine against Moderate to Severe Influenza Illness Compared With Efficacy against Mild Influenza Illness in Children

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Objective: Describe Ann Arbor strain live-attenuated influenza vaccine (LAIV) efficacy in children against moderate to severe and milder influenza.

Background: In an efficacy study of inactivated influenza vaccine (IIV) in children 3-8 years of age, vaccine efficacy (VE) compared to placebo was 73% against moderate to severe influenza (fever >39°C, acute otitis media, or lower respiratory tract illness) and 42% against milder influenza not meeting these criteria (Overall VE=55%).¹ Prior efficacy studies of LAIV were not evaluated in this manner.²

Methods: Two LAIV studies collected data in a manner that enabled analysis: a 2-year placebo-controlled study in children 15-71 months of age and a 1-year IIV-controlled study in children 6-59 months of age. Efficacy was stratified by illness severity and calculated for children ≥24 months of age for all strains regardless of antigenic match.

Results: Compared with placebo, the efficacy of LAIV against culture-confirmed moderate to severe influenza was 95.4% (95% CI: 88.5, 98.6) in year 1 (N=1330) and 88.5% (95% CI: 76.8, 94.9) in year 2 (N=1358); for culture-confirmed mild illness, efficacy was 90.3% (95% CI: 74.3, 97.1) and 82.8% (95% CI: 49.5, 95.2) in years 1 and 2, respectively. Compared with IIV (N=2083), the relative efficacy of LAIV was 52.2% (95% CI: 30.6, 67.6) against culture-confirmed moderate to severe illness and 43.6% (95% CI: 25.9, 57.4) against culture-confirmed mild illness.

Conclusions: LAIV provided greater efficacy than IIV in children against moderate to severe influenza illness and against milder influenza illness. Although efficacy of both vaccines trended higher against more severe influenza illness, LAIV efficacy was also high against mild influenza illness (83%-90%). Differences in vaccine-induced protection between IIV and LAIV can affect influenza morbidity and transmission among vaccinated children.

Sponsored by MedImmune, LLC.

References:
The Development of Serum Bactericidal Assays to Evaluate *Salmonella* Vaccines


Center for Vaccine Development, University of Maryland, School of Medicine, Baltimore, MD

**Objective:** Explain the role of serum bactericidal activity in protective immunity and mechanisms involved in serum bactericidal activity against *Salmonella* infection.

**Background:** Enteric fever, caused by *Salmonella enterica* serovars Typhi, Paratyphi A, and B, remains a challenging disease in developing nations where poor sanitation compromises sources of food and water. Non-Typhoidal *Salmonella* (NTS) serovars Enteritidis and Typhimurium are also among the most commonly isolated organisms from the blood of children with sepsis in Sub Saharan Africa. Several typhoidal and non-typhoidal *Salmonella* vaccines are being developed as countermeasures and require thorough evaluation including functional antibody assays such as opsonophagocytosis and serum bactericidal activity to better understand their *in vivo* effectiveness.

**Methods:** No standardized method of evaluation exists to measure antibody-mediated bactericidal activity induced by *Salmonella* vaccines. Through a systematic approach, we developed immunological assays that allowed us to obtain end-point serum bactericidal antibody titers to assess the immunogenicity of *S.* Typhi, *S.* Paratyphi A, *S.* Typhimurium, and *S.* Enteritidis vaccine candidates that have been evaluated in pre-clinical studies.

**Results:** Baby rabbit complement proved to be the superior complement source for measuring antibody-dependent serum bactericidal activity compared to complement from guinea pig, horse, goat, pig, calf, or adult rabbit. Log phase cultures as opposed to stationary phase cultures were optimal for evaluating serum bactericidal activity of *S.* Enteritidis, *S.* Typhimurium, and *S.* Typhi due to the length of the lipopolysaccharide. In contrast, *S.* Paratyphi A was equally susceptible to complement when grown to either stationary or log phase. *S.* Paratyphi A was the most sensitive to killing, followed by *S.* Typhi, *S.* Typhimurium, and *S.* Enteritidis.

**Conclusion:** The serum bactericidal assays that we have developed are now poised to be further validated and used by the *Salmonella* vaccine community.

**References:**

**Cross-Reactive, Linear B-Cell Epitopes in the Influenza Virus Matrix Protein 1**

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**Objective:** Evaluate antibody responses to the conserved influenza matrix protein.

**Background:** Little is known about the B-cell epitopes in conserved internal influenza proteins or their role in viral immunity and immunopathogenesis. Based on epitope information present in the Immune Epitope Database (IEDB) only one out of four matrix 1 protein B-cell epitopes of the 2009 pandemic H1N1 (pH1N1) virus was predicted to be conserved¹. In this study we have used *in-silico* and wet lab methods to validate these findings.

**Methods:** Immunogenic regions and linear B-cell epitopes on the influenza matrix 1 protein were predicted by antigenic index prediction and the IEDB B-cell epitope prediction tools. Sequential anti-sera against two pH1N1 strains (A/CA/04/09/H1N1 and A/Mex/4108/09/H1N1) and four contemporary swine influenza virus strains (A/IA/04/H1N1, A/MN07/HuH1N1, A/MN/03/H1N2, A/OH07/H1N1) were raised by experimental infection of piglets with the corresponding viruses. 15-mer synthetic peptides with a five amino acid overlap spanning the pH1N1 matrix protein were used to map linear B-cell epitopes.

**Results:** Five of the 10 immuno-dominant regions that were identified had strong antibody binding activity (>5 S/N ratio). All regions had broad cross reactivity to the swine H1 virus strains tested. Single amino acid changes in the sequence did not alter cross-reactivity. The Jameson-Wolf Antigenic Index, BiPred, and EliPro predicted the five major immunodominant regions accurately, but showed differences in predicting the other regions.

**Conclusions:** Previously unmapped linear B-cell epitopes in the influenza matrix protein 1 were identified. While conformational epitopes were not studied, all of the identified linear epitopes were conserved in the virus strains that were tested.

**Reference:**


**Construction of a Candidate Vaccine Strain against Helicobacter pylori, Expressing HpaA Antigen Present on Non-Toxigenic V. cholera**

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**Objective:** Gain further knowledge and exchange ideas based on the recent scientific reports and findings in the field of vaccinology, as presented during the conference.

**Background:** Infection with *Helicobacter pylori* is closely associated with development of gastric cancer. We believe that vaccination against *H. pylori* is an attractive alternative for controlling *H. pylori* infection, especially for the populations which are at the highest risk, i.e. in developing countries. *H. pylori* adhesion A (HpaA), one of
the virulence factors of *H. pylori*, has been shown to mediate colonization and also to confer protection against *H. pylori* infection in mice.

**Methods:** A therapeutic whole cell vaccine against *H. pylori* may be delivered to the stomach or proximal small intestine to induce a strong immune response in the gastric mucosa. Since *H. pylori* bacteria are inflammatogenic and also difficult to culture, we have constructed a candidate vaccine consisting of non-toxicigenic *V. cholerae* strain expressing high levels of HpaA, alone or together with CFA/I, a main colonization factor of enterotoxigenic *Escherichia coli* (ETEC), which binds to epithelial cells of the small intestine in human. Prophylactic immunization of mice with the inactivated recombinant strain and the reference strain Hel305 showed specific serum antibody responses.

**Results:** Challenging of the mice which were immunized with the recombinant strain, with the *H. pylori* model strain SS1, showed significant protection when compared with non-immunized control mice, although the protection was less pronounced than when mice had been immunized with the Hel305 strain.

**Conclusions:** These results indicate that our approach of heterologous expression of *H. pylori* antigens is promising, although further experiments are necessary to address whether the inactivation of the recombinant strain has reduced the protective capacity of the HpaA. Moreover, incorporation of additional *H. pylori* antigens in recombinant vaccine constructs, to increase the protective capacity of the vaccine strains, is examined.

**References:**


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**Phase 1 Study of Pandemic H1 DNA Vaccine in Healthy Adults**

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**NIH/NIAID/VRC, Bethesda, MD**

**Objective:** Learn the results of a Phase I study evaluating safety and immunogenicity of the pandemic H1 DNA vaccine and considerations for DNA prime-inactivated boost vaccine regimens.

**Background:** On 4/26/09 the US declared the 2009 H1N1 pandemic influenza a public health emergency. The IND for VRC-FLUDNA057-00-VP, a single plasmid DNA vaccine encoding hemagglutinin (HA) protein of the 2009 pandemic A/California/09(H1N1) influenza, was submitted on 7/9/09, and first vaccination administered in the VRC 308 trial on 8/24/09.

**Methods:** Twenty subjects received three H1 DNA vaccinations (4 mg intramuscularly with Biojector®) at 4-week intervals. When the licensed pandemic H1N1 monovalent inactivated vaccine (MIV) became available, 18 subjects opted to receive an MIV boost. The interval between the last H1 DNA injection and MIV boost ranged
from 3-17 weeks. Vaccine safety was assessed by clinical observation, laboratory parameters, and 7-day Diary Cards for reactogenicity. Antibody responses were assessed by ELISA, HAI, and neutralization assays.

**Results:** Vaccinations were well-tolerated, with no serious adverse events. Most subjects (90%) reported mild local reactogenicity. For systemic reactogenicity, 25% reported none, 60% reported mild, and 15% reported moderate symptoms. As evaluated by HAI, 6/20 (30%) developed positive responses at 4 weeks after last H1 DNA injection (GMT=16, 95% CI=9-27), and 13/18 (72%) at 4 weeks after the MIV boost (GMT=180, 95% CI=86-377). Similar results were detected in neutralization assay, 6/20 (30%) had positive response after H1 DNA injections (GMT=117, 95%CI=78-175) and 12/20 (60%) after MIV boost (GMT=313, 95%CI=182-539).

**Conclusions:** The investigational pandemic H1 DNA vaccine demonstrated the potential for rapid DNA vaccine production and was well-tolerated, but had limited immunogenicity as a single agent. The 2009 H1N1 strain has been included in trivalent seasonal influenza vaccines 2010-12. Based on promising results with other DNA prime-inactivated vaccine boost regimens, evaluation of the H1 DNA plasmid as one component of seasonal HA DNA-TIV boost regimens continues.

**References:**

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**Full Adjuvant Activity of the Whole Cell Pertussis Vaccine in Combination with the Pneumococcal Surface Protein A Requires Pertussis Toxin**

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**Objective:** Evaluate the pertussis components that are responsible for the adjuvant activity when combined to pneumococcal antigens.

**Background:** Despite the availability of conjugate vaccines against *Streptococcus pneumoniae*, this bacterium remains a significant cause of death in children less than 5 years old, worldwide. PspA is the best characterized antigen for the composition of pneumococcal protein vaccines. Effective immune responses against PspA in mice have been characterized by the induction of Th-1 immunity, with PspA-specific IgG2a and IFN-γ. Such response can be generated by the use of the whole cell pertussis (wP) as adjuvant. In this work we aimed to characterize the molecular basis of the adjuvant activity of wP in combination with PspA.

**Methods:** BALB/c mice were immunized through the nasal route with PspA combined with inactivated wild type *B. pertussis* (the wP vaccine produced at Instituto Butantan, Brazil and the BPSM strain, which is derived from the Tohama strain) or attenuated mutants that either present decreased expression of different virulence factors (BPLOW) or lack the pertussis toxin (PT) gene (BPRA).

**Results:** One single dose of PspA combined with wP or BPSM induced high levels of systemic anti-PspA IgG with balanced IgG1:IgG2a ratios. These formulations afforded protection to 83% of mice against an intranasal lethal dose of the homologous bacteria.
challenge with the ATC6303 pneumococcal strain. In contrast, the combination of PspA with BPLOW or BPRA preferentially induced the production of anti-PspA IgG1. Survival in these groups of mice was higher than in the group immunized with PspA alone, but not statistically significant. Importantly, a single nasal dose of PspA combined with PT conferred significant protection against the pneumococcal challenge and the humoral immune response was characterized by balanced anti-PspA IgG1:IgG2a ratios.

**Conclusion:** In conclusion, PT as adjuvant can elicit an optimized immune response against PspA.

**References:**


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**Improved Adjuvanting of Seasonal Influenza Vaccines: Pre-Clinical Studies of MVA-NP+M1 Co-Administration with Inactivated Influenza Vaccine**

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**Objectives:** Discuss the current limitations of seasonal influenza vaccines to demonstrate the need for improved vaccines and vaccination strategies.

**Background:** Licensed seasonal influenza vaccines induce antibody responses against influenza hemagglutinin and are limited in their ability to protect against different strains of influenza. Cytotoxic T lymphocytes (CTLs), recognizing the conserved internal nucleoprotein (NP) and matrix protein (M1), are capable of mediating a cross-subtype immune response against influenza. Modified vaccinia virus Ankara encoding NP and M1 (MVA-NP+M1) is designed to boost pre-existing T-cell responses in adults in order to elicit a cross-protective immune response.

**Methods & Results:** We examined the co-administration of hemagglutinin (HA) protein formulations and candidate MVA-NP+M1 influenza vaccines in three animal species. Antibody titers post-immunization were measured by ELISA in murine, avian, and swine models. Here we demonstrate that MVA-NP+M1 can act as an adjuvant enhancing antibody (Ab) responses to HA while simultaneously inducing potent T-cell responses to conserved internal antigens. We show that this regimen leads to the induction of cytophilic Ab isotypes that are capable of inhibiting hemagglutination and neutralizing pseudotyped lentiviruses. Furthermore, mice immunized with MVA-NP+M1 and inactivated influenza vaccine displayed increased protection in a homologous challenge model.

**Conclusion:** The simultaneous induction of T-cells and antibody responses with a single immunization has the potential to improve seasonal vaccine performance and could be employed in pandemic situations.
Chitosan-Encapsulated Plasmid Coding for LipL32 and Loa22: A Promising Formulation of Leptospirosis DNA Vaccine

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Objectives: Develop a formulation of leptospirosis DNA vaccine by using chitosan-encapsulated lipL32-loa22 containing plasmid. Utilize chitosan nanoparticle as a DNA vaccine delivery system to improve the immunogenicity DNA vaccine against leptospirosis.

Background: Leptospirosis is a zoonotic disease distributed worldwide. One of the obstacles for vaccine development is the variety of serovars that might prevent cross protection¹. Moreover, cellular immune response seemed to be required². The ability of DNA vaccine in expression of selected conserved antigens and induction of humoral and cellular responses fit with those challenges. The delivery system of DNA vaccine is critical. We hypothesized that encapsulation of DNA vaccine with chitosan (CS), which is believed to be a good vaccine carrier³, could improve the ability of DNA vaccine in stimulating the immune system.

Methods: LipL32 and Loa22 were selected as model antigens for a DNA vaccine against leptospirosis. CS was used as a vehicle to encapsulate plasmids encoding either lipL32 or loa22 (CS/lipL32, CS/loa22) or both (CS/lipL32-loa22) by coacervation method⁴. Encapsulated DNA vaccines were tested for expression efficacy in vitro and for immunogenicity in mice.

Results: Encapsulation of DNA vaccine with CS formed nanoparticles. CS enhanced the uptake of lipL32 and loa22 containing plasmids by 293 T-cell line. The highest transfection efficiency was observed at the amine/phosphate (N/P) ratio of 20:1 of CS/DNA. Expression of both antigens in the same cells could be detected by immunofluorescence staining. In vivo results showed that CS/lipL32-loa22 induced significantly higher antibody titer against Loa22 than CS/lipL32 and CS/loa22 co-administration. Additionally, T-cell proliferation assay revealed that cell-mediated immune response were induced upon vaccination with CS/lipL32-loa22 or CS/lipL32 and CS/loa22.

Conclusion: From expression pattern and immunogenicity, CS/lipL32-loa22 DNA nanoparticles could be a promising formulation for DNA vaccine against leptospirosis.
Characterization of a *Yersinia pestis* Double Isogenic Mutant \( \Delta \text{lpp}/\Delta \text{pla} \) Mutant in a Mouse Model of Pneumonic and Bubonic Plague: A Potential New Live-Attenuated Vaccine

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**Objective:** Characterize the double isogenic mutant \( \Delta \text{lpp}/\Delta \text{pla} \) of *Y. pestis* both at the molecular and immunological level as a new live-attenuated vaccine against both bubonic and pneumonic plague.

**Background:** *Yersinia pestis* is the causative agent of bubonic and pneumonic plague, there is no FDA approved vaccine against this bioterrorism agent. Current subunit vaccines under investigation consist of a type - 3 secretion system-associated low calcium response V (LcrV) antigen and the F1 capsular antigen. Active immunization of cynomolgus macaques elicited high antibody titers to these antigens and the animals were well protected against the severest form of plague (i.e., pneumonic), however, protection was highly variable in African green monkeys. This raises concerns regarding the role of humoral immune response alone in providing protection against plague, as cell-mediated immunity has also been shown to play an important role in protection.

**Methods:** As live-attenuated vaccine will generate both humoral and cellular immunity, the chromosomally-encoded Braun lipoprotein (lpp) gene, a major cell wall component, was deleted. A plasmid-encoded plasminogen-activating protease (pla) gene which facilitates bacterial dissemination to peripheral organs. from *Y. pestis* CO92 strain was also deleted.

**Results & Conclusions:** The \( \Delta \text{lpp}/\Delta \text{pla} \) mutant was highly attenuated in evoking both bubonic and pneumonic plague in a mouse model. Further, animals immunized with \( \Delta \text{lpp}/\Delta \text{pla} \) mutant were significantly protected against subsequent challenge with wild-type (WT) *Y. pestis* CO92. The \( \Delta \text{lpp}/\Delta \text{pla} \) mutant poorly disseminated to peripheral organs compared to the WT bacteria in models of both bubonic and pneumonic plague with a concomitant decrease in the production of pro-inflammatory cytokines. Further, histopathology results indicated reduced damaged in the lungs, liver, and spleen of mice infected with the mutant compared to WT bacteria-infected animals. The mutant induced humoral immune response to LcrV and F1 antigens. We also found an induction of *Y. pestis* specific T-cell response by \( \Delta \text{lpp}/\Delta \text{pla} \) mutant which indicates a specific adaptive immune response.

**References:**
Genetic Stability of Rift Valley Fever Virus MP-12 Lacking NSs in Type-I Interferon-Incompetent Vero Cells

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**Objective:** Discuss DIVA for Rift Valley Fever and the genetic stability of MP-12 vaccine with a truncated NSs gene.

**Background:** Rift Valley fever virus (RVFV) (genus: *Phlebovirus*, family: *Bunyaviridae*) is endemic to sub-Saharan Africa, transmitted by mosquitoes. It is known to cause high rate of abortions in ruminants; among humans, it causes hemorrhagic fever, neurological disorders, or blindness. The live-attenuated candidate vaccine, MP-12, has Investigational New Drug status made in certified MRC-5 cells in the United States, as MP-12 is immunogenic in both humans and ruminants. However, MP-12 vaccine lacks a marker to differentiate infected from vaccinated animals (DIVA) for veterinary use, and an improved MP-12 was generated by truncation of NSs gene. Since NSs is an interferon (IFN) antagonist, MP-12 lacking NSs can no longer replicate efficiently in type-I IFN-competent MRC-5 cells, while it replicates well in type-I IFN-incompetent Vero cells. Thus, we aimed to determine genetic stability of MP-12 lacking NSs in Vero cells during multiple passages.

**Methods:** MP-12 and MP-12 encoding truncated NSs (rMP12-C13type, rMP12-NSdel1~11) underwent 25 serial passages in Vero cells as duplicates at moi of 0.01 to 0.1. Each virus at 25 passages was plaque-purified, and amplified once in Vero E6 cells, while viruses at different passages were stored for future analysis.

**Results:** After 25 passages, most viruses changed their plaque phenotypes in plaque assay using Vero E6 cells with agar overlay; e.g., very large or small plaques. Virion RNAs of selected viruses were extracted from culture supernatants after removal of non-protected RNA by benzonase nuclease treatment. We are currently analyzing the full-genome sequences of them.

**Conclusions:** Our study suggests that MP-12 lacking NSs is not genetically stable after 25 passages in Vero cells. We will determine the emergence of specific viral populations during passages, and replication kinetics of those mutants.

**References:**


**P22 WITHDRAWN**
Immune Suppression Induced by Vi Capsular Polysaccharide is Overcome by Vi-DT Conjugate Vaccine

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Objectives: Examine hyporesponsiveness to Salmonella typhi Vi polysaccharide vaccine and how to overcome the hyporesponsiveness using a Vi conjugate vaccine. Examine immunogenicity of varying amounts of free Vi polysaccharide mixed with a Vi conjugate vaccine in mice.

Background: The Vi conjugate vaccine (Vi-DT) developed at the International Vaccine Institute consists of Vi capsular polysaccharide purified from Salmonella typhi bound to diphtheria toxoid. Polysaccharide - only vaccines can induce hyporesponsiveness to subsequent doses. The current study examined if pre-exposure of mice to Vi polysaccharide reduced the Vi response to a subsequent dose of Vi-DT conjugate. We also examined the effect of having free Vi mixed with Vi-DT conjugate.

Methods: Mice were injected subcutaneously with three 2.5 µg doses at 4 - week intervals of Vi either as Vi or Vi-DT. Different dosing regimens were examined and included priming with either free Vi or Vi-DT followed by second and third doses of either Vi or Vi-DT. Additionally, mixtures of free Vi and Vi-DT were delivered using the same dosing schedule with the dose of Vi as conjugate fixed at 2.5 µg.

Results: Priming of mice with Vi suppressed the anti-Vi response to a subsequent dose of Vi-DT. However, the suppression was overcome by a second dose of Vi-DT. Priming with Vi-DT prevented suppression of the anti- Vi response and subsequent dosing with Vi raised anti-Vi levels back to levels seen after one dose of Vi-DT. The presence of free Vi, up to 50% in the conjugate preparation, enhanced both the anti-Vi and DT responses, the free Vi in the presence of Vi-DT appeared to behave like an adjuvant.

Conclusions: Pre-exposure to free Vi induces hyporesponsiveness to subsequent doses of Vi or Vi-DT and it takes two doses of Vi-DT to overcome the hyporesponsiveness. The presence of up to 50% free Vi mixed with Vi-DT enhanced the anti-Vi and DT responses.

References:
Objective: Discuss the dual functions of Sandfly Fever Sicilian Virus (SFSV) NSs and the application to Rift Valley fever (RVF) virus vaccine development.

Background: Rift Valley fever virus (RVFV: family Bunyaviridae, genus Phlebovirus) is a negative-stranded RNA virus, originated from Africa, and causes mosquito-borne zoonotic diseases in ruminants and humans. Live-attenuated candidate vaccine MP-12 lacks a marker to differentiate infected from vaccinated animals (DIVA). A major virulence factor NSs is fully functional in MP-12, and inhibits general host transcription while promoting degradation of dsRNA-dependent protein kinase, PKR. To introduce a DIVA marker into MP-12 without affecting the efficacy, we previously generated recombinant MP-12 encoding SFSV NSs (rMP12-SFSNSs). Unexpectedly, co-expression of SFSV NSs significantly increased reporter gene expression under SV40 promoter. In this study, we aimed to characterize the function of SFSV NSs which increases host gene expression.

Methods: Western blot, Northern blot, and luciferase reporter assays were used for functional characterization of SFS NSs.

Results: 293 cells transfected with plasmid-encoding Renilla luciferase (rLuc), under SV40 promoter, increased rLuc activity when in vitro synthesized RNA encoding SFSV NSs was co-transfected. However, we didn’t observe the increase of rLuc activity when those cells were treated with transcription inhibitor, actinomycin D (ActD). Furthermore, 293 cells infected with rMP12-rLuc (MP-12 encoding rLuc in place of NSs) increased rLuc activity in the presence of SFSV NSs. Phosphorylation of PKR and eIF2α by rMP12-rLuc were not affected by SFSV NSs.

Conclusions: In contrast to RVFV NSs, SFSV NSs increased host and viral gene expressions without inhibiting PKR. We are currently characterizing detailed mechanism of host and viral gene up-regulation by SFSV NSs using wt SFSV NSs and the mutants. This novel SFSV NSs function may be useful for improving vaccine immunogenicity.

References:
Development of a Novel Method for Deriving Thresholds of Toxicological Concerns for Vaccine Constituents

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Objective: Define thresholds of toxicological concern (TTCs) and apply a novel method for deriving TTCs for vaccine constituents.

Background: Safety assessment relating to the presence of impurities, residual materials, and contaminants in vaccines is a focus area of research at the Food and Drug Administration (FDA). Sponsors who submit Investigational New Drug (IND) applications for new vaccine products must report the results of safety assessments to the Division of Vaccines and Related Products Applications (DVRPA). Scientifically defining thresholds of toxicological concern (TTCs) as they apply to vaccine constituents will provide a useful aid to the sponsors and public regarding safety assessments of compounds for which there is little or no toxicity data. TTCs are mathematically modeled and extrapolated levels, below which adverse human health effects are not expected to occur.

Methods & Results: In this project, we mined DVRPA's submission databases to yield a total of 228 chemicals. Using INCHEM and TOXNET, we added probit data, and employed cluster analysis using JMP software to verify that natural clusters of data were present. Using the Cramer decision tree for reference, an algorithm will be developed to assign chemicals into classes based on structural alerts. For each class, the probit data will be extrapolated to a TTC value using Joint Monitoring Program (JMP) and safety estimates derived using uncertainty factors (UF). Currently, the only methodology for deriving TTCs uses NOAELs, which are not always reliable. The method for linear extrapolation of TD50 data to a virtually safe dose may also be modified based on qualitative and quantitative aspects our data. TTC values for each class will be tested for statistical significance in JMP and the algorithm will be subjected to external validation to determine the sensitivity and specificity of the model.

Conclusion: If the TTC's are validated, sponsors may use them as reference values for compounds of unknown toxicity.

References:

Fatigue and Fear with Shifting Polio Eradication Strategies in India: A Study of Social Resistance to Vaccination

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Objective: Determine the causes of social resistance to vaccination and recognize the barriers of top-down eradication initiatives from both social and biological perspectives and vaccine design.

Background: Shifting polio eradication strategies may have generated fear and “resistance” to the program in Aligarh, India during the summer of 2009. “Resistance” to the program due to rumors about the vaccine, frustration with the slow pace of development, and distrust of the authorities has been widely documented¹.

Methods & Results: However, rapid ethnographic methods including participant observation of the program, in-depth interviews, and semi-focus groups with 107 people from May to August 2009 indicated that the intensified frequency of vaccination was correlated with patients’ doubt in the efficacy of the vaccine. This doubt was exacerbated in a few cases when families, uninformed of polio serotypes and the targeted use of the monovalent mOPV1, saw the continued occurrence of P3 despite vaccination. Many families had also come to believe that their children had been adversely affected by OPV after being told the vaccine carried no risk. Though it is more likely adverse events occurred proximate to, rather than because of vaccination, the doubt highlighted challenges faced with non-disclosure of risks including VAPP and VDPV²,³.

Conclusions: Polio is now largely eradicated in India, with only a single case in 2011. Nonetheless, lessons from the eradication initiative indicate greater transparency about changes with vaccination policy may need to be considered to build trust with the public in future eradication programs⁴.

References:
Perception of Childhood Immunization: A Qualitative Study of Fathers in Kano, Northern Nigeria

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Objective: Apply strategies to improve community demand for immunization and review factors that influence decision-making regarding childhood immunizations.

Background: Childhood immunization has been responsible for marked progress in global health from control of diseases and their spread among individuals and populations. Success of immunization programs for children depends a great deal on their parents’ understanding and subsequent decision to accept the recommended vaccines. Even though mothers are largely responsible for taking their children for immunizations, Northern Nigeria, being a patriarchal society, depends on the fathers to make the decisions to accept or refuse immunization and also provide the financial means. This study aims to understand how fathers reach these decisions based on the health belief model of perceptions of severity, susceptibility, benefits, and barriers.

Methods: Fathers of children under 5 years old were purposely selected in four randomly selected rural communities of Kano State, Nigeria. Eight focus group discussions involving 32 fathers were conducted.

Results: Participants recognized that measles and malaria were the most serious childhood diseases, and only a few identified other vaccine-preventable diseases as being serious, giving reasons such as not being familiar with their disease presentation. Most fathers agreed that children were at risk of several infections, notable among which were respiratory tract infections, malaria, and measles. Participants generally identified vaccines against poliomyelitis, measles, and meningitis as protective; and only a few believed that immunizations were completely non-beneficial or even harmful. Perceived barriers discussed were adverse effects of vaccines, confusion about immunization schedule, lack of information about diseases and their vaccines, illness of children, and long queues in health facilities.

Conclusion: This study found that fathers were ill-equipped with proper information about immunizations to be fully empowered to make informed decisions regarding their children’s health.

References:
Treatment with Aqueous Phyllanthusniruri Extract Promotes the Phenotypic Maturation of Bone Marrow-Derived Dendritic Cells and their Antigen Presentation Functions, *In Vitro*

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**Objective:** Evaluate the effect of an herbal immune-booster, *Phyllanthusniruri*, on dentic cells (DCs) maturation and functions.

**Background:** Decoctions of *Phyllanthusniruri* (PN) (Fam. *Euphorbiaceae*) is promoted in traditional medicine of Africa, Asia, and South America as a beneficial supplement for different infectious diseases, especially for viral hepatitis, tumor, and for immunocompromised patients. This stimulated the interest in understanding the mechanisms by which the whole extract of the plant could stimulate the immune system. Dendritic cells (DCs) are professional antigen-presenting cells and provide a link between the innate and the adaptive immune responses. In the present study, the effects of lyophilized aqueous extract of PN on structural and functional maturation of murine bone marrow-derived DCs (BM-DCs) were investigated.

**Methods:** Bone marrow cells were cultured in the presence of granulocyte macrophage-colony stimulating factor and interleukin-4 (IL-4) and the generated immature DCs were stimulated with PN (25, 50, and 100 μg/mL) or lipopolysaccharide (10 μg/mL) for 48 hours.

**Results:** Results showed that treatment with PN increased the expression of major histocompatibility complex-II and the various makers for DCs maturation (CD40), activation (CD83), and costimulation (CD86) in a concentration-dependent manner. Consistent with the increase in phenotypic makers, functional maturation assay showed that treatment of BM-DCs with PN caused a decrease in fluorescein isothiocyanatedextran pinocytosis and an increase in IL-12 in the supernatant. In a transgenic T-cell activation model, PN-treated BM-DCs presented Ova antigen to Ova-specific CD8+ T-cells from OT-1 mice more efficiently as demonstrated by increased T-cells proliferation and IL-2 production. Therefore, PN enhances the structural and functional maturation of BM-DCs and their antigen-presenting function.

**Conclusion:** These effects are relevant in immunodeficient conditions, tumor control, and in infectious diseases.

**Reference:**
Immunomodulatory Potential of QS-21 on Protective Efficacy of DPT Vaccine

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Objectives: Identify the immunostimulatory potential of QS-21 with alum-adjuvanted vaccines and its antigen sparing effect in combination vaccines. Explain how inclusion of a co-adjuvant enhances the quality of immune responses when administered with alum-adsorbed vaccines. Compare the immunomodulatory potential of QS-21 to induce shift in Th1/Th2 paradigm in the presence of alum.

Background: Combined use of vaccines and immunostimulants is emerging as one of the innovative approaches in adjuvant development. Various immunomodulators such as QS-21, MDP, and MF-59 are currently under consideration for possible inclusion in alum-containing vaccines.

Methods: A guinea pig model was used for the study. Host challenge procedure was used wherein diluted doses of DPT vaccine (1:80 and 1:160) and diphtheria toxin (10LD50) were used as antigen and challenge respectively. Antitoxin levels, IFN-γ/IL-4 level ratios, sera cortisol, and survival rate were used as markers of immune efficacy. Vero cell assay and ELISA techniques were used to determine antitoxin and cytokine levels respectively.

Results: Co-administration of QS-21 (250 µg/Kg) with DPT vaccine resulted in significant increase (p<0.05) of after-challenge diphtheria antitoxin levels (0.219 ± 0.060 IU/ml) as compared to same and double dose of control (0.076 ± 0.045 and 0.160 ± 0.064 IU/ml respectively). Moreover, IFN-γ/IL-4 ratios were significantly (p<0.05) raised (0.80 vs. 0.51), suggesting a mixed Th1/Th2 response of QS-21 as compared to more limited responses of alum alone. Serological findings were supported by decreased morbidity and mortality (100% survival in QS-21 treated group vs. 57% and 80% in control groups at 1:160 and 1:80 dilutions respectively). Histology of injection site revealed no untoward toxicity.

Conclusions: This study establishes the immunoadjuvant potential of QS-21 with DPT vaccine as indicated by significantly enhanced protective efficacy when compared (to control) using Kaplan-Meier survival analysis, significantly higher antitoxin and cytokine levels when compared using Mann-Whitney test, even at higher dilution (1:160) of vaccine, suggesting antigen sparing effect. Such approaches will be helpful in further reduction of antigenic requirements for obtaining protective immunity, thus increasing production capacity and decreasing cost.

References:

**TG2**

**Pichia pastoris-Expressed Dengue 2 Envelope Forms Virus-Like Particles and Induces High Titer Neutralizing Antibodies**  
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**Objectives:** Discuss the use of a high yielding yeast expression system for producing Dengue 2 Envelope Forms Virus-Like Particles (DENV VLPs). Explain how use of DENV VLPs may impact the development of safe, efficacious and inexpensive dengue vaccine candidates.

**Background:** Dengue is a mosquito-borne viral disease with a global prevalence. It is caused by four closely-related types of dengue viruses (DENVs 1-4). A preventive dengue vaccine that can protect against all four viruses is an unmet public health need. Live attenuated vaccine development efforts have encountered unexpected interactions between the vaccine viruses raising safety concerns. This has emphasized the need to explore non-replicating dengue vaccine options. VLPs, which can serve to elicit robust immunity in the absence of infection offer promise for the development of non-replicating dengue vaccine alternatives.

**Methods:** We designed a synthetic codon-optimized gene, encoding the N-terminal 395 amino acid residues of the DENV-2 E protein. It also included 5’ pre-membrane-derived signal peptide-encoding sequences to ensure proper translational processing, and 3’ 6× His tag-encoding sequences to facilitate purification of the expressed protein. This gene was integrated into the genome of *P. pastoris* host and expressed from the alcohol oxidase 1 promoter by methanol induction.

**Results:** Recombinant DENV-2 protein, which was present in the insoluble membrane fraction was extracted and purified using Ni2+-affinity chromatography under denaturing conditions. Amino terminal sequencing and detection of glycosylation indicated that DENV-2 E had undergone proper post-translational processing. Electron microscopy revealed the presence of discrete VLPs in purified protein preparation after dialysis. The DENV-2 E VLPs formulated in alum were highly immunogenic in inbred and outbred strains of mice eliciting virus neutralizing titers as high as ~1:1200 in flow cytometry based assays.

**Conclusions:** The formation of highly immunogenic DENV-2 E VLPs in the absence of pre-membrane protein highlights the potential of *P. pastoris* in developing non-replicating, safe, efficacious, and affordable dengue vaccine.

**References:**


Allelic Diversity of Merozoite Surface Protein 2 Gene of *Plasmodium falciparum* among Children in Osogbo, Nigeria

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**Objectives:** Explain the extent of genetic diversity among the falciparum malaria population and why it is important in understanding the immune response to falciparum malaria. Discuss why genetic diversity in vaccine antigens is needed to guide rational vaccine design and to interpret the results of vaccine efficacy trials conducted in malaria endemic areas.

**Background:** The genetic diversity of *P. falciparum* infection in humans is implicated in the pathogenesis of malaria and it is an important subject in vaccine development. This study provides the first estimate of the genetic diversity and genotype multiplicity of infection in children with uncomplicated *P. falciparum* malaria in Osogbo, Nigeria.

**Methods:** One hundred and one isolates were used for analysis of parasite population polymorphism and genotyped by nested-PCR of Merozoite Surface Protein 2 (MSP2) block 3. Amplicons were obtained for all the 101 genotyped samples in MSP2 PCR with 9 alleles varying in size between 300 and 800 base pair.

**Results:** Thirty-three (31.7%) samples had FC27 allele while 27 (26.7%) had 3D7 allele and 35 (34.7%) had mixed alleles (3D7+FC27). The Multiplicity of Infection (MOI) in the population was 1.6. Children in the age group 4-8 years had the highest number of different genotypes in their samples (1.8). The number of MSP2 bands per isolate was lower in the older age group (1.3) but the difference was not statistically significant. Children with parasite density range 5,001-10,000 had the highest MOI of 2 while those with parasite density range 1,000-5,000 had the lowest range: 1.5.

**Conclusions:** The present study shows that the field isolates are highly diverse in respect of MSP2 and multiplicity of infection was neither age nor parasite density dependent in the study population.

**Reference:**

**Concern and Resistance to Immunization and their Causes among Key Stakeholders in the Context of Introduction of Rotavirus Vaccine in Georgia**

**M. Topuridze, M. Shishniashvili**
National Center for Disease Control and Public Health, Tbilisi, Georgia

**Objectives:** Identify the major barriers for immunization and rotavirus (RV) vaccine introduction. Discuss the importance of using qualitative research results for planning future communication campaigns. Discuss the importance of public education interventions and efforts undertaken for strengthening both the technical capacity and interpersonal communication skills of healthcare professionals (HCPs) regarding immunization.

**Background:** Rotavirus disease burden is high in the Republic of Georgia, causing 37% of diarrhea-associated hospitalizations in children under 5 years of age. Given this, the decision was made to add the rotavirus vaccine to the national immunization program. To help implement this change, we collected up-to-date local information on barriers to immunization from Tbilisi and from two rural regions with low vaccine coverage.
**Methods:** Stakeholders’ knowledge, perceptions, and practices were examined quantitatively and qualitatively through self-administered questionnaires, focus groups, and in-depth interviews.

**Results:** Quantitative surveys of 462 HCPs found that respondents saw pediatric diarrhea as a serious (62%) and common (70%) health problem. However, only 36% of HCPs considered rotavirus to be a concern and only 44% recommended vaccination. Vaccine awareness and acceptance was lower among HCPs from rural settlements. Safety concerns (OR=1.5; CI (1.16 - 2.03); p≤0.003), poor awareness (OR=1.6; CI (1.40 - 1.87); p≤0.000), and non-reliance on international experience (OR=1.7; CI (1.44 - 1.98); p≤0.000) were the key barriers to vaccination. Qualitative results from focus groups (39 HCPs, 40 mothers, and eight media representatives) and in-depth interviews (two religious leaders and two insurance company managers) similarly found that concerns about safety and efficacy were the largest barriers to immunization.

**Conclusions:** Poor awareness of need and concerns about vaccine safety and efficacy (spread primarily via the Internet and by the media) are the primary barriers to widespread adoption of rotavirus vaccine in Georgia. Despite this, HCPs and caregivers will likely adopt the rotavirus vaccine if guaranteed of its necessity, safety, and efficiency. Increasing stakeholders’ knowledge and strengthening the technical capacity and interpersonal communication skills of HCPs will be integral to a successful vaccination program.

**References:**

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**TG5**

**Ensuring Comprehension of Study Information among Vaccine Trial Participants in The Gambia**

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**Objectives:** Discuss the limitations of the current consent procedures in obtaining genuine informed consent in developing countries. Review the use of a new procedure for obtaining informed consent. Discuss strengths and weaknesses of the new informed consent procedure.

**Background:** Most sponsors, in wanting to comply with certain international standards, request African investigators to translate informed consent into local languages using Arabic or Latin scripts. Although well intentioned, this practice may be meaningless in settings where local languages are only spoken and not written, and may end up with participants being issued consent forms that neither they nor other members in their families can read. Recognizing this challenge, the ethics committee in The Gambia recommended a new consent procedure that takes into account the local realities. The objective of this paper was to assess the effectiveness
of this new procedure in conveying key trial information among participants in a vaccine trial in The Gambia.

**Methods:** Consent was obtained from 1,200 parents using the new procedure. Comprehension was then assessed using a tool that contained questions on key aspects of the trial.

**Results:** Although the majority (83.5%) of respondents were illiterate, almost all of them had a sound understanding of the trial. However, comprehension of complex concepts, like randomization and study design, was poorer than that of other aspects. Variables such as age, gender, education, ethnicity, and occupation had minimal effect on comprehension.

**Conclusions:** Our data suggest that the new consent procedure is effective in conveying key research information to research participants. The procedure is promising in that it has eliminated the need for repeatedly translating and back-translating informed consents. It also guarantees that the study team expresses research concepts in the same way.

**References:**

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**Predictors of Delay in Immunization of Children in Rural Communities of Kano, Northern Nigeria**

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**Objectives:** Explain reasons for immunization delays and methods to enhance timeliness of vaccine uptake. Review the current national immunization program and policy in Nigeria. Assess measures of integrating supplemental immunization activities to reach children in remote areas.

**Background:** Immunizations have saved millions of lives. To fully reap the benefits of immunization, it is essential that children receive all vaccines at the recommended times. Delay of childhood vaccines will not only fail to protect the child but can result in delay of subsequent ones or even default vaccination.

**Methods:** A cross-sectional study of 420 children age 12-23 months was carried out in six villages. Data were collected using an interviewer-administered questionnaire. Immunization status and ages at receipt of each vaccine were determined and analyzed using SPSS (16.0). A vaccine was termed delayed if received four weeks after the recommended date. Maternal and child characteristics in addition to factors related to the health system were analyzed for association with delay.

**Results:** Less than half (49.8%) had received at least one vaccine. Delay in receipt of at least one vaccine was found in 83.7% with only 16.3% receiving all the vaccines on schedule. On multivariate analysis, marital status (OR: 5.39[1.51-19.20]) and immunization status (OR: 13.95[5.03:38.68]) were the only significant predictors of delay. Reasons for delay were; illness, distance to health facility, and availability of recommended vaccines.

**Conclusions:** This study shows that out of the few children that are immunized, very few receive immunizations when recommended. In order to increase adherence, there is a need to ensure timeliness of immunizations and explore innovative ways to prevent delays.
TG7

Immunization Knowledge, Attitude, and Practice among Parents: Malaysian Experience
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Objectives: Test the reliability and validity of the translated version of knowledge, attitude, and practice (KAP) questionnaire on immunization. Evaluate the immunization KAP among Malaysian parents and determine the differences of KAP among groups.

Background: Parents’ knowledge, attitude, and practice (KAP) regarding immunization in general can potentially affect the immunization or vaccination status of children.

Methods: A cross-sectional prospective survey was carried out among 88 Malaysian parents to obtain demographic data of parents. Other data were collected using translated KAP immunization questionnaires (Malaysian version) consisting of 40 questions (20 questions about knowledge, 10 questions about attitude, and 10 questions about practice). Scoring of the questions was determined by giving one point (1) for each correct answer and zero (0) for incorrect answers or no response (don’t know). Descriptive statistics were used, and reliability was tested for internal consistency using Cronbach’s alpha coefficient.

Results: Employing the recommended scoring method, the mean ± standard deviation (SD) of the KAP scores was 22.86±5.4. Good internal consistency was found (Cronbach’s alpha=0.762); the test-retest reliability value was 0.740 (p=0.014). For validity, three pharmacist specialists judged the face and content validity of the questionnaire. A significant difference was found in KAP scores among parents’ gender (p=0.003) and education level (p=0.001). The level of immunization knowledge among parents was positively associated with the attitude and practices of immunization (P<0.001).

Conclusions: The study concluded that the translated KAP immunization questionnaire appears to be reliable and valid for measuring the knowledge, attitude, and practices among Malaysian parents and that it can be used in future research. Due to mothers’ experience regarding childcare, mothers have a higher KAP score than fathers. In addition, the KAP score of parents increases with education level.

References:
TG8

Knowledge and Practice of Injection Safety amongst Primary Healthcare Professionals in Kano, North Nigeria

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Objective: Assess the knowledge and practice of injection safety amongst primary healthcare professionals (HCPs) in Kano metropolis.

Background: The World Health Organization (WHO) estimates that approximately one billion injections are given worldwide each year during childhood vaccinations¹. Primary HCPs frequently administer injections and are the first-line of contact for patients in the Nigerian public health system. Unsafe and indiscriminate injections coupled with immunization campaigns may contribute to the burden of preventable blood-borne infections. This study assessed the knowledge and practice of injection safety amongst primary HCPs in Kano metropolis.

Methods: Multistage sampling technique was used to select 134 individuals out of 356 primary HCPs who worked at one of 17 PHC facilities in Nassarawa LGA, Kano, Nigeria, and were studied using a cross-sectional design. The collected data were analyzed using MINITAB statistical software (ver. 12.21).

Results: Mean age of the respondents was 28 +/- 5.7 years. Few respondents had good knowledge regarding injection safety and knew hepatitis C could be iatrogenically transmitted. Only 22.3% were aware of the National Policy on Injection Safety and Waste Management. Open burning of used safety boxes was mentioned by 34.3% as an ideal method of waste disposal. Up to 17.1% of respondents had poor injection practices. Respondents’ sex had a statistically significant association with good injection safety practice. New AD syringes were used in 44.4% of all observed injections, however unsafe practices, such as two-handed needle recapping, was observed.

Conclusions: There is need for pre-service curriculum review as well as on-the-job and on-site training on injection safety for primary HCPs with routine integrated supportive supervision, including during immunization campaigns. Additionally there is a need for continuing advocacy for rational use of oral and injectable medications.

References:


Induction of Protective Immune Response in Mice by a DNA Vaccine Encoding ε-Toxin Gene of *Clostridium perfringens*, a Causative Agent of Enterotoxemia in Sheep

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**Objectives:** Understand the role of heterologous booster with DNA vaccine to enhance the humoral and cell mediated immune response. Recognize the effect of amount, dose, and adjuvant to induce immune response in the case of DNA vaccine. Understand the effect of antigen on immune system expressing in different cell organelles from DNA vaccine.

**Background:** The *Clostridium perfringens* epsilon toxin (Etx) is highly toxic and causes a severe, often fatal enterotoxemia in sheep and goat causing large-scale mortality resulting in major economic losses to farmers. As antibiotics are not effective after the onset of clinical symptoms of the disease, vaccines are urgently needed to prevent enterotoxemia.

**Methods:** To develop a DNA-based vaccine against enterotoxemia in animals, we cloned 846 bp antigen (Etx gene) in eukaryotic expression plasmids with or without tags for targeted expression. *In vitro* expression of recombinant Etx was confirmed in CHO-K1 cells transfected with DNA constructs using microscopy and western blotting. BALB/c mice vaccinated with these constructs produced antibodies which were found to be highly specific to Etx. Other studies have also demonstrated that DNA vaccine expressing antigens in different cellular location generate different immune responses.

**Results:** Anti-sera raised against these DNA vaccine constructs was able to offer protection against toxin, however, the antibody titers were low. To enhance the efficacy of DNA vaccine, heterologous booster strategy was followed, where animal were immunized with DNA and one booster of heat inactivated Etx was applied. Significant increase in antibody titer, *in vitro* protection, cell mediated immunity dominating IFN-y indicated by ELISPOT and animal protection up to 50 LD50 after challenge experiment.

**Conclusions:** These results indicate that DNA vaccine combined with heterologous booster strategy can provide strong immunogenicity and can be a potential alternative in developing a vaccine against Etx of *Clostridium perfringens*.

**References:**
Translational Fusion of Heat Labile Enterotoxin B Subunit (LTB) and Immunodominant Epitopes of Epsilon Toxin of Clostridium perfringens and its Evaluation as a Potential Subunit Vaccine

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Objectives: Describe how epitope analysis can play an important step in the development of more effective vaccines and diagnostic tools for various infections. Demonstrate how labile enterotoxin B subunit (LTB) can be used as a carrier protein or as an adjuvant needed to enhance the immunogenicity of vaccine antigens. Show how an epitope-based vaccine might play an important role in eradication of infectious diseases.

Background: Clostridium perfringens is a major causative organism for chronic enterotoxaemia in sheep and goats. The epsilon toxin (Etx) produced by Clostridium perfringens type B and D damage endothelial cells, leading to subsequent death. Etx is listed among the most lethal toxins known worldwide. Many reports substantiate that subunit vaccines have great potential against several toxin-related diseases like hepatitis B and human papilloma virus. The present study shows the potential of a subunit vaccine against Etx by making translational fusion of Etx epitopes with a highly proven adjuvant beta subunit of heat LTB.

Methods & Results: B-cell epitopes of Etx with high predicted antigenicity and physiochemical score were investigated by using various bioinformatic tools. Epitopes of Etx fused with LTB were successfully expressed in a secretory expression system. Recombinant fusion proteins were purified to near homogeneity by cation-exchange chromatography. Like native LTB, the recombinant fusion proteins retained the ability to pentamerize and affinity to bind to GM1 ganglioside receptor. CD spectra of LTB and fusion proteins showed similar secondary structures. Western Blot analysis and ELISA showed that the antibody raised against the fusion protein were highly specific to Etx and LTB and were also able to neutralize the lethal dose of epsilon toxin.

Conclusions: The data present in this study clearly demonstrate that the potential of Etx epitope-LTB fusion proteins as a candidate vaccine against Clostridium perfringens.

References:
Objectives: Measure the value of considering tuberculosis (TB) exposed and TB infected infants for inclusion in efficacy trials that seek to understand the mechanisms of vaccine-induced protection against TB.

Background: TB exposed and TB infected infants should be considered a high-risk target group for inclusion in efficacy trials that seek to understand the mechanisms of vaccine-induced protection against TB.

Methods: Infants were screened for enrolment in a clinical trial of a novel TB vaccine (MVA85A) from 2009-2011. Infants excluded due to known household TB contact (TB exposure), or positive QuantiFERON® TB Gold in-tube (QFT-GIT) test (TB infection), were analyzed. TB exposed or infected infants were referred for IPT. Thereafter, two-year cumulative incidence of TB disease was calculated from data in TB clinic notification registers.

Results: 2.8% (135/4758) of infants screened at median 18 (IQR: 17-19) weeks of age had household TB exposure. A QFT-GIT result was available in 3,417 infants (excluding those with a TB household contact), of whom 273 (8%) were positive. Only 123/408 infants (30%) received IPT. Two-year cumulative incidence of TB disease was 13% (54/408) (95% CI: 10 -16.6). Risk of TB disease was not significantly lower in infants after receiving IPT (hazard ratio: 0.52; 95%CI: 0.26-1.1, P=0.07) Ten percent (6/60) of QFT-GIT positive infants on IPT developed TB disease, compared to 6% (4/63) of TB exposed infants on IPT (p>0.05). Among QFT-GIT positive infants not on IPT, 15 % (32/210) developed TB disease; amongst TB exposed infants not on IPT, 17 % (12/72) developed TB disease (p>0.05).

Conclusions: TB exposed and infected infants are at high risk of developing TB disease, even after receiving IPT, and therefore would be a suitable study population for TB vaccine efficacy trials.

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The following online resources provide additional information about vaccine-preventable diseases from NFID and coalition partners.

### Preventchildhoodinfluenza.org

The *Childhood Influenza Immunization Coalition* (CIIC) is a leading advocate for childhood influenza immunization. Established by NFID in 2007, CIIC includes more than 30 of the nation’s leading public health, medical, patient, and parent groups and seeks to address and improve low influenza immunization rates among children.

[www.preventchildhoodinfluenza.org](http://www.preventchildhoodinfluenza.org) provides pediatric-focused information and resources on seasonal influenza and vaccination for consumers, healthcare professionals, and the media.

### Adolescentvaccination.org

[www.adolescentvaccination.org](http://www.adolescentvaccination.org) provides resources and professional tools highlighting the importance of vaccination to protect US adolescents from vaccine-preventable diseases and supporting a comprehensive approach toward improving vaccination rates.

Information is available for the general public, healthcare professionals, and media.

### Adultvaccination.org

[www.adultvaccination.org](http://www.adultvaccination.org) provides information on the impact of infectious diseases on adults and vaccines available to provide protection. Resources include disease-specific backgrounders and healthcare professional practice toolkits. Select materials are also available in Spanish.

Information is available for the general public, healthcare professionals, and media.

February 2013
ONLINE CONTINUING PROFESSIONAL EDUCATION

NFID provides continuing professional education for physicians, nurses, pharmacists, and other healthcare professionals. Visit www.nfid.org/professional-education/online for a complete listing of available online education offerings.

ADULT IMMUNIZATION
CME LEARNING CENTER

Includes key clinical content and CME/CE activities specific to adult immunization recommendations, safety, and efficacy of recommended and emerging vaccines, and the best approaches for successfully implementing vaccine recommendations. The interactive web-based programs provide timely access to critical data and educational activities as well as journal articles, guidelines, relevant conference coverage, news, and editorials.

BUILDING AN ADULT IMMUNIZATION PRACTICE:
THE PRIMARY CARE PHYSICIAN’S ROLE IN DISEASE PREVENTION

Through evidence-based presentations and faculty discussions, this 10-module online activity, provides evidence supporting the importance of adult vaccination and describes the current recommendations. It also addresses the challenges primary care providers may face in promoting adult vaccination and identifies strategies that can be implemented in clinical practice to increase immunization rates.

CLINICAL VACCINOLOGY COURSE ENDURING MATERIALS

Developed in collaboration with CMEinfo, the Clinical Vaccinology Course focuses on new developments and issues related to the use of vaccines. Expert faculty provide the latest information on both current and prospective vaccines, updated recommendations for vaccinations across the lifespan, and innovative and practical strategies for ensuring timely and appropriate vaccination. Leading infectious disease experts discuss newly available vaccines, vaccines in the pipeline, and established vaccines whose continued administration is essential to improving disease prevention efforts. Enduring materials based on the November 2011 live course are available in a multimedia format for purchase through CMEinfo.

METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS (MRSA)
CME LEARNING CENTER

Includes relevant content and CME/CE activities targeted to healthcare professionals regarding the prevention and management of MRSA infections. The interactive web-based programs provide timely access to critical data and educational opportunities as well as journal articles, guidelines, relevant conference coverage, news, and editorials.
Thank you for attending the 16th Annual Conference on Vaccine Research

Please join us at:

17th Annual Conference on Vaccine Research
April 28-30, 2014
Bethesda North Marriott Hotel and Conference Center
Bethesda, MD

18th Annual Conference on Vaccine Research
April 13-15, 2015
Bethesda North Marriott Hotel and Conference Center
Bethesda, MD